THE PROGNOSTIC VALUE OF FRAILTY IN MAJOR TRAUMA IN OLDER PEOPLE

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List of Abbreviations

ADL	Activities of Daily Living
AIS	Abbreviated Injury Scale
AMT	Abbreviated Mental Test
AUC	Area Under the Curve
BGC	British Geriatrics Society
BPT	Best Practice Tariff
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
DV	Dependent Variable
ED	Emergency Department
FI	Frailty Index
GFR	Glomerular Filtration Rate
GTFI	Geriatric Trauma Frailty Index
GP	General Practitioner
Hb	Haemoglobin Level
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ISS	Injury Severity Score
IQR	Interquartile Range
LOS	Length of Stay
MOI	Mechanism of Injury
MTC	Major Trauma Centre
NHFD	National Hip Fracture Database
NHFS	Nottingham Hip Fracture Score
NTFI	Nottingham Trauma Frailty Index
ROC	Receiver-operator Curve/ Receiver Operating Characteristic

TARN	Trauma Audit and Research Network
TBI	Traumatic Brain Injury
TRIPOD	Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
TSFI	Trauma-Specific Frailty Index
PEO	Population, Exposure and Outcome– a method of structuring research questions
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines
U	Urea
UTI	Urinary Tract infection

Abstract

Background: The incidence of major trauma in older people is rising. Frailty significantly raises the probability of poor trauma outcomes in older people. The purpose of this thesis is to investigate the predictive value of frailty in major trauma as well as to determine the need for developing a frailty evaluation instrument specifically for older individuals who have had major trauma.

Methods: An overview and review of relevant literature concerning frailty and major trauma in older people was conducted. A systematic review and meta-analysis were undertaken to investigate the frailty concept's influence on the outcomes of older trauma patients. A trauma frailty index was created as a tool for diagnosing frailty in older people who had experienced trauma using routinely collected data. The index was verified against adverse outcomes using two samples in and out of sample data sets to prove its relevance and validity in a larger population of trauma patients. Two further validations were conducted to determine the index's ideal threshold for the development of adverse outcomes.

Results: Frailty status in older persons with major trauma was linked to higher in-patient mortality, duration of hospital stay, discharge location, and comorbidities. Frailty was consistently a better predictor of death and unfavourable discharge location than age or injury severity. Frailty detection methods do not seem to be suitable for use with traumatically injured older people. The Nottingham Trauma Frailty Index (NTFI) has identified five variables that strongly predict frailty (regression coefficient B = 6.383 (95% confidence interval 5.03 to 7.74), $p < 0.001$): age, Abbreviated Mental Test score, admission haemoglobin concentration (g/l), pre-admission mobility (requiring assistance

or not), and mechanism of injury (falls from standing height). During validation, there was a strong agreement between the NTFI and the CFS (mean difference 0.02), with no obvious systematic bias. In two validations against clinical outcomes, growing NTFI was related to adverse outcomes that included in-hospital complications, adverse discharge destinations, the increase in dependency level, and length of stay. NTFI ≥ 4.345 was a significant predictive threshold for adverse outcomes including discharge to rehabilitation unit, discharge to nursing care home, discharge to residential care home, mortality, increase in dependency level, and in-hospital complications.

Conclusion: The frailty state of older trauma patients is a better predictor of poor outcomes than their age or injury severity score. The NTFI has shown a noteworthy performance in predicting clinical outcomes in both in-sample and out-of-sample data sets. The NTFI is a practical tool that clinicians and researchers may use to direct patient care and analyse quality improvement and research initiatives. It utilises readily and regularly recorded physiological and functional characteristics.

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Publications

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- Alqarni AG, Gladman JR, Obasi AA, Ollivere B. Does frailty status predict outcome in major trauma in older people? A systematic review and meta-analysis. Age and ageing. 2023 May 1;52(5):afad073.

- Alqarni AG, Nightingale J, Norrish A, Gladman JR, Ollivere B. Development and validation of a trauma frailty scale in severely injured patients: the Nottingham Trauma Frailty Index. Bone and joint journal. 2024 Apr 1;106(4):412-8.

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- Alqarni AG, Ollivere B, Gladman J. The prognostic value of frailty in major trauma in older people. June 2022. Centre for Doctoral Training in Rehabilitation and Healthcare Research Seminar Series for 2022.

- Alqarni AG, Ollivere B, Gladman J. The prognostic value of frailty in major trauma in older people. Medicine Postgraduate Impact Forum 2022.

- Alqarni AG, Ollivere B, Gladman J. The prognostic value of frailty in major trauma in older people. March 2023. Sue Watson PGR Oral Presentation Event 2023.

Others:

- The Nottingham Trauma Frailty Index (NTFI) Calculator: https://app.calconic.com/public/calculator/636a8ea33971690029f3b0d9?layouts=true

Chapter 1: Frailty and Major Trauma in Older People

1.1 Introduction

The purpose of this PhD thesis is to evaluate the impact of frailty on major traumas in older persons. This initial chapter discusses a general overview of the literature to learn about the intended investigation. The chapter will explore the epidemiology of older people with major trauma injuries, as well as the concept of frailty and its impact on major trauma systems and outcomes. Based on observations of the literature, this general review will cover the essential major trauma topics concerning the older population. As this thesis seeks to answer the specific research question, “What is the prognostic value of frailty in majorly injured older patients?”, this chapter may not cover all elements that influence outcomes following major trauma in older people with frailty, and this will require further research.

1.2 Epidemiology

1.2.1 Older population

The number of people over the age of 65 is steadily increasing. By 2030, one in every five people in the United Kingdom (UK) will be over the age of 65 (1). According to the same projection, by 2041 the older population will account for more than 25% of the UK population. The fastest-growing age group is of those aged 85 and above, which is expected to double to 3.2 million by mid-2041 and triple by 2066 (2). This indicates that

the overall shift in population will require changes in socioeconomic resources and in health-care systems and structures.

The rise in the number of older people will prove a challenge to health-care systems worldwide because this age group uses health-care services more often than younger individuals (3). This is owing to the fact that older individuals face various challenges than younger ones. These difficulties are mostly caused by frailty and are distinguished by system failures and the existence of "geriatric conditions" such as falls, incontinence, and confusion (4). This implies that as the population ages, the burden on hospitals and primary care settings is likely to increase dramatically. As a result, the healthcare system will need to adapt to meet increased demand for care for older people. In the United Kingdom, for example, a systematic study found that there are only 1,350 geriatric medicine consultants compared to 3,996 paediatric medicine consultants (5, 6). The shortage of geriatric experts will inevitably raise the burden on geriatric care, perhaps resulting in an inadequate provision of care to older people. In order to bridge this disparity, healthcare organisations must structure their hospitals and personnel to provide a superior quality of care that is suitable for the needs of older people. However, geriatric care has improved significantly since the establishment of the British Geriatrics Society (1947), including comprehensive geriatric assessment, which improves the hospital environment and the time required for intervention and diagnostic response (7).

1.2.1.1 Terms used to describe older adults

The age considered for an individual to be older is generally above 65 years; this age, however, might vary depending on life expectancy, cultural norms, and health-care

systems (8). In light of this, WHO also considers it in its global and policy reports. In less developed countries, the age of 60 and over is frequently used to designate older people, however in more developed countries, the age of 65 and above is commonly used because it is also connected with retirement age. WHO often uses 60 or 65 when examining the older individuals, even though it recognises that age categories must be context-specific and flexible.

Certain terminology commonly employed to define older populations has been deemed inappropriate for academic research and other contexts due to its association with ageist biases that potentially foster prejudice, discrimination, and negative perceptions of older people (9). Some of these phrases describe older people as different, such as the “elderly”, or young as good, such as using “seniors”, or others with negative connotations, such as the “aged or ageing dependents” (9, 10). It is obvious that assumptions and judgements can be encoded implicitly or explicitly in the language used to describe older persons. In order to ensure that older people are treated with respect and equity, it is crucial that clinical practice employ terminology that specifically addresses language bias. Consequently, this thesis utilises broad and considerate terminology, including "older people," "older adults," and "older persons," to denote this demographic group.

1.2.2 Ageing process

Several definitions related to ageing have been operationalised to address ageing. The simplest definition of ageing is the accumulation of a variety of negative changes in cells and tissues as people get older (8, 11). This results in a gradual loss of physical and mental function, increased disease risk and, eventually, death. However, these changes

are neither linear nor consistent, and they are only loosely related to a person's chronological age (8).

Definitions of ageing are divided into two types: chronological age and biological age. Chronological age is the actual number of years since birth (12). The second theory is the biological age, also known as physiological age, which refers to the individual's development and the functioning of internal organs at cellular and organ levels, taking into account the influence of genetic, environmental, and lifestyle factors (8). Although both definitions seem accurate, healthcare systems should base their understanding of this on need and ability to benefit rather than age, as age is not a reliable indicator of either need or ability to benefit.

Ageing is a relatively multi-dimensional concept that represents functional, cognitive, and social status (13). Age varies from ageing, as chronological age is only one parameter to assess for ageing process (14). The mixed usage of the terms age and ageing in clinical settings and of their definitions, may lead to a major impact on trauma care for older people. The definition to be utilised by researchers and whether ageing is chronological or an accumulation of dimensions, must first be determined. Frailty seems to be a reliable indicator of biological ageing and, thus, more suitable than age alone for determining the need or capacity to benefit. Additional investigation is required to determine the accuracy of these classifications in the context of trauma treatment and its correlation to frailty. However, chronological age seems to be a reasonably simple criterion to assess rather than a reliable predictor of growth, and it provides objective standards with the numerical features needed for statistical tests.

1.3 The concept of frailty

Frailty is a relatively new concept that describes the health status of older people. It is a clinically identifiable condition of heightened vulnerability caused by ageing-related declines in reserve and function across several physiologic systems, compromising the capacity to deal with ordinary or acute stressors (15). Frailty, according to the British Geriatrics Society, is a separate health condition associated with the ageing process in which numerous bodily systems progressively lose their built-in reserves (16). There are various frailty operational definitions, but Fried et al. “frailty phenotype” and Rockwood “the cumulative deficit frailty index” are currently the two most reliable evaluation models for use by clinicians and researchers (17). Fried et al. and Rockwood were operationalised two prevalent frailty models: Fried et al. utilised a phenotypic model, while Rookwood utilised a syndromic concept.

Fried et al. operationalised frailty as satisfying three out of five phenotypic criteria suggesting reduced energetics: poor grip strength, low energy, reduced waking speed, poor physical activity, and/or weight loss (18). Fried et al.’s clinical phenotype has been adapted in the literature in a variety of ways, most of which have been prompted by measurements in individual research rather than conceptual differences. Fried’s frailty phenotype has been utilised in significant research to test its utility as a measure for classifying older adults’ vulnerability. When used on the oldest old people, it is rather unreliable since the condition might be related to functional dimensions or intrinsic conditions (19).

Alternatively, frailty has been defined by Rockwood as a risk index known as the "frailty index" (FI). It is determined by counting the number of deficits that accumulate over time, such as disability, diseases, physical and cognitive impairments, and geriatric syndromes like urinary incontinence, delirium, and falls. (20). It has been stated that FI is a more sensitive predictor of poor health outcomes than Fried's frailty phenotype because of its finer-graded risk scale and its robustness in clinical inferences with respect to the quantity and actual composition of the FI components (15). Although both approaches are effective and overlap, the Rockwood method is more often used in clinical settings for diagnosing frailty in older people owing to its straightforward implementation. Nevertheless, although these approaches are effective in identifying older patients who are frail, they may not be practical or have limitations when used for older adults who are admitted to the emergency department (ED) (21). For instance, evaluating the gait speed, which is not feasible in this particular situation, along with other components of the phenotype that may be affected by the incident condition rather than any underlying frailty. Additional research in emergency and major trauma care is required to assess and establish the impact of frailty and its correlation with outcomes. Because most registries are focused on age and are unfamiliar with frailty, utilising it as a predictor of outcome may result in significant improvements in emergency and trauma care. Some healthcare organisations have included specialised care strategies and other factors in the care pathway, which has resulted in better outcomes. For instance, the implementation of the best practice tariff (BPT) for hip fractures for patients aged 60 and up aimed to provide guidance on the operational aspects of providing the best practice tariff for fragility hip fracture treatment, such as timely geriatrician and geriatric assessment. The use of BPT

has led to a notable reduction in mortality compared to those who did not achieve BPT (6% vs. 21%), as well as an improvement in one-year survival rates (28.6% vs. 42.0%) (22). As a result, the inclusion of frailty in the diagnostic process may provide better outcomes and a shorter time from admission to intervention for older people.

1.3.1 Frailty assessment instruments

Many frailty assessment tools have been developed in recent years to be used in clinical or public contexts, based on the Rockwood and Fried frameworks. A systematic review of frailty assessments identified 67 frailty measures for use in various clinical settings (23), with some developed for general frailty screening at the community level and others specialised for clinical use or particular populations. The range of instruments used to assess frailty stems from the fact that frailty cannot be evaluated using a single standard measure that can be used across many healthcare settings. Testing predictions against observable factors in various settings led to the development of some of these tools. For example, the electronic frailty index (eFI) uses current electronic health record data to identify and assess frailty. The technique adopted is a cumulative deficit frailty paradigm, which defines frailty as the accumulation of deficits, which might include clinical signs, symptoms, illnesses, or disability (24). The eFI was recently improved to be usable in trauma settings by using the risk of poor outcomes to identify and enhance the identification of people at risk of adverse outcomes during hospital admission, resulting in the trauma-specific frailty index (TSFI). TSFI was created by selecting 15 factors from frailty index (50-FI) that were linked with unfavourable outcomes, such as comorbidities, functional status, nutritional status, cognition, and emotional state, with 11 of the variables

self-reported by patients (25). A similar procedure was utilised for the geriatric trauma-specific frailty index (GTFI), although it was developed differently, employing diagnostic codes from the International Classification of Diseases (ICD-10) related to prognostic outcomes (26). However, the Clinical Frailty Scale (CFS) is one of the most widely used measures in all older people admitted to the hospital, including trauma, and is estimated after a thorough history and examination, and validated with a collateral history where necessary (27). The CFS score ranges from 1 (very fit) to 9 (terminally ill) (see Figure1-1), which is kind of mix of aspects of the phenotype with lower values reflecting features of the phenotypic and higher grades reflecting the severity of disability. It has also been verified in trauma against adverse outcomes, with substantial associations shown in various trauma contexts. Consequently, several frailty assessment tools have been utilised in trauma, highlighting the complexities of frailty in older trauma adults. Although some of these instruments, such as the GTFI and TSFI, were designed for trauma, this does not guarantee their practicality and usefulness in trauma settings where time, patients, and training are critical. As a result, the development of frailty instruments is a critical and ongoing process that changes based on the individual challenge being studied, and trauma is an especially challenging setting for older adults.

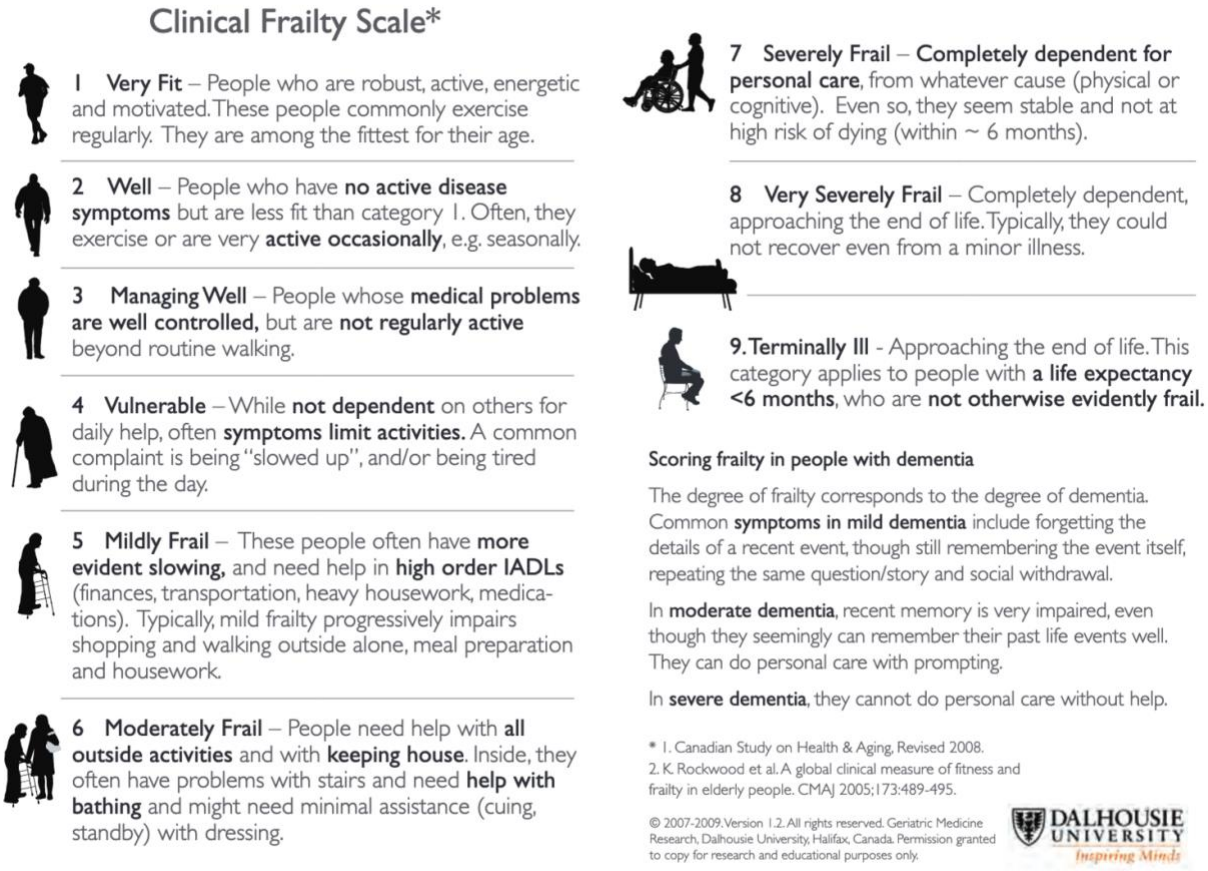


Figure 1- 1: The Clinical Frailty Scale

1.4 Major trauma for older people

Trauma care has become a global issue and a major cause of morbidity and mortality. Many developed countries are still struggling with trauma, which affects over two million people each year and has significant social and economic effects (28). As previously stated in this chapter, the older population is rapidly growing, indicating that trauma will become more common in this age group. Trauma among older people accounts for 54% of all trauma cases in the UK, with 30% of those suffering from major trauma (29).

Major trauma is defined as a life-threatening injury or combination of injuries that could cause substantial disability or mortality (30). The Injury Severity Score (ISS) is often used to measure the severity of injuries, with a score of 15 or more being considered major trauma (31). The treatment strategy for patients with major trauma often includes a well-coordinated approach that includes prehospital care and timely transfer to a major trauma centre for immediate care and intervention. Lately, the major trauma category has emerged as a crucial categorization in trauma care for older people, due to its substantial impact and repercussions on older individuals, who are often the highest in this category when compared to younger people. This is because older major trauma patients with the same injury severity distribution will have poorer outcomes than younger individuals (29). Older individuals admitted to a major trauma centre (MTC) for a major trauma event had a mortality rate of 43% after a year, with half of those deaths occurring in the hospital within 30 days (32). As a consequence, despite the implementation of an improved treatment route for major trauma, the outcomes of severe trauma in older people remain poor. This suggests that individuals may be vulnerable due to the severity of their trauma or their pre-trauma status (e.g., frailty).

Age-related factors in older patients may affect the treatment route and have a significant impact on the outcomes following a trauma (29). Most older individuals who are frail will likely see worse outcomes when this is combined with major trauma. As a result, assessing the health condition of older major trauma patients may aid in assessing the likely consequence of the injury. A study found that frailty evaluated during ED triage (using the CFS) is a potentially significant predictor of negative outcomes, and its use in

ED triage may assist in and impact immediate clinical decision-making and service provided (33). Furthermore, evaluating frailty in the ED will aid in the advancement of interventions and diagnoses since older patients are less likely to be referred to specialist care and have longer wait times for both assessment and treatment (29). As a result, including frailty screening in major trauma patients with ISS and other variables may significantly help to reduce negative outcomes in older people.

1.4.1 Mechanism of injury

The mechanism of injury (MOI) concept is used to evaluate the forces involved in trauma and, as a consequence, the degree of wounds, fractures, and internal organ damage that may occur as a result of the injury (34). MOI assists clinicians in determining the severity of an injury and developing a treatment plan, as well as validating clinical results (diagnostics, differential diagnoses, and other therapies), monitoring clinical progress, and identifying preventive measures (35). It can be argued that MOI is an important predictor of the outcome of injury and can be the leading cause of major adverse outcomes.

For older people, MOI is significantly different from that of younger people. Several studies from across the globe have shown that older individuals are likely to be injured in falls and road accidents, and falls from standing height are the most frequent injury mechanism in the older age group (36-38).

Older individuals are vulnerable to falls from standing, resulting in severe complications. Falls in older people are a predictor of frailty, immobility, and acute or chronic health problems (39). Falls reduce function by causing serious injury, activity restrictions, fear of falling, and mobility loss (40). Additionally, they are the leading cause of injuries in older individuals; fractures of the hip, humerus, forearm, and pelvis are common as a consequence of the combined effects of falls and fragile bones (36). Falls in older individuals are a result of compromised homeostatic balance system and indicate the presence of multiple system deficits, including musculoskeletal, neurological, and visual impairments, and are a cardinal "frailty syndrome" (41, 42). Fractures in older individuals are caused by falls, which are often accompanied by osteoporosis, a condition that contributes to frailty (43). It is obvious that frailty plays a significant role in the increasing risk of serious fractures from falls in older people. Therefore, the involvement of frailty tools in the assessment of older people with falls seems to be a useful evaluation tool. A study found that those with a high frailty index FI who have a ground-level falls are likely to suffer numerous fractures and to be admitted to a hospital (44). As a result, detection of frailty in older people who have fallen may help in the prevention of future falls, as well as improving bone health and quality of life for older people.

1.4.2 Patterns of injury

Patterns of injury vary by gender, age, and mechanism of injury MOI (45). In older people, the severe patterns of injury are associated with the common injury mechanism in this age group. Age-related confounders may cause substantial changes in the body and lead to severe injury patterns. Frailty has the potential to impact both the outcome and severity

of trauma. This is due to various factors, such as different mechanisms of injury (MOIs) and the possibility of greater bodily damage in individuals with frailty, such as skin damage, fractures, and bleeding (46, 47). Additionally, frailty may lead to injuries occurring in specific areas of the body that are commonly associated with osteoporosis or result from the failure of reflex protective actions during a fall (48). Older people have a tendency to impact their hips rather than their wrists and often forget to protect their heads during a fall.

Traumatic brain injury (TBI) is the most frequent type of injury in older individuals who have experienced a major trauma, accounting for more than 75% of all major trauma cases (29). TBI is not only more common in older patients but is also the main cause of mortality in individuals aged 65 years and over following trauma (49). The higher prevalence of head injuries among older patients is due to their greater risk of falls. Falls were also identified as the leading cause of TBI in older people (51%), followed by pedestrian-involved motor vehicle accidents (9%) (49).

Thorax injuries are the second most severe pattern of injury in older patients, accounting for about 25% of major trauma patients in the UK (29). Thorax trauma is the leading cause of rib fractures, which raises the risk of pneumonia by 27% and the risk of mortality by almost 20% in individuals over the age of 65 (50). Rib fractures are also likely to occur in frail older adults, since osteoporosis may cause the rib to break into two or more fragments, complicating treatment and prognosis (50).

Pelvic fractures, hip fractures, and spinal injuries are among the other injuries seen more frequently in older people (51-53). Unsurprisingly, older patients have poorer outcomes following these injuries than younger patients, with greater mortality and morbidity and slower recovery (54).

1.4.3 Outcomes after major trauma in older people

Older individuals experience more unfavourable outcomes than younger individuals after experiencing major trauma (32). Research suggests that older adults, specifically those who are 65 years and older, experience a greater likelihood of death after a major trauma compared to younger individuals, even when accounting for the same degree of injury severity (55). The influence of age on trauma outcomes is attributed not only to the immediate consequences of the injury but also to the physiological alterations that occur with ageing, such as reduced physiological reserves and the presence of comorbid conditions (56, 57). These factors can complicate the management and recovery processes. Nevertheless, age alone is an indirect measure of risk as it fails to consider the individual variations in the process of ageing. Certain older individuals exhibit a notable degree of functionality and adaptability, while others undergo substantial decreases in physical ability and heightened susceptibility to stressors. It is important to note that these differences are not solely influenced by chronological age. Frailty, however, is a complex condition that better reflects the range of health statuses among older individuals. It is defined by a reduction in physiological and psychosocial capacities and an increase in clinical vulnerability that cannot be fully explained by one's chronological age (15). Studies in older individuals frequently use the following common

outcomes after major trauma: 30-day mortality, mortality, one-year survival, increased length of hospital stay, institutionalisation, and decreased ADL (38, 58).

One of the essential outcomes is mortality. The in-hospital mortality rate for older individuals with major trauma is 26% in those aged 65-74 and 13% to 39% in those aged 85 and more (38). This suggests that in-hospital mortality may be greater in individuals of advanced age, which might be a significant indicator of frailty in this population. Nevertheless, when considering frailty, the 30-day death rate for frail persons with trauma is 21.4%, while it is 6.9% for non-frail older individuals (59). This suggests the potential effect of frailty on the death rates and outcomes of older individuals who have had acute trauma.

The functional status of older patients after major trauma discharge is the second most important outcome. Patients over the age of 65 who have experienced serious trauma are often transferred to a specialised inpatient rehabilitation unit or a nursing facility. If older patients are frail, the outcomes are likely to be worse. Frailty, for example, was linked to a 43.2% increase in care requirements following major trauma discharge in moderately frail patients (59). It is apparent that even older individuals who have frailty and survive serious injuries seem to have more challenges in terms of independence after being released from the hospital compared to patients who aren't frail. Frailty plays a key role in major trauma and seems to be reliable predictor of unfavourable outcomes in older patients.

1.4.4 Frailty changes following trauma.

Frail older individuals who experience trauma may suffer not just immediate adverse outcomes but also a lasting influence on their quality of life after being discharged. Extended hospitalisation after trauma may result in acute sarcopenia, leading to further muscle mass loss and decreased functional capacity (60, 61). Hospitalisation was linked to muscular wasting, which developed quickly during the first week of admission in critically ill individuals (62). Older individuals with frailty who are released to their homes after trauma may not have a favourable outcome, as they may have difficulty with ADL due to a decline in functional capacity during their hospitalisation. Integrating rehabilitation during hospitalisation immediately was shown to preserve functional capacity (63), despite potential limitations due to the severity of the trauma. Further investigation may be needed to assess the functional alterations and ADL in trauma survivors with frailty outcomes.

The change in cognitive health status is another factor that might affect older individuals with frailty during and after discharge. Frailty and cognitive impairment prior to trauma were identified as important predictors of post-injury outcomes (64). Due to the heightened susceptibility to stressors that frailty can induce, the psychological well-being of frail older people may experience major shifts even in response to minor health concerns, such as initiating a new medication (65). Furthermore, acute delirium is another condition strongly associated with trauma in older people, particularly those with pre-existing conditions such as dementia, who are at a significantly higher risk of developing delirium following trauma due to their already compromised cognitive abilities, and surgical interventions, if necessary, can further increase the risk of delirium (66).

Additionally, as a result of the hospitalisation process, cognitive decline is a risk factor for older individuals who have experienced trauma (67). Frailty poses an important challenge for older people, and cognitive health complications following discharge may be further aggravated by trauma, thus requiring immediate identification and intervention.

It appears that early medical intervention, and inpatient rehabilitation can mitigate the effects of muscle loss and functional decline following an injury. Further investigation is warranted to examine the effects of trauma on muscle alterations in older people with frailty during and after their hospitalisation and discharge.

Consequently, cognitive recovery and post-discharge functional dependency may deteriorate in frail older people who have experienced trauma as a consequence of acute sarcopenia and a decline in cognitive health state that exacerbates frailty. Trauma appears to be a stressor of greater intensity that may necessitate various considerations regarding frailty, cognitive health status, and muscle loss. As a result, trauma in older people with frailty may result in a prolonged post-discharge deterioration in health that necessitates additional care and rehabilitation.

1.4.5 Prehospital role with major trauma in older persons

A critical early step in the management of major trauma is the recognition that a patient has potentially sustained major trauma. Prehospital care providers are the first responders in such situations. Paramedics ‘in the field’ are responsible for approaching an effective triage for all trauma patients.

In the UK, ambulance service follows triage criteria to determine which patients can be transferred to trauma units and which need to be taken directly to (MTC)s. Additionally,

trauma units may move patients with more severe injuries to an MTC, and care is organised differently in each facility. Some trauma receiving hospitals have specialised wards for serious patients, whereas others admit these patients to regular surgical and orthopaedic wards. Therefore, the most crucial element of this chain of treatment is appropriate prehospital triage. Prehospital care may become less efficient as a result of increased workload and requests for non-emergency cases. The implementation of a triage tool in prehospital settings has resulted in a significant reduction in the number of non-emergency cases (68-70). This demonstrates how a triage tool may help paramedics by decreasing their workload and providing care to the needy patient. However, field triage tools that utilise a mix of mechanism of injury, vital signs, and anatomical damage to detect major trauma in the older people are likely to be less sensitive (69). For example, in older patients with particular types of injuries, such as TBI, the major trauma triage tool has shown some unreliable outcomes. This is because a Glasgow Coma Score (GCS) of less than 14 is one of the criteria for transferring trauma patients to MTC, and older patients presenting with severe TBI often have GCS=14, which may lead to misdirection (71). Several studies have found that individuals with isolated severe TBI who are older may have a higher GCS than younger patients, and the use of GCS-based triage tools may need to be adjusted and validated (71-73).

Apart from this, frailty might be the main reason for under-triage in older people following major trauma. The characteristics of frailty play a vital role in decreasing the strength of trauma absorption. It is likely that frail patients will respond differently compared to others. Research in this area is needed to determine the impact of frailty on triaging older people following a major trauma.

1.4.6 Trauma systems

In developed countries, the most essential part of healthcare pathways is having a well-structured trauma system. Evidence from Germany (74), Australia (75) and the United States (76) indicates that trauma care improves and achieves the greatest outcomes when a network of hospitals with MTCs provides care within an area. In the United States, those states with trauma systems had a 9% lower crude mortality rate than states without (77).

In England and Wales, the Trauma Audit and Research Network (TARN) discovered significant variance in the quality of treatment, and comparison investigations revealed that outcomes after trauma did not match international standards (75). As a result, in 2012, trauma care in England was restructured, with ambulances bypassing local hospitals in favour of newly designated MTCs (78). According to a report from TARN, England is split into regions under this system, with one central hospital (MTCs) in each area providing specialised treatment for the most seriously injured patients (79). Each MTC is accompanied by smaller trauma hospitals called "trauma units" that can handle less severely injured patients. Each area typically has a single MTC with several trauma units. Following the establishment of major trauma networks in England, some important improvements in trauma care have occurred. To demonstrate, a major change implemented during the trauma system reorganisation was a substantial increase (from 29% to 63%) in a consultant presence as trauma team leader (78). Major trauma networks were also linked to a substantial 19% improvement in the odds of survival for trauma patients who arrived at the hospital (78).

It is obvious that the establishment of large trauma networks has resulted in significant advances, particularly in the UK. Furthermore, many findings were discovered after using the major trauma network in the United Kingdom. For example, there was a considerable increase in the number of older patients aged 65 and above who were referred to an MTC after falling less than two meters (78). Trauma researchers have recognised the necessity of systematic approaches to major trauma in older patients to reduce poor outcomes in this age group.

1.5 Conclusion

This chapter incorporates current findings regarding trauma and ageing to highlight some of the most significant elements of this topic. The relationship between major trauma and epidemiology in older trauma patients has raised some important issues that need to be addressed. It appears that the effects of major trauma are significantly influenced by patient characteristics, injury-related factors, physiological conditions, and the MOI. Apart from this, older patients continue to have poorer outcomes than younger patients who suffer from major trauma. Therefore, monitoring the functionality of older people before major trauma seems to be the key factor in outcomes, which need to be frequently evaluated in this age group.

In severely injured older patients, frailty is likely to produce negative consequences. To prevent over- or under-triage, older people's diagnoses must be carefully considered. Additionally, health care providers must be mindful of the significance of major trauma in older patients in terms of the severity of trauma and outcomes.

1.5.1 The need for a systematic review

The consequences of frailty on outcomes in older trauma patients need more investigation and evaluation. Whilst there are primary reports, there are no systematic reviews or evidence synthesis published on the subject. The initial step of this study was to conduct a scoping review to look at existing research and definitions of frailty and major trauma in older persons. A comprehensive systematic review is necessary to uncover the frailty and associated characteristics that influence outcome in older major trauma patients. The results of this systematic review will be compared to those of other persons in the same age group who do not have frailty in order to investigate the impact of frailty. Identifying frailty factors will aid in determining the elements impacting major trauma in older persons, as well as highlighting the aspects that lead to poor outcomes in older people with frailty after trauma. A systematic review is therefore necessary to synthesise and analyse the available research, as well as to assess the degree of diversity in the literature on the predictive usefulness of frailty in older people who have experienced trauma.

1.6 Aims and objectives of the thesis

Aims

1. To determine the relationship between frailty and major trauma in relation to clinical outcomes in older people.
2. To develop a validated major trauma frailty scale that can enhance the assessment of frailty in major trauma in older people.
3. To establish if there is an association between frailty and outcomes after major trauma in older persons.

Objectives

1. To examine the relationship between frailty and major trauma outcomes in older people and ascertain whether frailty is a better indicator of these outcomes than age.

2. To create a comprehensive, clinically applicable prediction model for frailty in older trauma patients by investigating the significance of various factors using routinely collected data and evaluating the independent contributions of demographic, patient-related, treatment-related, and injury-related variables.

3. To evaluate and validate the developed trauma frailty scale by investigating its link with clinical outcomes and discharge destinations, and its impact on various outcomes, including validating its relevance and validity in a broader trauma patient population using out-of-sample data.

4. To validate the diagnostic performance of the developed trauma frailty scale by examining its capacity to predict adverse outcomes, comparing its performance across several outcomes in different data sets, and identifying and validating the optimal threshold for predicting adverse outcomes.

Chapter 2: Does Frailty Status Predict Outcome in Major Trauma in Older People: a Systematic Review and Meta-analysis

2.1 Introduction

In older individuals, the outcomes of major trauma are worse than in younger people (80). There are two possible reasons for this; older individuals may suffer more severe injuries than younger people, resulting in poorer outcomes, or they may have worse outcomes than younger people for the same severity of injury because of age-related vulnerability. Both may be true causes. Prior research reveals that older individuals, aged 65 and above, are more prone than younger people to receive major injuries (AIS ≥ 3) (81). In the United Kingdom, a Trauma Audit and Research Network (TARN) study similarly showed that persons aged 65 and older are the more critically injured and have a higher death risk after trauma with ISS ≥ 15 than younger people (29). In addition, it was discovered that after blunt traumas of comparable severity, individuals aged 65 and older experienced more complex outcomes and diminished physical functioning than younger individuals (47% vs. 30%), indicating increased vulnerability at age 65 and older (56). These findings demonstrate the importance of including vulnerability assessment in older trauma patients to augment the prognostic value of injury severity scores with the frailty of the patient.

Frailty is a relatively recent term that describes an age-related vulnerability state; it represents the loss of homeostatic reserve as a result of the impacts of the ageing

process and the influence that age-related illness has on cell-, organ- and system functioning (15, 18, 20). The concept of frailty is similar to, but distinct from, disability and co-morbidity. There are two theoretical frameworks used to define frailty. Fried et al. defined frailty as the presence of at least three of five physiological abnormalities (weight loss, exhaustion, low physical activity, sluggishness, and weakness) (18). Rockwood defined frailty as the cumulative consequence of multiple functional impairments (20); this model has been utilised to develop "frailty indices" in which an individual's risk of frailty is proportional to the proportion of potential impairments they exhibit. Both operational models sought to differentiate between frail and robust groups of older individuals and provided a more accurate indication of the risks associated with age than age alone. However, Fried's tool involves knowledge of prior gait speed and hand-grip measurements, making it inappropriate for use in acute illnesses. Accordingly, several frailty detection tools for use in acute care that do not require such prior physiological measurement have been created.

Given the association between frailty and adverse outcome in other conditions (82-84), frailty may explain why outcomes for the same severity of injury are worse in older people than in younger individuals, and may even be a better predictor of adverse outcome than age. If so, clinicians could use frailty to make more accurate predictions of outcomes and thus improve the personalisation of an individual's care. Frailty would also be a better stratification variable than age in research and a better variable to adjust for case mix in quality improvement work.

This systematic review aimed to determine the extent to which frailty is associated with injury severity and injury outcomes, and whether it is a superior predictor than age. A

version of this systematic review and meta-analysis was published (Abdullah G Alqarni, John R F Gladman, Akanu A Obasi, Benjamin Ollivere, Does frailty status predict outcome in major trauma in older people? A systematic review and meta-analysis, *Age and Ageing*, Volume 52, Issue 5, May 2023) (85). This chapter offers a detailed description of the systematic review and meta-analysis that were conducted.

2.1.1 Objectives and Outcomes

The primary question was:

- What are the relationships between frailty and outcome of trauma in older people?

The secondary question was:

- Is frailty a better predictor of the outcome of trauma than age in older people?

Primary outcomes:

- Mortality
- Institutionalisation or length of stay (LOS)
- Independence in activities of daily living
- In-hospital complications
- Discharge destinations

Secondary outcomes:

- Mental health
- Cognition
- Delirium
- Depression and anxiety

2.2 Methods

2.2.1 Protocol and Registration

The protocol was submitted to the International Prospective Register of Ongoing Systematic Reviews (PROSPERO 2021 CRD42021240271) (86). The protocol was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA-P) (87). The systematic review protocol was also published in the East Midlands Research into Ageing Network (EMRAN) discussion paper series (88). This systematic review followed the format of the PRISMA 2020 checklist to cover the essential components of a systematic review structure (89).

2.2.2 Eligibility Criteria

This systematic review included cohort research studies since 2010, in the English language, in older patients (60 years of age and older), reporting the associations between frailty and the incidence and outcomes of trauma. Participants in eligible studies had a mean or median Injury Severity Score (ISS) of ≥9, Abbreviated Injury Scale (AIS) >3, or other trauma measures that classified them as severe. Eligible studies used a recognised measure of frailty and reported results on at least one of our outcomes of interest: mortality, length of stay (LOS), in-hospital complications, discharge destination, mental health complications such as depression, and delirium.

The research question determined the systematic review's area, search strategy and the formulation of inclusion and exclusion criteria (90). As this was a prognostic systemic review, the research questions were formulated using the Population, Exposure and

Outcome (PEO) method (91). Therefore, the following PEO represents the outline of this systematic review in terms of searching, eligibility criteria and objectives (Table 2-1).

Population:	Older adults aged 60 and older with major trauma (ISS ≥ 9 or equivalent) - Patients with AIS>3 of one injury - Patients with ISS ≥9
Exposure:	Frailty (directly or indirectly measured) - Direct measures (frailty tools) - Indirect measures means the use of synonyms to determine the frailty concept e.g. (previous disability or receipt of care)
Outcomes:	Primary and secondary outcomes - Mortality, institutionalisation, disability and activities of daily living (ADL), and other secondary outcomes.

Table 2- 1: PEO table to determine eligibility of research question

Studies that specifically focused on major trauma in older people without taking frailty into account were excluded. In addition, studies that did not contain ISS ≥ 9 or equivalent measurements were excluded.

2.2.3 Information Sources

A systematic review of the literature was carried out using the following bibliographic databases: Ovid MEDLINE, PubMed, Ovid Embase and CINAHL (Table 2-2). Citations from relevant research were also sourced using Google Scholar and Web of Science. Finally, the included databases were reviewed by an experienced subject librarian (DG) in order to conduct a thorough search in all relevant databases.

Database	Interface/Platform	Last Search Date
Ovid MEDLINE	Ovid	01 January 2023
PubMed	PubMed	01 January 2023
Ovid Embase	Ovid	01 January 2023
CINAHL	EBSCOhost	01 January 2023
Web of Science	Web of Science	01 January 2023

Table 2- 2: Databases Searched with Interfaces and Search Dates

2.2.4 Search Strategy

The search utilised three concepts: frailty, trauma and outcome. Keywords were employed in both singular and plural versions. Differences in spelling dialect between the United States (US) and the United Kingdom (UK) were considered by searching particular terms with ‘z’ instead of ‘s’, such as ‘institutionalization’ and ‘institutionalisation’. The search technique outlined in the tables below was developed with the experienced librarian (DG).

A comprehensive database search was conducted using the search format of each database. Differences in search terms for database subheadings were investigated, to identify subject terms for each database. Using the subheadings and keywords associated with the concepts, databases were then searched between 1 January 2010 and 1 January 2023 using the Mendeley reference software to organise selected citations (92, 93). This date range was selected to guarantee that it is pertinent to current practices in the recognition of major trauma and the assessment of frailty, as it is anticipated that substantial progress and the integration of frailty considerations into trauma care will have occurred after 2010. The two tables below illustrate the distinctions considered while

searching in Ovid Medline and PubMed in terms of search phrases and subheadings (see Tables 2-3 and 2.4) (92). Embase and CINAHL databases had the same restricted vocabulary as PubMed, but it is referred to as Emtree rather than MeSh. As a result, Tables 2-3 and 2-4 shows the overall search terms and concepts in all chosen databases, whereas Table 2.5 shows the overall search strategy.

	Concept 1	Concept 2	Concept 3
Key concepts	**Frailty**	**Trauma**	**Outcome**
Controlled vocabulary terms / Subject terms	- Frail elderly/ - Frailty/ - Geriatric Assessment/	- Trauma Severity Indices/ - Trauma Nursing/ - Trauma Centers/ - Multiple Trauma/ - Injury Severity Score/	- Activities of Daily Living/ - Mortality/ - Hospital Mortality/ - Disability Evaluation/ - Disabled Persons/ - institutionalization/ - Dementia/ - Cognition Disorders/ - Cognitive Disfunction/ - Chronic Disease/ - Multimorbidity/ - Delirium/ - Emergence Delirium/ - Polypharmacy/
Free text terms / natural language terms	- frail* - (Prefrail or Pre frail or Pre-frail). - Prior frail - Receipt of care - Prior disability	- Trauma* - Polytrauma - Injur* - Moderate trauma	- Mortality - Institutionalization - Institutionalisation - Dement* - Cognition - Cognitive - Multimorbidity - Multimorbidities - Morbidity - Morbidities

Table 2- 3: Ovid Medline search terms

	Concept 1	Concept 2	Concept 3
Key concepts	**Frailty**	**Trauma**	**Outcome**
Controlled vocabulary terms / Subject terms	- "Frailty"[MeSH Terms] - "Frail Elderly"[MeSH Terms]	- "Trauma Centers"[MeSH Terms] - "Multiple Trauma"[MeSH Terms] - "Trauma Severity Index"[MeSH Terms] -"injuries"[MeSH Subheading]	- "Activities of Daily Living"[MeSH Terms] - "Mortality"[MeSH Terms] - "Mortality"[MeSH Subheading] - "Hospital Mortality"[MeSH Terms]) - "Institutionalization"[MeSH Terms] - "Disabled Persons"[MeSH Terms] - "Disability Evaluation"[MeSH Terms] - "Cognition Disorders"[MeSH Terms] - "Cognition"[MeSH Terms] - "Chronic Disease"[MeSH Terms] - "Delirium"[MeSH Terms] - "Polypharmacy"[MeSH Terms]
Free text terms / natural language terms	- frail* - (Prefrail or Pre frail or Pre-frail). - Prior frail - Receipt of care - Prior disability	- Trauma* - Polytrauma - Injur* - Moderate trauma	- Mortality - Institutionalization - Institutionalisation - Cognition - Cognitive - Multimorbidity - Multimorbidities - Morbidity - Morbidities

Table 2- 4: PubMed Database search terms

Database	Search date	Results	Search terms
Ovid MEDLINE	01 January 2023	1419	1. frail*.ti,ab. 2. exp Frail Elderly/ or exp Frailty/ or Geriatric Assessment/ 3. (prefrail or pre frail or pre-frail).ti,ab. 4. Debility.ti,ab. 5. “Prior disability”.ti,ab. 6. 1 or 2 or 3 or 4 or 5 7. Trauma Severity Indices/ 8. Trauma*.ti. 9. Polytrauma.ti,ab. 10. “Major trauma”.ti,ab 11. “Moderate trauma”.ti,ab 12. Trauma Centers/ 13. exp Multiple Trauma/ 14. Injury Severity Score/ 15. Injur*.ti,ab. 16. “Wounds and Injuries”.ti,ab. 17. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18. Outcome*.ti,ab. 19. exp "Activities of Daily Living"/ 20. Hospital Mortality/ 21. Mortality/ 22. Mortality.ti,ab. 23. Disability Evaluation/ or Disabled Persons/ 24. (institutionalisation or institutionalization).ti,ab. 25. Institutionalization/ 26. Cognition Disorders/ or Cognitive Dysfunction/ 27. (Cognition or Cognitive).ti,ab. 28. Chronic Disease/ or Multimorbidity/ 29. Emergence Delirium/ or Delirium/ 30. (Multimorbidity or Multiple morbidities).ti,ab. 31. Polypharmacy/ 32. (morbidity or morbidities).ti,ab. 33. or/17-31 34. 6 and 16 and 32
CINAHL	01 January 2023	156	S28: S9 AND S14 AND S27 S27: S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 S26 (MH "Polypharmacy") S25 (MH "Morbidity") OR "morbidity" S24 "multiple morbidity" S23 "multimorbidity" S22 (MH "Chronic Disease") OR "chronic disease" S21 "cognition or cognitive" S20 "cognitive dysfunction" S19 (MH "Cognition Disorders") OR "cognition disorders" S18 (MH "Institutionalization") OR "institutionalisation" S17 (MH "Mortality") OR "mortality" OR (MH "Hospital Mortality") S16 (MH "Activities of Daily Living") OR "activities of daily living or adl" S15 "outcome" S14: S10 OR S11 OR S12 OR S13 S13 "injury severity score" S12 "moderate trauma" OR "Major trauma" S11 "polytrauma" S10 (MH "Trauma") OR "trauma" OR (MH "Severity of Injury") OR (MH "Trauma Severity Indices") OR (MH "Multiple Trauma") OR (MH "Trauma Centers") S9: S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 S8 "prior disability" S7 "debility" S6 "receipt of care"

			S5 "prior frail" S4 "prior frail" S3 "pre-frail" S2 (MH "Frail Elderly") OR "frail elderly" S1 "frailty" OR (MH "Frailty Syndrome"
PubMed	01 January 2023	1746	(("frailty"[MeSH Terms] OR "frail elderly"[MeSH Terms] OR "frail elderly"[MeSH Terms] OR "frail*"[Title/Abstract] OR "Prefrail"[Title/Abstract] OR "Pre-frail"[Title/Abstract] OR "Pre-frail"[Title/Abstract] OR "Debility"[Title/Abstract] OR "prior disability"[Title/Abstract]) AND ("trauma severity indices"[MeSH Terms] OR "Trauma"[Title] OR "Polytrauma"[Title/Abstract] OR "injur*"[Title/Abstract] OR "Moderate trauma"[Title/Abstract] OR "Major trauma"[Title/Abstract] OR "trauma centers"[MeSH Terms] OR "multiple trauma"[MeSH Terms] OR "wounds and injuries"[MeSH Terms]) AND ("activities of daily living"[MeSH Terms] OR "Mortality"[MeSH Terms] OR "hospital mortality"[MeSH Terms] OR "Institutionalization"[MeSH Terms] OR "disabled persons"[MeSH Terms] OR "disability evaluation"[MeSH Terms] OR "cognition disorders"[MeSH Terms] OR "cognition"[MeSH Terms] OR "chronic disease"[MeSH Terms] OR "Morbidity"[MeSH Terms] OR "delirium"[MeSH Terms] OR "polypharmacy"[MeSH Terms] OR "outcome*"[Title/Abstract] OR "Mortality"[Title/Abstract] OR "Institutionalization"[Title/Abstract] OR "Institutionalisation"[Title/Abstract] OR "cognition"[Title/Abstract] OR "cognitive"[Title/Abstract] OR "multimorbidit*"[Title/Abstract] OR "multiple morbidities"[Title/Abstract] OR "Morbidity"[Title/Abstract]))
Ovid Embase	01 January 2023	2206	1. frail*.ti,ab. 2. exp Frail Elderly/ or exp Frailty/ or Geriatric Assessment/ 3. (prefrail or pre frail or pre-frail).ti,ab. 4. Debility.ti,ab. 5. “Prior disability”.ti,ab. 6. 1 or 2 or 3 or 4 or 5 7. Trauma Severity Indices/ 8. Trauma*.ti. 9. Polytrauma.ti,ab. 10. “Major trauma”.ti,ab 11. “Moderate trauma”.ti,ab 12. Trauma Centers/ 13. exp Multiple Trauma/ 14. Injury Severity Score/ 15. Injur*.ti,ab. 16. “Wounds and Injuries”.ti,ab. 17. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18. Outcome*.ti,ab. 19. exp "Activities of Daily Living"/ 20. Hospital Mortality/ 21. Mortality/ 22. Mortality.ti,ab. 23. Disability Evaluation/ or Disabled Persons/ 24. (institutionalisation or institutionalization).ti,ab. 25. Institutionalization/ 26. Cognition Disorders/ or Cognitive Dysfunction/ 27. (Cognition or Cognitive).ti,ab. 28. Chronic Disease/ or Multimorbidity/ 29. Emergence Delirium/ or Delirium/ 30. (Multimorbidity or Multiple morbidities).ti,ab. 31. Polypharmacy/ 32. (morbidity or morbidities).ti,ab. 33. or/17-32 34. 6 and 17 and 33

Table 2- 5: Search strategy

2.2.5 Selection Process

Two different searches were performed by two independent reviewers (AA and AO) in all databases. For screening, all identified studies were loaded into Mendeley reference software (93). The two independent reviewers eliminated duplicates and evaluated the list of references (titles and abstracts) extracted from the search. The inclusion of articles was determined by comparing full-text articles to the eligibility criteria. Differences in the number of full-text studies found were retrieved and addressed among reviewers. During the eligibility criteria phase, identified studies were restricted to those written in English and published after 2010. Through discussion with a third reviewer (BO), inconsistencies were resolved at both phases. The reference lists of full text chosen studies were manually searched to locate papers that met the eligibility criteria but were missed by the computerised searches.

2.2.6 Data Collection Processes

The data from the selected studies was extracted by two independent reviewers using the Joanna Briggs Institute (JBI) data extraction format (94).

The following elements were collected from each study:

1- Authors, year of publication and country
2- Aspects such as design setting and intervention
3- The total number of participants and their ages
4- A tool for determining the severity of an injury
5- A tool for determining frailty, or an indication of frailty
6- The relationship between baseline frailty and severity of the injury
7- The clinical outcomes and how they were measured

8- The relationship between baseline frailty and clinical outcomes when injury severity was considered or matched.
9- The relationship between age and the severity of an injury.
10- The relationship between age and clinical outcomes when injury severity was considered or matched.

Discrepancies between the two reviewers were resolved through discussion and a third independent reviewer (BO) to produce a single data set (see Appendix: 3).

2.2.7 Data items

Data extracted from selected papers included paper summary descriptors (design, setting, and sample size), frailty measures, and outcomes of interest (mortality, length of stay (LOS), in-hospital complications, discharge destinations, mental health complications (e.g., depression), delirium, and independence in activities of daily living).

The methods and results of regression analyses examining the relationship between frailty, injury severity, and age with one or more of outcomes of interest were extracted from papers.

2.2.8 Study Risk of Bias Assessment

As the Joanna Briggs Institute (JBI) software was used for this systematic review, the two independent reviewers used the JBI risk assessment to critically review selected papers (95). The risk of bias was ranked as high when the study received up to 49% of "yes" scores, moderate when the study received 50% to 69% of "yes" scores, and low when the study received more than 70% of "yes" scores, according to JBI risk

assessment. The appendices included a copy of the JBI critical appraisal checklists for cohort study design (see Appendix: 1).

2.2.9 Measures of effect in analyses

In the analyses, the following effects were measured: in-hospital mortality, mean length of hospital stay (LOS), discharge to home or previous address versus other discharge destination, and the presence or absence of in-patient complications.

2.2.10 Synthesis methods

Grouping development was used to visualise the clinical heterogeneity of selected studies, as well as to generate suitable data for meta-analysis and regression synthesis (see Appendix: 2). Other findings were also tabulated to visualise the aggregate outcomes for meta-analysis and non-meta-analysis results. Variations in sample size, variability (heterogeneity) in research methodology and findings (treatment effects), and sensitivity of findings in the systematic review process (study selection and statistical analysis) were taken into account during meta-analysis (96). The χ^2 test and I^2 statistic were used to evaluate the studies' heterogeneity, with p values of 0.05 or I^2 more than 50% indicating substantial heterogeneity.

Meta-analysis was conducted to examine the relationship between frailty status and outcome, using the JBI systematic review software (94). In studies reporting results from more than one measure of frailty, the measure with the strongest relationship to outcome was used in the meta-analyses. The justification for this was that frailty tools, being indirect measures of frailty, may be prone to under-distinguish between frail and

non-frail individuals, and it was reasoned that the tool demonstrating the greatest effect size would be the best measure of frailty (97). In studies that reported results for more than two groups (e.g., frail, pre-frail, and non-frail) or that further subdivided frail groups into moderate and severe categories, the results from the most robust (lowest frailty scores) and the most frail (highest frailty scores) groups were used in the meta-analyses.

In the primary analysis, a fixed effect model was used, as the population is tightly defined and the definitions of frailty and outcomes are similar, it is reasonable to assume that all studies would have a similar effect size (98). To check the consequence of this decision, random effect model analyses were also performed; however, since no significant differences were observed, only the fixed effect result is presented here. Studies with outcomes of zero were not included in the meta-analysis to avoid the need for zero-events correction, as inclusion carries the risk of inflating the overall odds ratio (99).

Instead of estimating means and standard deviations from studies reporting medians and interquartile ranges and including them in the meta-analyses, a summary of studies reporting non-parametric outcomes and zero-events studies was provided, along with a statement about whether they were consistent with the meta-analysis results.

Because fewer than 10 papers were appropriate for inclusion in each meta-analysis, meta-regression and publication bias analyses were not performed (100). The predictive value of age, ISS, and frailty for available outcomes was compared using a

narrative synthesis of study results examining these relationships using multivariate regression analysis.

2.2.10.1 Sensitivity analysis

According to the protocol, sensitivity analysis was planned for the event that in studies employing proxy indictors of frailty rather than frailty tools. However, no such studies were identified.

2.2.11 Reporting bias assessment

The risk of bias for each meta-analysis result was summarised by providing a range of JBI risk of bias assessments (low, medium, and high) for the studies included in each analysis. Because there were fewer than ten studies in each instance, the potential of publication bias was presumed in each analysis.

2.2.12 Certainty assessment

The GRADE ratings (Grading of Recommendations Assessment, Development, and Evaluation) were used to rate the meta-analysis results' level of certainty (high, moderate, low, and very low) (101). This rating takes into account a number of elements that lessen the degree of certainty regarding the impact of frailty on outcomes calculated using meta-analysis, including the precision of the result, the risk of bias in the studies that were included, the consistency of the populations or results across studies, and potential publication bias.

2.3 Results

2.3.1 Search and selection

A total of 6015 studies were identified after a full search. Titles and abstracts of 3489 articles were reviewed after 2526 duplicate articles were removed. Next, 3113 studies were excluded after title and abstracts screenings. The full texts of the remaining 376 articles were then scrutinised for inclusion and exclusion criteria. As a consequence, 12 studies meeting the systematic review eligibility criteria were identified (see Figure 2-1) (102). Table 2-6 displays the characteristics of the included studies, and (Table 2-7) provides data on the synthesised findings of frailty and trauma measures, as well as outcomes.

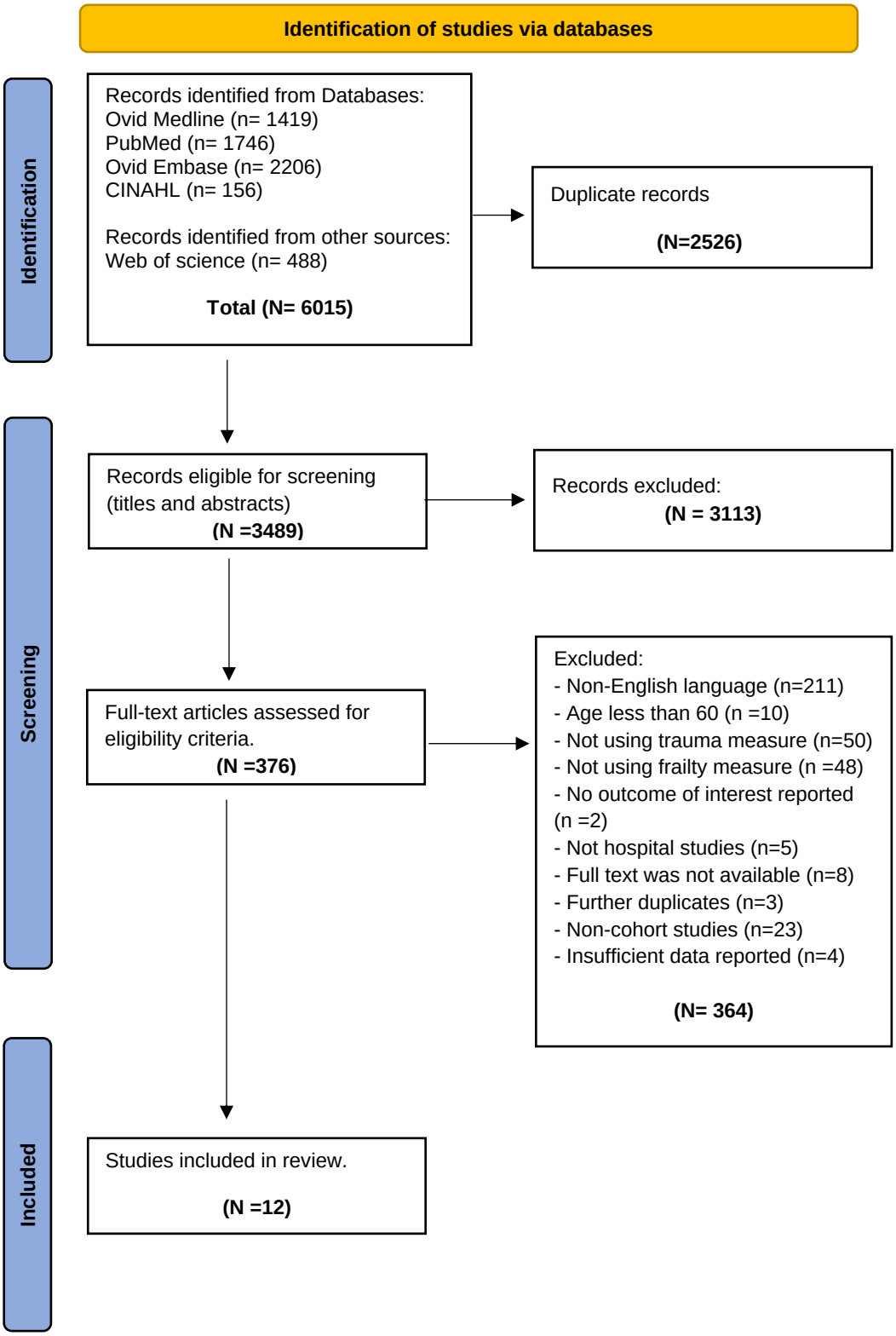


Figure 2- 1: Search and selection result

Reference (authors /year)	Country	Design	Setting	Population	Participants characteristics (sample)	Frailty measures	Clinical outcomes measured
Joseph B, et al. 2016 (103)	USA	Prospective cohort study	Level one trauma centre	Older trauma patients	N= 368 - Age ≥65, mean ± SD 74.79 ± 10.76 - Male 61.4% - Female 38.6%	**Trauma Specific Frailty Index (TSFI,15- items)**	- In-hospital complication - Discharge disposition - In-hospital mortality - Length of stay (LOS) - failure to rescue (FTR)
Cheung A, et al. 2017 (104)	USA	Retrospective cohort study	Level one trauma centre	Older trauma patients	N= 260 - Age ≥65, mean ± SD 76.5 ± 7.8 - Male 52.7% - Female 47.3%	Admission laboratory frailty index (FI-lab, 23-items) and **the Clinical Frailty Scale (CFS, 7-items)**	- Adverse discharge destination (mortality, long term care, chorionic care or home) -In-hospital complications
Pecheva M, et al. 2020 (46)	UK	Retrospective cohort study	Regional major trauma centre	Older trauma patients with ISS>15	N= 802 - Age > 60, mean ± SD 76.3 ± 9.49 - Male 59.7% - Female 40.3%	**modified Frailty Index (mFi, 11- items)**	- Mortality at discharge and at one year - Length of stay (LOS) - Glasgow outcome score on discharge from acute care - Serious medical complications
Joseph B, et al. 2017 (105)	USA	Prospective cohort study	Level one trauma centre	Older trauma patients with at least 1-day hospital admission	N= 350 - Age ≥65, mean ± SD 78 ± 8 - Male 60% - Female 40%	**Trauma Specific Frailty Index (TSFI, 15- items)**	Outcomes were measured at discharge as follows: - In-hospital complications - Discharge disposition - In-hospital mortality - Length of stay (LOS) - Mortality Outcomes at 6-months as follows: - Mortality - Trauma readmission - Recurrent falls - Trauma Specific Frailty Index (TSFI)
Joseph B, et al. 2014 (106)	USA	Prospective cohort study	Level one trauma centre	Geriatric trauma patients	N= 250 - Age ≥65, mean ± SD 77.9 ± 8.1 - Male 69.2% - Female 30.8%	**Frailty Index (FI, 50-items)**	- In-hospital complications - Discharge disposition (home, rehab or SNF) - In-hospital mortality - Length of stay (LOS)
Hamidi M, et al. 2019 (107)	USA	Prospective cohort study	Banner-University medical Centre Tucson	Older trauma patients	N= 341 - Age ≥65, mean ± SD 76 ± 9 - Male 68% - Female 32%	Trauma Specific Frailty Index (TSFI, 15- items), The modified Frailty Index (mFI, 11- items), **Clinical Frailty Scale (CFS, 7-items)** and Fried frailty phenotype (5-items)	- In-hospital complications - SNF disposition - Mortality - 30-day readmission
Jarman H, et al. 2021 (108)	UK	Prospective cohort study	Five major trauma canters	Older major trauma patients	N= 372 - Age ≥65, Median (IQR) 80 (73-86) - Male= 172 (46.2%) - Female= 200 (53.8%)	Clinical Frailty Scale (CFS, 7-items), **Program of Research to Integrate services for the Maintenance of Anatomy 7**	- Identification of frailty - In-hospital mortality - Critical care and hospital length of stay - Discharge to the usual place of residence

						(PRISMA7, 7-items) and Trauma Specific Frailty Index (TSFI, 15- items)	
Rickard F, et al. 2020 (59)	UK	Prospective cohort study	Major trauma centre	Older trauma patients	N= 300 - Age ≥65, Median (IQR) 82(74-88) - Male= 127(42.8%) - Female= 173(57.2%)	**Clinical Frailty Scale (CFS, 9-points)**	- 30-d mortality - Number of major complications - Length of stay (LOS) - Increased care requirement at discharge
Shah SP, et al. 2019 (109)	USA	Prospective cross-sectional study	Level one trauma centre	Older trauma patients	N= 65 - Age ≥65, -Frail group, n= 15, mean ± SD 79.5 ± 7.36, female 47% - Non-frail group, n= 50, mean ± SD 76.8± 8.38, female 50%	**FRAIL scale (5-items) and Clinical Frailty Scale (CFS, 9-points) physicians**/subject-surrogate based	- In-hospital mortality - Length of stay (LOS) - Hospital discharge: • Home health • Home • MORGUE • Transferred to another acute care facility • Skilled Nursing facility (SNF)
Thompson A, et al. 2021 (110)	UK	Retrospective cohort study	Major trauma centre	Older trauma patients	N= 729 - Age ≥65, Median (IQR) 84 (79, 89) - Male= 275(37.7%) - Female= 454(62.3%)	**Clinical Frailty Scale (CFS, (9- points)**	- Mortality during admission - Length of stay (LOS) - Trauma call activation received - Discharge to unusual residence
Herklots M, et al. 2022 (111)	Netherlands	Retrospective cohort study	Level one trauma centre	Older patients with traumatic brain injury	N= 126 - Age ≥60, Median (range) 70(60-94) - Male= 79 (62.7%) - Female= 47 (37.3%)	**Clinical Frailty Scale (CFS, 9 items)**	- Mortality within 24 hours - In- hospital mortality - Glasgow Outcome Scale (GOS) at discharge and after 6 months - In- hospital complications - Length of stay (LOS)
Guiab K, et al. 2022 (112)	USA	Retrospective cohort study	National database study	Older trauma patients	N= 26963 - Age ≥65, Median (IQR) 76(70, 82) - Male= 16588 (61.5%) - Female= 10375 (38.5%)	**The 5 items modified frailty index (mFI-5, 5 items)**	- Mortality - In- hospital complications - Length of stay (LOS)

Bold: the frailty measures were used in meta-analyses.

Table 2- 6: Study and patient characteristics of the included studies

Study	Frailty tools	Frailty criteria and groups	Injury severity score for groups	Mortality	Length of Stay (LOS)	Discharge disposition	Cognition	In-hospital complications
Joseph B, et al. 2016 (103)	Trauma Specific Frailty Index (TSFI).	- Non-frail (TSFI≤0.12) - Pre-frail (TSFI=0.13-0.25) - Frail (TSFI>0.25)	- Non-frail= 9(9-14) - Pre-frail= 11(9-14) - Frail=13(9-19) (Median(IQR))	In-hospital mortality	- Hospital - ICU - Ventilator days	- Home - Rehab - SNiF	X	- UTI - Pneumonia – AKI – DVT – HF - Anaemia
Cheung A, et al. 2017 (104)	Admission laboratory frailty index (FI-lab) and the 7-point clinical frailty scale (CFS)	- Non-frail (CFS= 1-3) - Apparently vulnerable (CFS= 4) - Mildly frail (CFS=5) - Frail (CFS= 6-7)	- Non-frail = 17(13-24) - Apparently vulnerable = 19(14-25) - Mildly frail=17(11-22) - Frail =17 (9-24) (Median(IQR))	Mortality at discharge	X	- Transfer to another acute care hospital - Chronic care facility or long-term care - Home - Rehabilitation with or without support	X	- Number of total complications (0, 1, 2, 3 and +4)
Pecheva M, et al. 2020 (46)	modified Frailty Index (mFi)	- Low (mFI<0.18) - Intermediate (mFI 0.18 - 0.35) - High (mFI>0.36)	- Low, Mean (SD) = 25.2 (8.9). - Intermediate, Mean (SD) = 23.2 (7.26) - High, Mean (SD) = 24.1 (5.77)	- Mortality at discharge - Mortality at one year	- Hospital - ICU	- Rehab - Local hospital - Nursing care - Own home - Long term residential care - Died in hospital - specialist treatment - Home country	X	- No complication - >1 complication – Pneumonia – Unplanned intubation – Ventilator dependency – Cardiac arrest/MI – CVA – Infection treatment – Acute renal failure – Progressive renal failure – Reoperation – Surgical site infection
Joseph B, et al. 2017 (105)	Trauma Specific Frailty Index(TSFI)	- Non-frail (TSFI≤0.12) - Pre-frail (TSFI=0.13-0.27) - Frail (TSFI>0.27)	- Non-frail=10(9-15) - Pre-frail= 10(9-14) - Frail=12(9-19) (Median(IQR))	- In-hospital mortality - 6-month mortality	- Hospital - ICU	- Home - Rehab - SNiF	X	- UTI - Pneumonia – Sepsis – DVT/PE – DIC - Reoperation
Joseph B, et al. 2014 (106)	Frailty Index (FI)	- Non-frail (FI<0.25) - Frail (FI≥0.25)	- Non-frail= 15(9-15) - Frail= 16(9-16) (Median(IQR))	In-hospital mortality	- Hospital - ICU - Ventilator use days	- Home - Rehab - SNiF	X	- UTI - Pneumonia – Sepsis – DVT -PE – DIC - Reoperation
Hamidi M, et al. 2019 (107)	Trauma Specific Frailty Index (TSFI), The modified Frailty Index (mFI), Rockwood Clinical Frailty Scale (RFS) and 5-item Fried's phenotypic model (FS)	- [TSFI]Non-frail (<0.25) - [TSFI] Frail (≥0.25) - [mFI]Non-frail (<0.25) - [mFI]Frail (≥0.25) - [FS]Non-frail (0-2) - [FS]Frail (>2) - [RFS]Non-frail (1-4) - [RFS]Frail (≥5)	- [TSFI]Non-frail=12(10-17) - [TSFI]Frail= 12(9-18) - [mFI]Non-frail=13(9-17) - [mFI]Frail=13(8-18) - [FS]Non-frail=12(8-17) - [FS] Frail=13(9-18) - [RFS]Non-frail=13(8-17) - [RFS] Frail= 14(9-18) (Median(IQR))	In-hospital mortality	- Hospital - ICU	- SNF	Delirium	In-hospital complication number and %
Jarman H, et al. 2021 (108)	Clinical Frailty Scale (CFS), Program of	- [TSFI]Non-frail (≤0.27) - [TSFI]frail (>0.27)	- [TSFI]Non-frail=23(20-29) - [TSFI]frail=17(9-26)	In-hospital mortality	- Critical care stay	Discharge to usual place of residence		

	Research to Integrate services for the Maintenance of Anatomy 7 (PRISMA7) and Trauma Specific Frailty Index (TSFI)	- [PRISMA7] Non-frail (<3) - [PRISMA7] frail (≥3) - [CFS] Non-frail (1-4) - [CFS] frail (≥5)	- [PRISMA7] Non-frail=16(9-22) - [PRISMA7] frail=13(9-20) - [CFS] Non-frail=16(9-22) - [CFS] frail=13(9-22) (Median(IQR))		- Total major trauma centre length of stay		X	X
Rickard F, et al. 2020 (59)	Frailty Score (9-points)	- Non-frail= CFS(1-4) - Mild to moderate-frail=CFS(5-6) - Severe-frail= CFS(7-9)	- Non-frail=16 (9-25) - Mild to moderate-frail= 9 (8-17) - Severe-frail= 1(4-16) (Median(IQR))	30-day mortality	- Major trauma centre length of stay - Total length of hospital stay	Increased care requirement at discharge	X	- In MTC, number of patients with major complications
Shah SP, et al. 2019 (109)	Simple FRAIL scale items (FRAIL-5) which are Fatigue, Resistance, Ambulation, Illness and Loss of weight. And Clinical Frailty Scale (9-points)	- [Simple FRAIL score] frail ≥3 - [Simple FRAIL score] non-frail<3 - [CFS-self reported] frail ≥4 - [CFS-self reported] non-frail <4 - [CFS- physician] frail ≥4 - [CFS- physician] non-frail <4	- [Simple FRAIL score] frail, mean(SD)= 15.9(18.2) - [Simple FRAIL score] non-frail= 12.3 (6.7) - [CFS-self reported] frail= 15.4 (15.9) - [CFS-self reported] non-frail= 12.2 (6.6) - [CFS- physician] frail= 15 (15.5) - [CFS- physician] non-frail= 12.5(5.97)	In-hospital mortality	- Hospital days - ICU hours	Hospital disposition: - Home health - Home - MORGUE - Transferred to another acute care facility - Skilled Nursing facility (SNF)	X	X
Thompson A, et al. 2021(110)	Clinical Frailty Scale CFS (9-points)	- Non-frail, CFS (1-4) - Frail, CFS (5-9)	- Non-frail =16 (9-21) - Frail = 10 (9-17)	In-hospital mortality	-Total length of stay	Discharge to usual residence	X	X
Herklots M, et al. 2022 (111)	Clinical Frailty Scale (CFS, 9 items)	- Low frailty, CFS (1-2) - High frailty, CFS(3-9)	- Low frailty, mean (SD) = 30 (11.6) - High frailty, mean (SD)= 25 (6.4)	- Mortality within 24 hours - In- hospital mortality	- Length of stay (LOS)	- Glasgow Outcome Scale (GOS) at discharge and after 6 months	X	- In- hospital complications
Guiab K, et al. 2022 (112)	The 5 items modified frailty index (mFI-5, 5 items)	- 0 No frailty - 0.2 Moderate frailty - ≥0.4 Severe frailty	- 0 No frailty, median (IQR) = 21 (14.26) - 0.2 Moderate frailty, median (IQR)= 18(12,26) - ≥0.4 Severe frailty, median (IQR) = 17(10,25)	In-hospital mortality	- Length of stay (LOS)	- Discharge to home - Non-home discharge	X	- In- hospital complications

Table 2- 7: A summary of frailty tools, trauma measures, and outcomes of included studies

2.3.2.1 Excluded studies

Numerous publications were excluded at various stages of the search strategy, including during the synthesis phase. Although some of the excluded studies contained the three critical variables required for inclusion in the systematic review (frailty, trauma, and outcome), they did not differentiate between non-frail and frail individuals in their frailty assessments. Additionally, some studies categorised frail patients based on outcomes, such as Joseph et al (2014), who categorised patients with unfavourable discharge disposition as frail and those with favourable discharge disposition as non-frail, without investigating frailty categories in terms of mortality or other outcomes of interest (25). Therefore, these studies were excluded because they lacked sufficient information to answer the specific systematic review questions.

2.3.3 Risk of bias in studies

Using the JBI risk assessment instrument, two studies had a low risk of bias (70%), six had a moderate risk (50-69%), and four had a high risk (49%) (Table 2-8).

Cohort Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	%yes	Risk
Cheung A, et al. 2017 (104)	N	N	N	U	N	Y	Y	Y	Y	Y	Y	55%	Moderate
Joseph B, et al. 2016.(103)	Y	Y	N	N	U	N	Y	N	Y	N	N	36%	High
Joseph B, et al. 2017 (105)	N/A	Y	Y	N	Y	Y	Y	Y	N	N	Y	63%	Moderate
Joseph B, et al. 2014 (106)	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	73%	Low
Hamidi M, et al. 2019 (107)	Y	Y	Y	Y	Y	U	Y	U	Y	U	Y	73%	Low
Jarman H, et al. 2021 (108)	Y	N	Y	N	U	U	Y	Y	N	U	Y	45%	High
Pecheva M, et al. 2020 (46)	N/A	Y	Y	U	Y	Y	Y	N	N	N	Y	55%	Moderate
Rickard F, et al. 2020 (59)	N/A	N	Y	Y	Y	Y	Y	N	Y	N	Y	64%	Moderate
Thompson A, et al. 2021 (110)	U	N	Y	Y	N	U	Y	N	Y	N	Y	45%	High
Shah SP, et al. 2019 (109)	Y	Y	Y	N	N	Y	Y	Y	N	N	N	55%	Moderate
Herklots M, et al. 2022 (111)	Y	Y	N	N	N	U	Y	Y	Y	N	Y	55%	Moderate
Guiab K, et al. 2022 (112)	U	Y	N	N	N	Y	Y	N	N	N	Y	36%	High

Abbreviations:
JBI: Joanna Briggs Institute "Q1 – Q11 indicate questions 1 to 11 based on the JBI risk assessment
Notes: The risk of bias was ranked as high when the study reached up to 49% of "yes" scores, moderate when the study reached from 50 to 69% of "yes" scores, and low when the study reached more than 70% of "yes" scores. 'Y' indicates yes, 'N' indicates no, 'U' indicates unclear and 'N/A' indicates not applicable

Table 2- 8: Risk of bias results

2.3.4 Results of syntheses

Results from the 12 selected papers were included into the meta-analyses (46, 59, 103-112). Nine studies on in-hospital mortality (46, 103-105, 107, 108, 110-112), three on length of stay (106, 107, 109), nine on discharge to home (46, 103-106, 108-110, 112), and eight on in-hospital complications (46, 59, 103-105, 107, 111, 112) were included.

2.3.4.1 Frailty and in-hospital mortality

The outcome of mortality was evaluated differentially across studies (see Appendix: 4). The majority of included studies assessed death at the in-hospital mortality stage, which may be a significant limitation of mortality outcomes following major trauma in older people with frailty, given that frailty is a long-term condition that may manifest in trauma outcomes at later stages (113, 114). Only Pecheva M, et al. (2020) investigated death at discharge and one year later and discovered that the increase in mortality is roughly double in the frail group after one year (26.4% at discharge vs 51% at one-year) (46). The meta-analysis of nine eligible studies (46, 103-105, 107, 108, 110-112) revealed that patients with frailty were more likely to die in the hospital than non-frail patients (OR= 1.12, 95% CI 1.05, 1.19) (see Figure 2-2). The GRADE rating for this outcome was very low certainty. The level of certainty was decreased due to a high risk of bias (four studies had a high risk of bias (103, 108, 110, 112), four had a moderate risk (46, 104, 105, 111) and one had a low risk (107)), potential publication bias, and inconsistency (substantial heterogeneity, I^2 = 77). The inconsistency is largely attributable to the large Guiab et al (2022) study, which predominated and demonstrated a smaller effect of frailty on mortality than other studies. Three studies yielded results that were not included in the meta-analysis, but were consistent with the findings. Two (106, 109) were excluded because they reported no deaths in their non-frail groups and a small number of deaths in their frail groups, n=5 (106) and n=1 (109) respectively. Rickard et al. (2020) was excluded because they reported 30-day mortality as opposed to in-patient mortality, which was 14.3% in the frail group and 4.5% in the non-frail group (59).

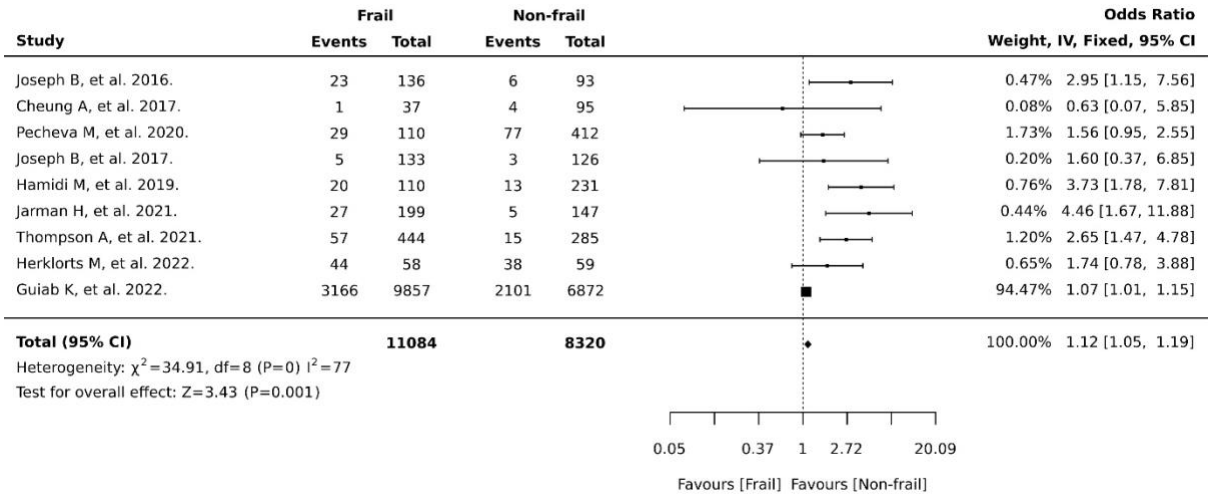


Figure 2- 2: Forest plot for frailty and in-hospital mortality

2.3.4.2 Frailty and length of stay (LOS)

The majority of the included studies were discovered that frail individuals are at high risk of demand greater care and support. All associated outcomes to length of stay (LOS) such as, total in-hospital days, total major trauma centre days, critical care days, or ventilator days were summarised to identify relevant results for meta-analysis (see Appendix: 5). There were no significant variations in critical care / intensive care unit days and ventilator days when compared to non-frail patients.

This meta-analysis included results from three studies (106, 107, 109). Figure 2-3 illustrates that patients with frailty spent more time in the hospital than patients without frailty (2.04 days, 95% CI 1.51, 2.56). The GRADE evaluation for this outcome indicated a low degree of certainty.

Eight studies reported data that were unsuitable for inclusion in the meta-analysis, although seven of them were consistent with it. Six studies provided non-parametric results in which the median lengths of stay in the frail groups were significantly higher

than in the non-frail groups: (5 vs. 4) (103), (5 vs. 3) (105), (13 vs. 12) (108), (12 vs. 11) (59), (12 vs. 11) (110), and (13 vs. 12) (112). In another study (46), the mean duration of stay for the frail group was 18.8 days (range 1-157), compared to 18.0 days (range 1-114) for the non-frail group. However, the findings of one additional study contradicted the meta-analysis; the median duration of stay was greater for non-frail patients than for frail patients (16.7 (0-77) vs. 8.4 (0-52)) (111). The authors of this study attributed this unexpected result to survival bias due to earlier mortality in the frailty group, and they provided evidence that this earlier mortality was not the outcome of less aggressive clinical management.

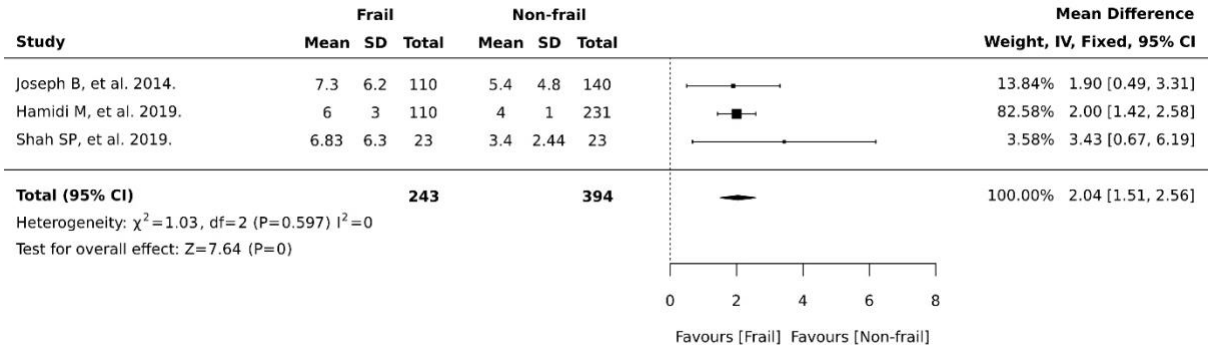


Figure 2- 3: Forest plot for frailty and Length of stay

2.3.4.3 Frailty and discharge to home

It was challenging to synthesise discharge destinations due to the variation between studies in measuring this outcome (See Appendix: 6). Three prevalent discharge destinations were evaluated differently across studies: discharge to home, rehabilitation, and skill nursing facility (SNF) discharge. Home discharge was used because it was the most appropriate discharge destination to demonstrate whether or

not older trauma patients with frailty are able to return home after sustaining a major trauma.

The meta-analysis of nine studies (46, 103-106, 108-110, 112) revealed that patients with frailty were less likely to be discharged to their usual home address than non-frail patients (OR= 0.58, 95% CI: 0.53, 0.63) (Figure 2-4). The GRADE rating for this outcome was very low certainty. The level of certainty was reduced due to the high risk of bias (four studies had a high risk of bias (103, 108, 110, 112), four had a moderate (46, 104, 105, 109), and one had a low (106)), the high heterogeneity across studies (I^2 = 81), and the possibility of publication bias.

One study provided relevant, but inapplicable to the meta-analysis, and which were consistent with it. Rickard et al. (2020) reported an increased care requirement at discharge in the frail group by 42.9% compared to 27.3% in the non-frail group (59).

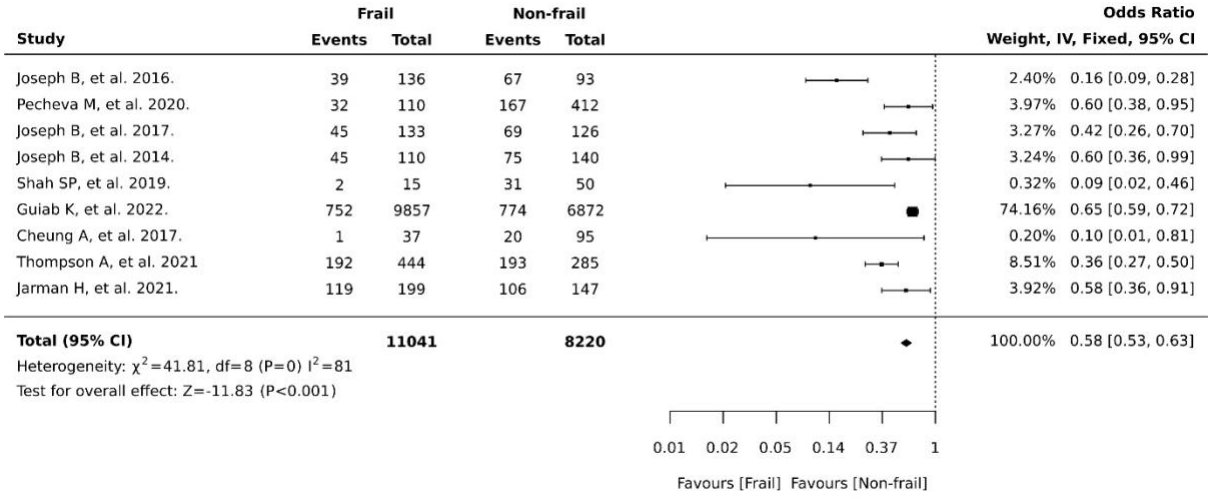


Figure 2- 4: Forest plot for frailty and discharge to home

2.3.4.4 Frailty and in-hospital complications

Multiple outcomes were used to measure complications across studies, including the number of complications, total in-hospital complications, and complications as

diseases such as pneumonia infections or others (See Appendix: 7). In order to synthesise this outcome, studies that used the number of individuals who had in-hospital complications were included in the meta-analysis. However, studies that divided complications into numbers such as 1, 2, 3, and +4 complications were summed as a dichotomous variable for meta-analysis as follows:

Total in-hospital complications*= (1 complication sample) + (2 complications sample) + (3 complications sample) + (+4 complications sample)*

The variable entered in the meta-analysis was then the sum of patients with one, two, three, or more than four complications versus patients with no complications. This equation was used to two studies in order to obtain the actual impacted patients with in-hospital complications in meta-analysis (46, 104).

Eight studies (46, 59, 103-105, 107, 111, 112) were included in the meta-analysis, which revealed that patients with frailty had a higher rate of one or more complications than non-frail patients (OR = 1.17, 95% CI = 1.10, 1.24; Figure 2-5). The GRADE rating for this outcome was very low certainty. The level of certainty was reduced due to the high heterogeneity and potential publication bias.

One study was excluded from the meta-analysis because it evaluated just the incidence of post-operative pneumonia between frail and non-frail patients, rather than all complications. The results of this study were consistent with the meta-analysis since the incidence of pneumonia was higher in the frail group (9.1%) than in the non-frail group (4.3%) (106).

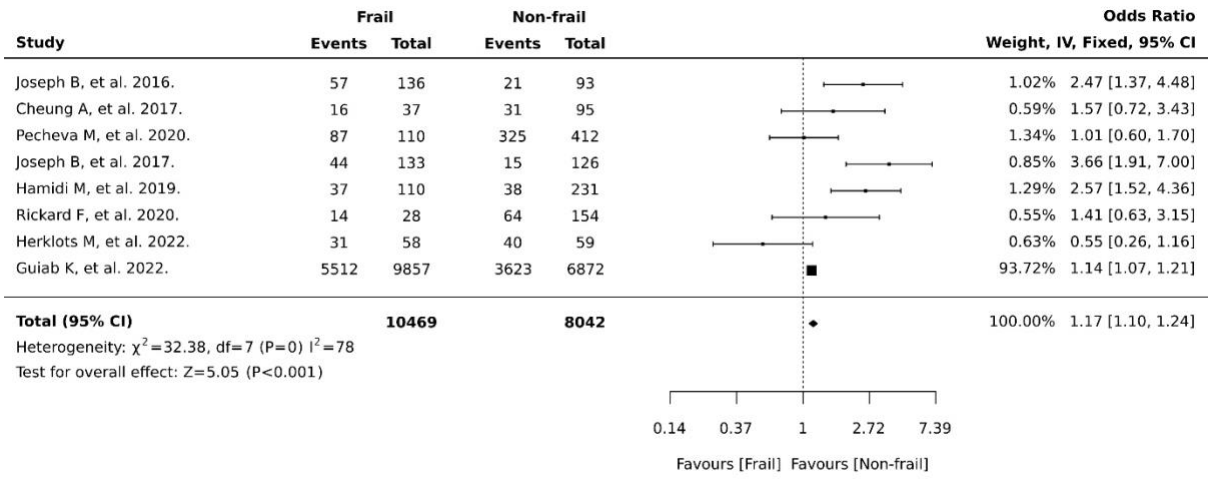


Figure 2- 5: Forest plot for frailty and in-hospital complications

2.3.4.5 Frailty and delirium / mental health outcomes, activities of daily living (ADL)

In the protocol for this review, it was proposed to assess delirium, changes in ADL, and other mental health outcomes; however, no publications reported results for these outcomes that were suitable for meta-analysis. Only delirium was evaluated, but differentially in two studies; in one, delirium was measured as an admission comorbidity (107), while in the other, it was measured as an outcome using regression analysis (59). The Hamidi et al. (2019) study found that delirium was more prevalent in older people with frailty 5% than in non-frail patients 3% (107). Rickard et al.'s study, which measured delirium as an outcome, found that post-injury delirium in frail older persons was associated with a higher level of care at discharge (OR 2.59; 95% CI 1.43-4.67; p<0.001) (59).

2.3.4.6 Relationships of frailty, age and ISS to outcome

The relationships of frailty, ISS, and age to outcomes were covered in studies that employed a multivariable regression of these variables versus outcomes. To

accurately investigate the relationships, the primary outcome was mortality or a related event such as failure to rescue (FTR). In nine studies, multivariable regressions were used to test predictors related to poor outcomes (46, 59, 103-107, 110, 112). Only six studies included age and ISS with frailty in multivariate regression upon outcomes.

Table 2-8 summarises the findings of six studies that compared the effects of frailty, ISS, and age on adverse outcomes using individual multivariable regression analyses. Among the adverse outcomes reported were mortality (59, 105, 112), failure to rescue (103), and adverse discharge destinations (including mortality) (104, 106). Two studies had a high risk of bias (103, 112), three had a moderate risk of bias (59, 104, 105), and one had a low risk of low (106).

Two of the six studies in Table 2-9 found that age was significantly, but weakly, associated with adverse outcomes, while the other four studies found no such association. Similarly, only two of the six studies demonstrated a significant association between injury severity and adverse outcomes, while the other four did not. All six studies demonstrated a significant association between frailty and adverse outcomes. This indicates that frailty is the only independent predictor that is significant across studies.

Study	Frailty group measure	Trauma measure	Outcome measure	Strategy for Multivariate regression	Multivariate regression analysis results		
					Age OR [95%CI], p value	ISS OR [95%CI], p value	Frailty OR [95%CI], p value
Joseph B, et al. 2016 (103)	TSFI>0.25	ISS, median was 11 (IQR 9 - 17)	Failure to rescue	Variables with significant (p≤0.20) association in univariate analysis	Not significant in univariate analysis	Not significant in univariate analysis	5.07 [1.65-13.11] ***p*=0.01**
Cheung A, et al. 2017 (104)	CFS (6 or 7)	ISS, median was 17 (IQR 13 - 24)	Adverse discharge destinations (including mortality)	Using variables based on the literature on geriatric trauma	1.1 [1.0–1.1] ***p*=0.005**	ISS (9-15) 0.9 [0.3 – 2.6] *p*=0.83 ISS (16-24) 1.4 [0.5-3.7] *p*=0.52	5.1 [2.0-13.2] ***p*<0.001**
Joseph B, et al. (2017) (105)	TSFI>0.27	ISS, median was 11 (IQR 9 - 17)	In-hospital mortality	Variables with significant (p≤0.20) association in univariate analysis	Not significant in univariate analysis	1.06 [1.01–1.09] ***p*=0.01**	1.1 [1.04–4.7] ***p*=0.04**
Joseph B, et al. 2014 (106)	FI (FI≥0.25)	ISS, median was 14 (IQR 9 - 17)	Adverse discharge destinations (including mortality)	Variables with significant (p≤0.20) association in univariate analysis	(75-84) group 1.1 [0.7-2.9] *p*=0.22 (≥85) group 1.3 [0.9-2.1] *p*=0.16	ISS (9-15) 1.1 [0.9-3.2] *p*=0.16 ISS (≥16) 1.4 [0.7-5.6] *p*=0.09	1.6 [1.1-2.4] ***p*=0.001**
Rickard F, et al. 2020 (59)	CFS(5-6) and (7-9)	ISS, median (IQR) was 14 (9-24)	30-day mortality	Variables with significant (p≤0.20) association in univariate analysis	1.01 [0.98-1.05] *p*=0.53	Not significant in univariate analysis	CFS (5-6) =2.32 [1.23-4.36] ***p*<0.01** CFS (7-9) =2.14 [0.81-5.68] *p*=0.13
Guiab K, et al. (2022) (112)	mFI-5≥0.4	ISS, median (IQR) was 17 (10-26)	Mortality	Variables with significant (p<0.05) association in univariate analysis	1.068 [1.064-1.072] ***P*<0.001**	1.037 [1.034-1.040] ***P*<0.001**	1.231 [1.146-1.322] ***P*<0.001**

Abbreviations:
TSFI: trauma-specific frailty tool; **CFS**: clinical frailty scale; **FI**: frailty index; **ISS**: injury severity score; **mFI-5**: 5-item modified frailty index; **CI:** confidence interval; **OR:** odds ratio

Table 2- 9: Summary of multivariate regression results for mortality or adverse outcomes in relation to age, ISS and frailty

2.3.5 GRADE assessment

GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) profile evidence was utilised to comprehensively summarise the evidence base and present the pooled estimates and certainty of the evidence for each outcome (Table 2-10). The assessment of certainty included indirectness, which was employed to compare study populations and results of frail and non-frail groups against outcomes; inconsistency, which determined whether there was variability in effect estimates across studies or high heterogeneity; and imprecision in the case of a wide confidence interval. As each group population was compared to the correct outcome group, no significant indirectness was discovered between studies. No significant imprecision was found between studies, but inconsistency was found in two studies with different outcomes owing to meta-analyses revealing fluctuation in effect estimates and high heterogeneity (104, 111). Due to the limited number of included studies, publication bias was not evaluated, as the funnel plot asymmetry reliability is affected by the number of included studies and is not recommended when fewer than ten studies are included in the meta-analysis (115); consequently, publication bias was assumed for each outcome (116).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Frail	non-frail	Relative (95% CI)	Absolute (95% CI)		
In-hospital mortality												
9	observational studies	Serious [a]	Serious [b,c]	not serious	not serious [d]	none	3372/11084 (30.4%)	2262/8320 (27.2%)	**OR 1.12** (1.05 to 1.19)	**23 more per 1,000** (from 10 more to 36 more)	⊕◯◯◯ Very low	CRITICAL
Length of Stay (LOS)												
3	observational studies	not serious	not serious	not serious	not serious	none	243	394	-	Mean difference **2.04 higher** (1.51 higher to 2.56 higher)	⊕⊕◯◯ Low	CRITICAL
Discharge to home												
9	observational studies	Serious [e]	Serious [c]	not serious	not serious	none	1227/11041 (11.1%)	1502/8220 (18.3%)	**OR 0.58** (0.53 to 0.63)	**68 fewer per 1,000** (from 77 fewer to 59 fewer)	⊕◯◯◯ Very low	IMPORTANT
In-hospital complications												
8	observational studies	not serious	Serious [c,f]	not serious	not serious	none	5798/10469 (55.4%)	4157/8042 (51.7%)	**OR 1.17** (1.10 to 1.24)	**39 more per 1,000** (from 24 more to 53 more)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **OR:** odds ratio

Explanations

a. Four studies had a high risk of bias, four at moderate risk and one at low risk.
b. Cheung A, et al. (2017) study has shown no effect.
c. High heterogeneity
d. No serious wide CIs
e. Four studies were at high risk of bias, four were at moderate, and one at low risk.
f. Herklots M, et al. (2022) study has shown no effect.

Table 2- 10: GRADE assessment

2.4 Discussion

The meta-analyses of this systematic review showed that frailty was associated with increased in-patient mortality, lengthened hospital stays, adverse discharge destinations, and in-patient complications. Additionally, the pooled data from studies using multivariate regression analyses revealed that frailty was a more consistent predictor of adverse outcomes—such as mortality, failure to rescue, and adverse discharge destinations—compared to age or injury severity.

Despite the systematic nature of the search, a small number of studies were available for review, reducing the certainty of the conclusions. No studies reported clinically significant outcomes such as activities of daily living or mental health outcomes, so no conclusions could be drawn regarding the association between frailty and the risk of these outcomes. However, delirium was included in two studies, one of which examined its association with frailty as an outcome and discovered that delirium was associated with patients who were frail.

Despite efforts to reduce biases, certain biases are unavoidable in systematic reviews. The important ones to consider at this stage include publication bias (a form of selection bias), outcomes reporting bias, or language bias (117). The systematic review necessitated the inclusion of observational studies and their inherent biases. To reduce outcomes reporting biases, outcomes were synthesised in two unique forms: data pooled in a meta-analysis and data for regressions, as well as certain data synthesised from several outcomes that were not clearly defined, such as total complications. Prior to initiating the systematic review, the published protocol included relevant information about the review questions, inclusion criteria, outcomes, and analyses. The clear outlines of objectives, methods, and procedures prior to the

execution of the review aided in preventing bias and increasing transparency of decisions (118). Unavailable data were duly acknowledged to ensure the reliability and validity of the review. Although non-English-language studies were not included in the analysis, it is likely that their inclusion would not substantially alter the results, other than increasing the level of precision. The search strategy utilised proxy frailty measures to include more pertinent studies quantifying frailty indirectly. Although it was anticipated that studies would rely on proxy measures, no studies were discovered that used proxy frailty measures. Consequently, the findings are more reliable since they were derived from studies that used valid frailty tools. The search was restricted to studies published after 2010 to increase the relevance of the findings to the present. It is known that the introduction of comprehensive geriatric and orthogeriatric care along with other pathway-based interventions enhanced outcomes for the injured older person (119), and it is unlikely that earlier research studies would compare care pathways to those currently in use. In this particular case, the use of literature from the past 12 years is further justified because the concept of major trauma was defined by recent clinical developments, such as the commissioning of major trauma centres in the United Kingdom (69, 120) and the use of modern, valid frailty assessment tools, which emerged around the same time. The threshold age of 60 was used to define older people to avoid excluding relevant studies, given that this age is used in hip fractures studies and guidelines (121, 122), however, it is accepted that the definition of older people does vary.

This is the first meta-analysis to investigate the association between frailty and adverse outcomes in older individuals with major trauma. The findings of this systematic review are consistent with and contribute to the existing body of knowledge. Frailty predicts adverse outcomes in a wide range of situations, including those

requiring hospitalisation, such as in non-trauma patients (123, 124), hip fracture patients (125, 126), or COVID-19 patients (127). In line with other research findings, frailty is a more consistent predictor of adverse outcomes in major trauma than age and injury severity.

There was considerable heterogeneity in the findings, which was largely attributable to one large national trauma database study from the United States (112), in which the effects of frailty on outcomes were generally smaller than in the remaining studies: the results from this large study dominated the meta-analyses to which it contributed. The smaller effect of frailty on outcome in this study may be due to the use of a very brief frailty measure (the 5-item modified Frailty Index), of which four items assessed co-morbidity and only one assessed functioning. It is conceivable that this was less able to distinguish between frail and healthy individuals. Although sensitivity analysis was performed by excluding this major study from the meta-analysis, there was no significant change in the overall odds ratio. The inclusion resulted in more homogeneous findings. As a result, no further sensitivity checks were necessary since removing this study would not impact the direction of the results. However, our findings are consistent with that of other systematic reviews in showing that frailty is significantly associated with adverse outcomes across a broad range of studies. This appears strong irrespective of the particular instruments used for measuring frailty or the sample size underlying it. The results of this systematic review are insufficient to ascertain which frailty assessment tool is optimal in this setting. It became apparent that certain frailty measures primarily employ co-morbidity measures as markers of frailty, which will have had an influence on discriminating between frailty groups based on outcomes. This also highlighted a difficulty with the frailty measurements employed in trauma, since no direct measure of frailty in trauma existed. However, clinicians and

researchers should exercise caution when employing brief or predominantly co-morbidity measures as indicators of frailty. Prior to the availability of direct measures of homeostatic vulnerability to indicate frailty, functional deficits appear to be the greatest indicator of the effect of frailty on outcome.

A relevant clinical implication of the findings of this systematic review is that they support the use of frailty status rather than age or age alone in the assessment of prognosis in the care planning of older people with major trauma - for example, in sharing expectations with patients and their families, preparing prognosis-based care plans, and even planning and directing the intensity of medical care. In clinical benchmarking exercises and clinical trials, frailty status would also be a valuable stratification variable, either in place of or in addition to age.

Despite the low level of certainty of the findings of this review, given their consistency with what is already known about frailty in other conditions, it is unlikely that additional research is required to increase the certainty of these results. However, additional research is warranted to determine the extent to which frailty status predicts adverse outcomes of major trauma that have not yet been investigated, such as activities of daily living, complications such as depression, and economic outcomes such as quality of life and costs. Furthermore, there is a considerable knowledge vacuum regarding the impact of frailty on patient-reported outcome measures (PROMs) and health-related quality of life (HRQoL), which are critical for capturing the patient's perspective on recovery and long-term well-being.

Given that the science of frailty measurement is relatively new, future studies (and future practitioners) should use the best performing frailty measures in the intended

population. In contexts involving major trauma, it is typically impossible to obtain pre-trauma measurements of gait speed or grip strength, and it may also be challenging to obtain sufficient historical data to complete a frailty index. This is likely the reason why the majority of studies included in this review utilised the Clinical Frailty Scale (59, 104, 107-111), which was devised for the acute setting: it is a global clinical assessment of a patient that requires a few minutes and a concise clinical history to complete. Further research should investigate whether routinely accessible physiological and historical patient data could be used to generate a frailty score that is more accurate, less susceptible to assessor bias, and even simpler to implement if automated. Future evaluations of current and novel interventions should incorporate frailty assessments, in the event that frailty not only affects outcomes but also the response to interventions – some interventions may perform better or worse in the presence of frailty. New clinical interventions (such as specific nutritional support) aimed at mitigating the negative impact of frailty on outcome should be developed and evaluated.

2.5 Conclusion

Frailty status is a substantial independent predictor of outcomes in major trauma. Frail patients are more likely to have higher in-hospital mortality rate, prolonged hospital stays, in-hospital complications, and adverse discharge disposition. Although age and ISS are important factors, frailty state has a greater impact on trauma outcomes. Identification of frailty status at early prognostic stages is critical for older adults. Frailty and trauma research should include long-term outcomes and ADL, as frailty is a long-term condition that may develop after trauma.

2.5.1 The need for a frailty assessment tool in trauma care.

This chapter has identified the presence of multiple frailty measures that have the ability to predict outcomes. This chapter not only identifies the value of frailty in predicting outcomes, but also draws attention to particular challenges that are inherent in current frailty assessment instruments. Particularly in the fast-paced and high-pressure environment of acute settings, where time is of the essence, these tools require specialised training and the investment of substantial time and effort to collect additional data. As a result, the creation of a reliable frailty assessment instrument capable of utilising routinely collected clinical variables becomes necessary. The implementation of such a tool would not only optimise the evaluation procedure but also augment its practicality and relevance in the field of trauma practice. The following chapter delves into the development and validation of a candidate frailty assessment tool and provides insights into the practical application of frailty assessment in trauma settings and answering the outstanding research questions.

Chapter 3: Development and validation of a frailty scale in major trauma patients

3.1 Introduction

Older people are known to be susceptible to poor outcomes after major trauma due to both frailty and comorbidity. The use of age ≥ 65 or ISS ≥ 15 alone as a criterion for unfavourable outcomes in this age group is ineffective for determining the consequences of major trauma in older adults (59, 103, 104, 106). Frailty is a major independent predictor of in-hospital complications, length of stay, unfavourable discharge destination, and in-hospital mortality among older trauma patients (85). The early identification and evaluation of older individuals with frailty is a key prognostic factor for trauma patients. Measures used to quantify frailty in older trauma patients vary. Many existing frailty instruments are unsuitable for use in acute settings such as trauma (e.g., those that need a pre-injury gait speed) (18), and others using the Rockwood cumulative deficit (20) or hybrid approaches (25) require historical information about previous medical history of functioning that might not be immediately or reliably available in the acute setting.

Alternative tools employed prognostic instruments to forecast unfavourable clinical outcomes, such as the Nottingham Hip Fracture Score (NHFS), which is particularly notable for its use in the hip fracture population (128). The NHFS provides prognostic estimates for mortality (129) and hospitalisation duration (130) in patients with hip fractures, as well as in other individuals with fragility fractures (131). However, frailty measures are increasingly being used to guide management in populations with a high frailty prevalence, such as in the National Hip Fracture Database (132) and in

response to UK policy (133). This is because these measures are considered to be more effective in accounting for the increased vulnerability caused by multiple system deficits that are characteristic of the frailty state compared to other tools. The Clinical Frailty Scale (CFS) is a widely used measure for assessing frailty in acute care settings. It assigns a score between 1 and 9 and has shown the ability to predict various outcomes in patients with hip fractures and other traumatic injuries. In order to ensure the accuracy of CFS, it is essential that all staff get consistent training in its use. This is because CFS includes subjective assessment, and if employed by inexperienced workers or different staff, its accuracy may be undermined (134). However, earlier research (135) showed that using CFS to measure frailty might give useful prognostic information for fitter individuals, with a plateau in greater frailty hip fracture and possible challenges in clinicians discriminating between higher frailty grades in acute settings. Hence, it is imperative to create a tool that not only assists in detecting and improving the assessment of frailty in trauma but also accurately predicts outcomes in older trauma patients with frailty. An effective approach to improving the detection and assessment of frailty in acute trauma patients in clinical settings is to utilise routinely collected clinical data. This approach would eliminate the requirement for staff training, minimise subjectivity, and likely result in a higher number of patients undergoing frailty assessments. The main aim of this chapter is to identify routinely collected variables that are predictive of frailty and to develop, validate, and verify a frailty scale suitable for use in older patients with traumatic injuries.

3.1.1 Aims

To build a validated model that can improve the evaluation of frailty in major trauma in older people.

3.1.2 The research question

This chapter will explore multiple objectives that require a research question for each objective to be answered in a separate work. The main research topic for this chapter, however, is:

“What variables are associated with frailty in major trauma patients, and how can they be successfully quantified to provide a reliable and accurate instrument for measuring frailty in older major trauma patients?”

3.1.3 Objectives

To develop an objective, clinically practical prediction model for frailty in older people after acute trauma using readily assessed physiological and functional characteristics.

3.2 Methodology

There are a range of described modelling methods that have been created to address the lack of standardised healthcare procedures that reflect the viewpoints of all healthcare stakeholders (136). The utilisation of predictive models in healthcare is broad, and the process for developing outcome predictions and predicting values for new occurrences is well described (94).The wide application of predictive models in healthcare is known to improve the decision-making of healthcare organisations regarding clinical outcomes, resource allocation, and cost reduction (137). Consequently, using a predictive model with older patients seems to be one of the most effective methods for improving older-care practices and outcomes at the patient, provider, and organisation levels. Different types of predictive models exist:

1. The classification model is used to conduct a categorical analysis of historical data (138).

2. The clustering model is used to collect data and divide it into categories according to their shared characteristics (139).

3. The outliers model is used to detect anomalous data on its own or in conjunction with other categories and figures (140).

4. The forecast model is used to manage metric value forecasts by calculating new data values using data insights from the past (141).

5. The time series model is used to analyse datasets with time sequences as the input parameter (142).

These diverse models vary according to the data type and hypotheses used to answer the research question. Using the available data and hypotheses, a forecasting (prognostic) model was the best option for answering the objectives of this chapter. In health care settings, the forecasting (prognostic) model is one of the most prevalent methods, as it is used to predict the occurrence of a particular condition or outcome by generating numerical values and managing multiple parameters (94, 141). There are two principal categories of prognostic models:

- Prognostic model at the patient population level
- Prognostic model at the individual patient level

Individual patient models are used to provide therapeutic guidance and give patient-centred consultation, while patient population models concentrate on identifying patterns or differences in groups of patients (143). The purpose of this model was to identify frailty predictors in the older major trauma patient population. A patient population level was used. Creating an accurate frailty scale model needs a number

of steps, including defining the problem, gathering data, selecting the best method, and validating the model (144). The following steps were taken to develop the model:

Step 1: The project definition for the model's objectives, hypotheses, and desired outcomes.

Step 2: Identification of a suitable dataset

Step 3: Obtaining institutional approval to utilise the dataset

Step 4: Data exploration and exploratory analysis

Step 5: Data preparation, data set cleansing, and transforming

Step 6: Identify highly correlated variables

Step 7: Model creation, evaluation, verification, and validation.

These were addressed by analysing a trauma dataset to understand where and to what extent frailty can affect trauma outcomes and by exploring and developing a number of key variables from clinical data to build the predictive model. However, success in constructing a predictive model necessitates a number of data requirements. For example, datasets must be organised and coded to be reliably tested by a statistical package. Therefore, the obtained database went through several processing and modelling phases to ensure that the predictive model criteria were met. A train-test split and validate procedure was used to avoid model from overfitting and accurately assess the model's performance (145). A flow chart of the processes that were undertaken was created to provide an overview of the method structure and processes (see Figure 3-1).

In general, the processing began with a thorough initial screening for available variables, which were then transferred to new distinct databases for testing and training. Then, a hypothesis for each variable was formulated in order to generate a predictive model that provides meaningful observations for each variable (94).

Hypotheses as well as the inclusion and exclusion criteria were applied to evaluate the available variables. The model was reported in accordance with a full series of phases utilising transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) to ensure that the methodological approach of this model was properly implemented (146). TRIPOD covers the important aspects of developing and validating predictive models, including participant processing, the model development process, model specification, and model performance. A model verification phase was added to TRIPOD to verify that the model was implemented appropriately to match the stated assumptions. The data were initially input into Excel (147); however, Excel's limited analytical capabilities necessitated the preparation and coding of the data for entry into IBM SPSS Statistics (version 28.0.0.0) (148).

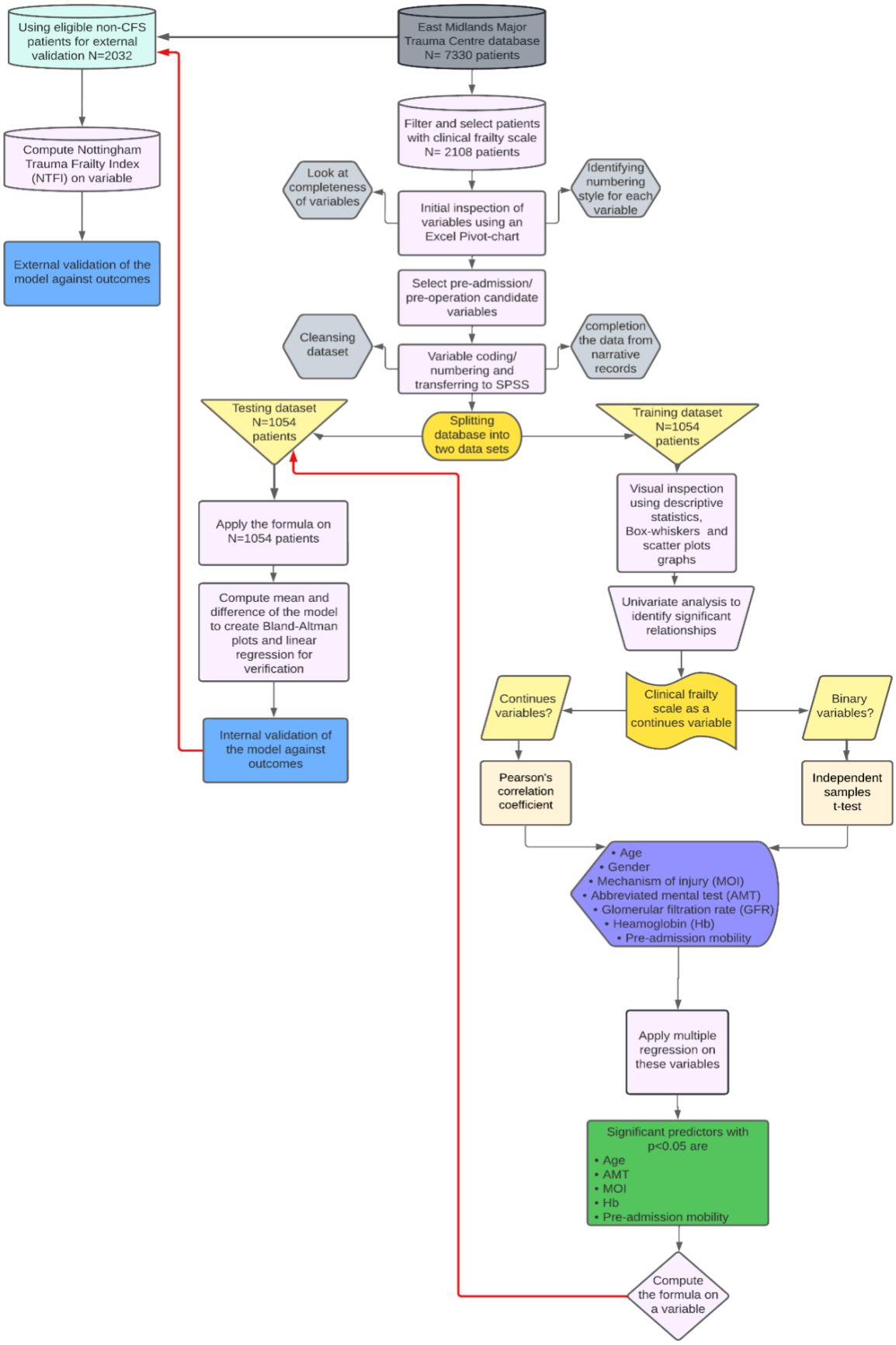


Figure 3- 1: A flowchart showing the overall model development process.

3.2.1 Source of data

3.2.1.1 Clinical audit approval

As the project's objectives and requirements were designed to create a prediction model that would enhance frailty evaluation in older trauma patients using routinely collected data, a clinical audit was considered to be the most suitable approach. A clinical audit registration form was then completed, reviewed, and sent for approval to the clinical effectiveness team. An approval has been obtained for data collection and analysis of the audit, and the project approval number is 21-040C (the audit approval is in Appendix: 8). The database management complied with the Caldicott principles and ensured patient anonymity and confidentiality. In addition, to comply with the Data Protection Act and preserve patient anonymity, no personal information was entered on the data collection form, including hospital ID number, name, address, or date of birth.

3.2.1.2 Dataset design

The database included 7,441 patients aged 60 years old and over who were admitted to the East Midlands Major Trauma Centre in Nottingham, UK, for orthopaedic surgery from October 1, 2015, to July 31, 2020. The used dataset is a compilation of three routinely collected clinical datasets from the Nottingham Trauma Registry that give a complete picture of the whole older population presenting with fractures, including databases for fragility fractures (fractures sustained through a low energy fall), hip fractures, and adult trauma. There were 7441 adult fractures; 6002 were fragility fractures, 3801 of which were hip fractures. Data from patients is collected prospectively by dedicated hospital audit officers and reviewed by the orthopaedics and trauma research team. Missing values and values that varied significantly from

the norm were cross-checked amongst datasets and addressed with the orthopaedics and trauma research team for correction and completeness.

3.2.1.3 Data authenticity and initial screening

Nottingham University Hospitals (NUH) data is protected in terms of database validity by the Health Research Authority (HRA), which is the national authority that protects and promotes patients' and the public's interests in health and social care research (149). Furthermore, NUH is committed to keeping records safe, secure, and accurate and to using the submitted records in accordance with data protection regulations and legislation (149). Nonetheless, a number of steps were performed to evaluate the data's veracity, including checks for implausibly high or low numbers and validity, as well as the plotting of multiple graphs in search of unusual or extreme results. Following that, the database was transferred to separate Excel sheets for analysis and coding after being checked for database validity. The data was then visually screened to determine numerical styles, shortcuts meaning, and missing data using IBM SPSS.

3.2.2 Participants

3.2.2.1 Inclusion and exclusion criteria

The obtained dataset includes 47 variables for 7441 patients, and the data was initially filtered using the following criteria:

- Patients aged 65 years and older
- The main complaint is trauma
- A CFS completed on admission

A sifting procedure was used to identify duplication in variables during this phase. Duplicated variables were used to compare values between the main variable and the duplicates as part of the cross-checking procedure. Age was further filtered to include only patients aged 65 and over, since this was the mean age for the older population reported in the systematic review, as well as the marker for the older population age according to the United Kingdom and World Health Organization (WHO) (8). Following the exclusion of patients aged 64 and younger, the total number of patients aged 65 and over in the dataset was **7330**. Subsequently, the dataset was restricted to include only patients with reported CFS, resulting in a total of **2108** individuals. The subsequent section contains additional details regarding the CFS dataset.

3.2.2.2 Clinical Frailty Scale (CFS) dataset

As the CFS was the tool used to measure frailty in the dataset, the model was constructed using the CFS as a dependent variable to identify frailty-related trauma factors from demographic, patient-related, treatment-related, and injury-related variables. Therefore, the database was separated into two separate datasets depending on the presence of the clinical frailty scale. The first dataset included **2108** patients with CFS, whereas the second dataset contains patients without CFS (non-CFS dataset) (see Figure 3-2).

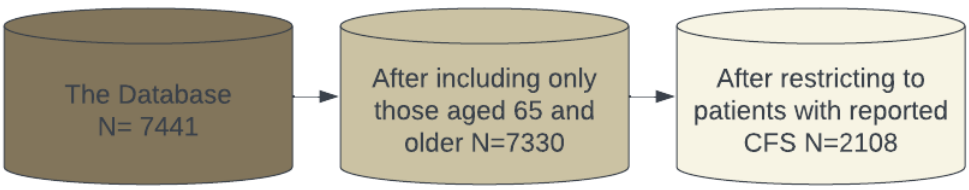


Figure 3- 2: Model database preparation processes

CFS is a widely validated instrument that was originally designed as a 7-point scale, but it was later modified to a 9-point scale in order to better accommodate to individuals with multiple symptoms (21, 27). In research, it is often reported as a dichotomous variable with non-standardised labels. Some studies classify CFS into two (107, 108, 150), three (59) or four categories (104), or use various labelling categories to meet their statistical analysis objectives. In order to minimise dichotomising bias of CFS, this predictive model was constructed using CFS as a continuous variable, since its normal distribution in normality tests confirmed its suitability for multiple regression analysis (151). Two normality tests, the normal curve of the histogram and normal Q-Q plots, were conducted to establish if the assumption that the data are approximately normally distributed is true. The Q-Q plots were performed to plot the observed value for each score versus the expected value from the normal distribution (see Figures 3-3 and 3-4) (152).

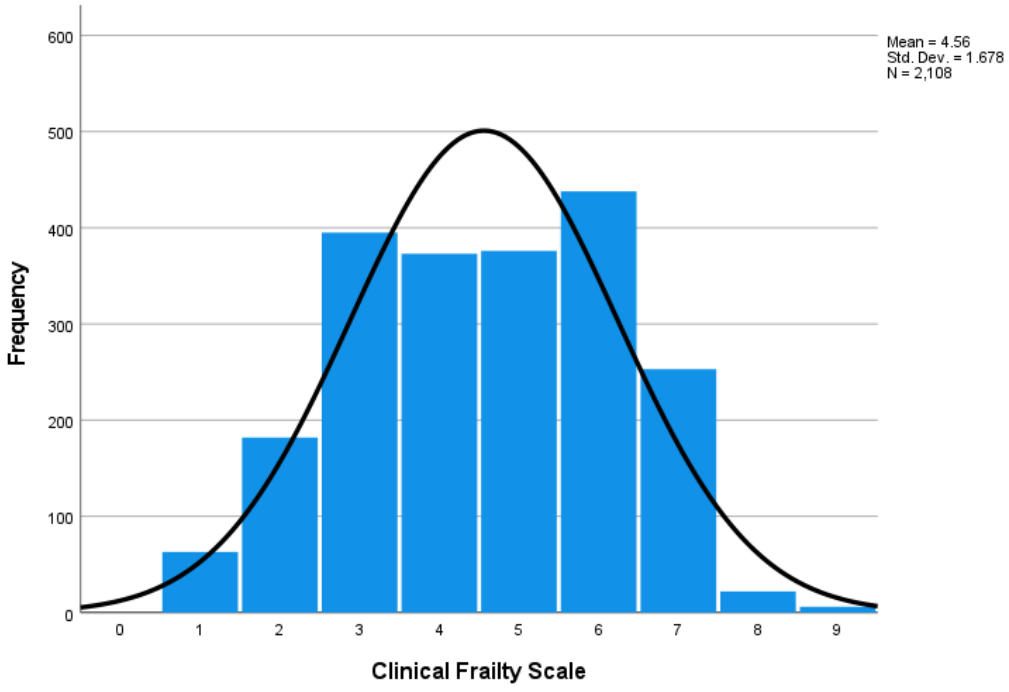


Figure 3- 3: A histogram of the whole CFS dataset depicting the distribution of CFS.

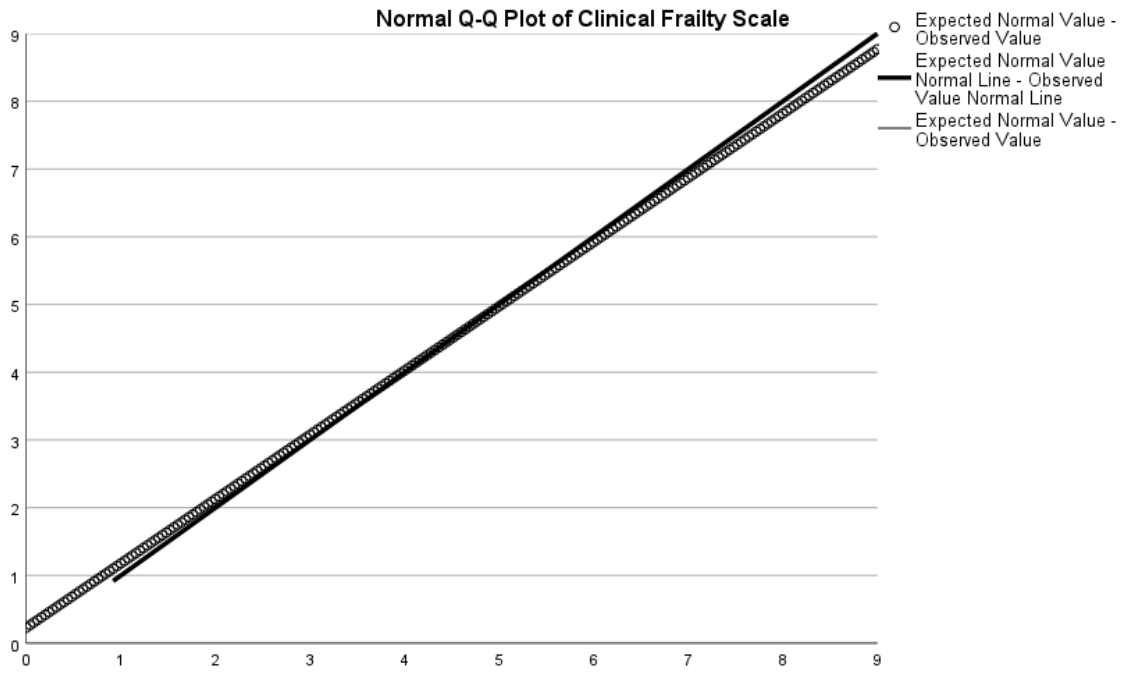


Figure 3- 4: A Q-Q plot of the whole CFS dataset depicting the distribution of CFS.

3.2.3 Outcome

The recorded CFS of the participants was used to forecast the primary outcome, which was the degree of frailty. The reason for this is that the model is specifically intended to assess the level of frailty in these people. Although frailty is recognised as a significant indicator of adverse outcomes, it is crucial to acknowledge that utilising adverse outcomes in predicting frailty may not accurately include the essence of frailty since frailty is distinct from the outcomes themselves. Therefore, the model was constructed using CFS as the outcome variable. After confirming the validity and accuracy of the model, further validations will be carried out to assess the accuracy and reliability of this developed frailty scale in predicting clinical outcomes.

3.2.4 Predictors

Dataset cleansing is the removal or modification of inaccurate, fraudulent, incomplete, incorrectly formatted, or duplicate data (153). This process was performed on the full dataset to ensure predictors were complete, unbiased, consistent, and organised. An important instance of the dataset cleansing procedure is the discrepancy in the units used to record haemoglobin levels. In some cases, the haemoglobin level was recorded in grammes per decilitre (g/dL), while the complete haemoglobin data was reported in grammes per litre (g/L). This discrepancy necessitates a conversion step. On the other hand, categorical variables were classified into the proper nominal, ordinal, and dichotomous categories, while continuous data were processed, with specific variables classified as interval or ratio variables. In addition, only pre-operative variables were included to prevent confounding factors related to injury outcomes or surgical complications. Other post-operative variables were transferred to a separate database for later validation of the model against outcomes. Candidate predictors were 27 of the 47 variables that were recorded on admission by clinicians and coded by audit staff (see Table 3-1).

Demographics	**Mental health variables**	**Chronic diseases**	**Biological variables**	**Physical state**
• Age • Gender • Mechanism of Injury • Alcohol Excess • Visual Acuity	• Abbreviated Mental Test • Alzheimer • Dementia	• Diabetes • Atrial Fibrillation • Hypertension • Osteoporosis • Malignancy	• Glomerular filtration rate (eGFR) • Platelets count (Plt) • Lactate • White cell count (WCC) • Haemoglobin level (Hb) • Creatinine level • Urea (U) • Sodium level (Na) • Potassium level (K) • Calcium level (Ca)	• Residential home resident • Living alone • Nursing home resident • Pre-admission mobility

Table 3- 1: Dataset candidates for the whole CFS dataset on categories

3.2.5 Sample Size

Multiple sources recommend that conducting multivariate analyses requires a minimum of 10 - 20 instances per independent variable, while others suggest a sample size of at least 500 cases (154). When it comes to predictive modelling, larger sample sizes lead to the creation of more reliable models, decrease the likelihood of overfitting, and improve the precision and accuracy of predictions (155). Therefore, a dataset of 2108 patients who met the inclusion criteria was considered sufficient to achieve the intended objectives.

The dataset included 2108 older trauma patients who were classified as having CFS. The mean age was 83.95 ± 7.908 years; 70.6% were female, and 29.4% were female. The mean CFS was 4.56 ± 1.678, and hip fracture patients were 1654 (78.5%) patients. The most common mechanism of injury was falls from standing height (93.4%), which was significantly higher than other MOI categories. The following table presents the general demographic characteristics of patients included in the database (see Table 3-2):

Variable	Categories	N	%
Gender	Female	1489	70.6%
	Male	619	29.4%
Clinical Frailty Score	1	63	3.0%
	2	182	8.6%
	3	395	18.7%
	4	373	17.7%
	5	376	17.8%
	6	438	20.8%
	7	253	12.0%
	8	22	1.0%
	9	6	0.3%
Age	(65-75)	404	19.2%
	(76-85)	759	36.0%
	(86-95)	841	39.9%
	(96-105)	104	4.9%
MOI	Fall from standing height	1978	93.8%
	Fall from height	48	2.3%
	RTC	27	1.3%
	No MOI	33	1.6%
	Others	16	.8%

Osteoporosis	Yes	127	6%
	No	1981	94%
Alzheimer	Yes	77	4%
	No	2031	96%
Alcohol excess	Yes	96	5%
	No	2012	95%
Atrial Fibrillation	Yes	428	21%
	No	1680	79%
Malignancy	Yes	402	19%
	No	1706	81%
Dementia	Yes	576	27%
	No	1532	73%
Diabetes	Yes	354	17%
	No	1754	83%
Lives alone	Yes	576	27%
	No	1532	73%
Residential home resident	Yes	380	18%
	No	1614	76.5%
Nursing home resident	Yes	209	10%
	No	1899	90%
Pre-admission mobility	Needs assistant	1275	60.5%
	Freely mobile	701	33.3%
Hypertension	Yes	1134	73.8%
	No	974	46.20%
Visual acuity	Normal	1928	91.4%
	Abnormal	180	8.6%
Haemoglobin (Hb)	Cases	2028	96.20%
Urea (U)	Cases	1975	94%
Sodium (Na)	Cases	1995	95%
White cells count (WCC)	Cases	2021	96%
Creatinine (Creat)	Cases	1980	94%
Glomerular filtration rate (GFR)	Cases	1877	89%
Potassium (K)	Cases	1870	89%
Platelets count (Plt)	Cases	1996	95%
Abbreviated Mental Test (AMT)	Cases	2000	95%
Lactate	Cases	16	0.8%
Calcium level	Cases	697	33%

Table 3- 2: Descriptive statistics for all variables available in the whole CFS dataset.

3.2.6 Missing data

In almost all research, missing data may have a significant influence on the conclusions that can be drawn from the data (156). It may decrease the statistical power required to reject the null hypothesis (157). Particularly in the case of predictive modelling and machine learning algorithms that rely on full data, these methodologies are most affected by missing data (158, 159). Since missing data at random (MAR)

and regression required complete case analysis, the listwise deletion (complete case) method was utilised to generate unbiased estimates of means, variances, and regression weights (160). There is a risk that if data are not missing at random, a bias will be introduced into the predictive model using this method. However, listwise deletion does allow for complete case inclusion, which is important in regression models where variables are likely to interact. In addition, complete variables were deleted when more than 20% of their values were missing, since this would introduce bias and reduce the power of the analysis by reducing the effective sample size (161, 162). Lactate and calcium levels variables were eliminated entirely owing to >20% of missing data (Table 3-2). As a consequence, it may be necessary to investigate these two factors in further research, as they were shown to be associated with worse outcomes among older persons but not with frailty (163-169).

3.2.7 Statistical Analysis Methods

In healthcare, the train-test split approach is one of the most widely used and valid strategies for constructing predictive models (170-172). A train-test split is the division of data into a training set and a testing set, with the training set used to train the model and the testing set used to evaluate the model's accuracy on an unseen testing set. This method is used to avoid reinforcement biases and is effective when a large dataset contains sufficient observations to separate into training and testing datasets (173). As shown in the flowchart below, this method was used to create this model (see Figure 3-5). In the training dataset, potential predictor variables were assessed using univariate and multivariate analyses against the CFS in an effort to identify significant predictors. A multivariate regression model was then computed in a separate variable of the testing dataset for validation. This strategy allowed for a

balanced approach to the model's creation and validation, resulting in an effective evaluation of the model's performance. Additional information on statistical analysis methods will be presented in the next sections.

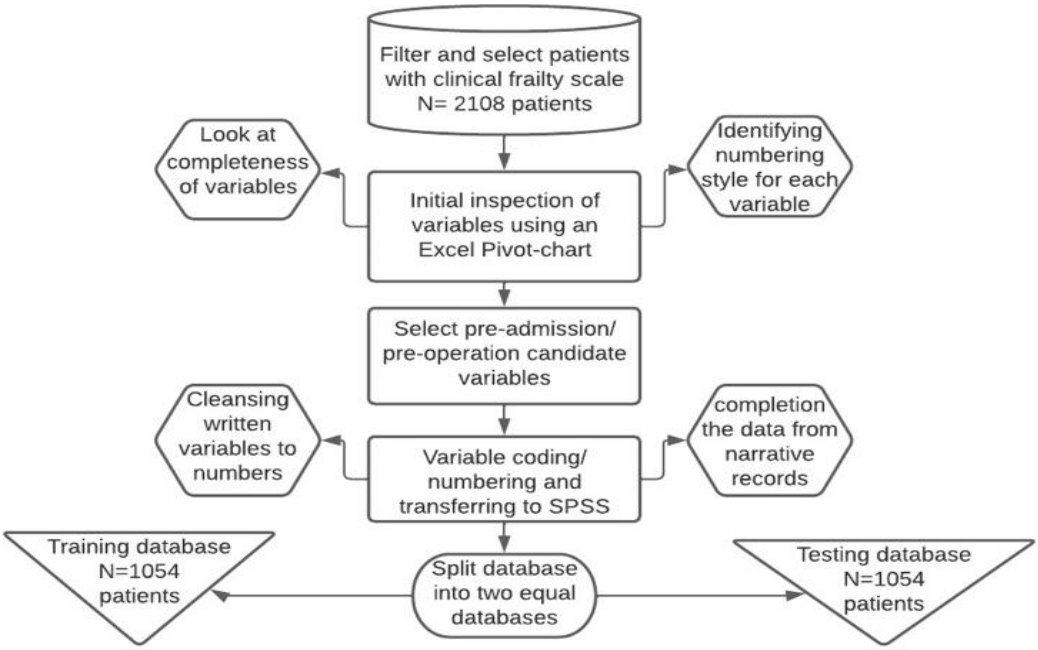


Figure 3- 5: Flow chart showing the processes of splitting the whole CFS dataset.

3.2.7.1 Splitting the CFS database.

In predictive modelling, the percentage of datasets split into training and testing data sets varies. Common percentage splits for modelling are (training: 80%, testing: 20%), (training: 67%, testing: 33%), and (training: 50%, testing 50%). For large datasets, it is suggested to use the optimal feasible splitting with consideration of the included parameters to minimise larger variance, and the proportion of remaining data must be sufficient to generate a valid model (173). Therefore, the uneven dividing of the dataset may introduce bias in this model since CFS is a scale variable and other splitting

percentages may arbitrarily choose the most frail individuals in the training dataset compared to the testing dataset, resulting in inaccurate mathematical conclusions. Consequently, 50% training and 50% testing were used for this model (see Figure 3-6). Furthermore, the splitting of datasets was quasi-randomly performed based on the sequence of odd and even case numbers to ensure datasets are representative of the original dataset and not subject to changes in case mix or standards of care over time. Cases were selected at random from the database in the order in which they were presented, with no data filtering or grouping performed to eliminate selection bias. The odd (training) dataset was used to generate the machine-learning model, while the even (testing) dataset was used to assess the fit of the model.

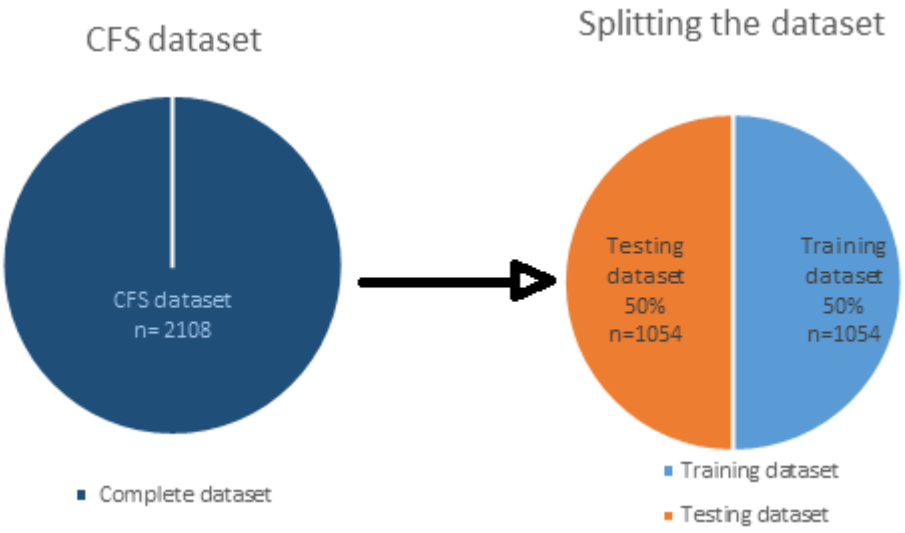


Figure 3- 6: Pie chart illustrating the splitting of the CFS data set.

3.2.7.2 Development

Multiple regression analysis is an extension of linear regression that predicts the value of a variable based on the values of two or more other variables (174). Multiple regression is used to determine the model's overall fit and the proportional contribution of each predictor to the total variance explained (175). Normality of the dependent

variable is one of the most important requirements for a viable multiple regression model. The CFS was the dependent variable or outcome, and it had previously shown a normal distribution throughout the full CFS data set (see Section 3.2.2.2). To check that the CFS was likewise normally distributed in the training dataset, a second normality test was performed to guarantee that the dataset met the requirements for multiple regression analysis (see Figures 3-7 and 3-8).

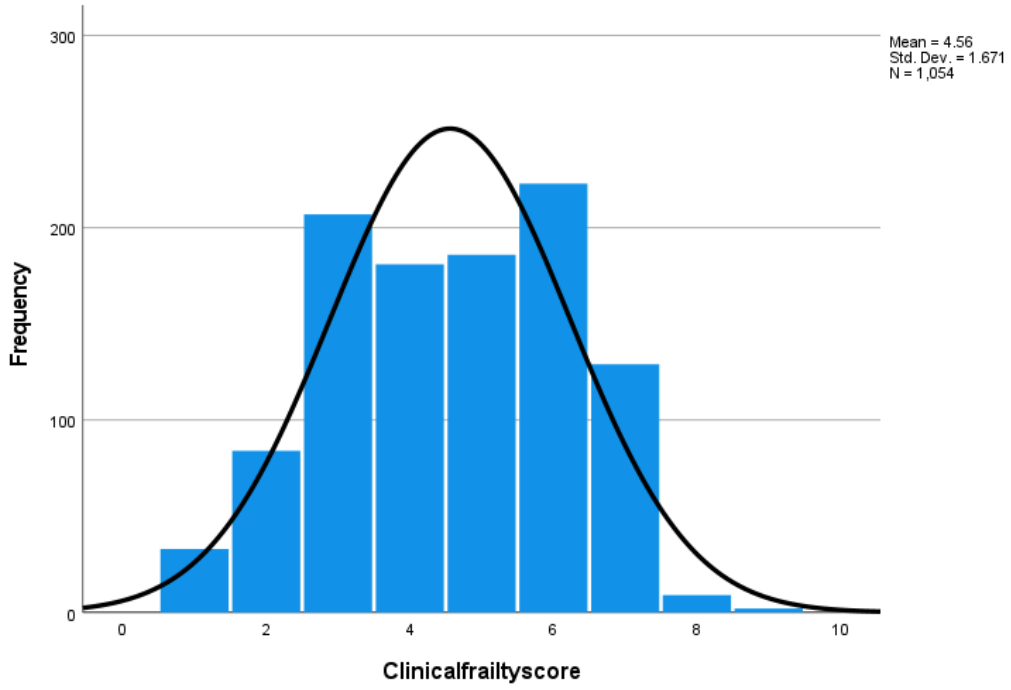


Figure 3- 7: histogram to graph the distribution of CFS in the training dataset.

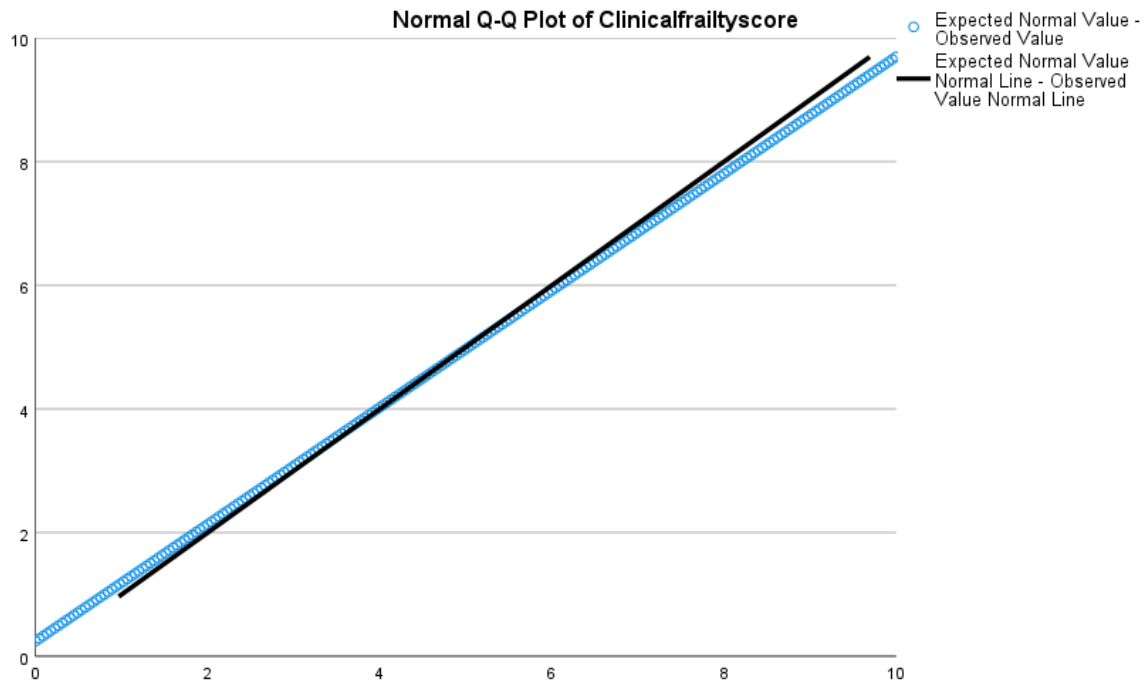


Figure 3- 8: Q-Q plots to graph the distribution of CFS in the training dataset.

After establishing the data's appropriateness for multiple regression analysis, the second step was to determine the relevant predictors by visual inspection. In the training sample, the relationship between the CFS and the candidate variables was initially examined by visually examining the data using bar charts, and scatter plots. Variables showing no obvious relationship to the CFS were excluded from further analysis. Depending on the variable type, descriptive analysis and graphing were performed on each variable in the training dataset. Scatterplots and histograms were used to visualise continuous variables. Box-whiskers plots, pie charts, and histograms were used to depict categorical data for binary and ordinal variables (see Table 3-3).

Categorical variables	Continuous variables
• Diabetes • Gender • Alcohol Excess • Mechanism of Injury • Glomerular filtration rate(GFR) • Hypertension • Alzheimer • Atrial Fibrillation • Osteoporosis • Dementia • Pre-admission mobility • Malignancy • Visual Acuity • Residential home resident • Living alone • Nursing home resident	• Age • Abbreviated Mental Test • Lactate • Potassium level (K) • Calcium level (Ca) • Platelet count (Plt) • Haemoglobin level (Hb) • Urea (U) • Sodium level (Na) • White cell count (WCC) • Creatinine level

Table 3- 3: Included variables based on the types of values.

Missing values were discretized to assess the completeness of each variable. In order to visualise numerical data, the mean, median, mode, range, and interquartile percentiles were computed, as well as box-whiskers plots. To prevent overfitting the model, variables with abnormalities of less than 10% and no apparent connection with CFS were eliminated. For variables with binary or multiple groups, box and whiskers graphs were utilised to visualise the groups' medians and distribution versus CFS. Biological continuous variables were dichotomised depending on their normalcy in order to be compared in box-whiskers graphs.

A univariate analysis was conducted on the remaining variables. Pearson's correlation and independent t-test were used as univariate analyses to demonstrate the existence of a linear connection between the variables with CFS before multiple regression.

Pearson's correlation coefficient (r) was used to examine continuous data, whereas the independent t-test was used for categorical (binary) variables.

Subsequently, a multiple linear regression analysis was conducted, including candidate variables that had a significant ($p<0.05$) univariate relationship with the CFS. Additionally, continuous variables were included if they showed a good correlation (r >0.2), while binary variables were included if they had good effects (Cohen's d >0.2).

3.2.7.3 Verification

The final findings of the multiple regression analysis were utilised to create an equation for the Nottingham Trauma Frailty Index (NTFI), as well as verification tests for homoscedasticity and multi-collinearity. Homoscedasticity was examined (to determine if the variance of the residual, or error term in a regression model, is constant) using a scatterplot of the predicted values and residuals. Multi-collinearity, which occurs when independent variables in a regression model have significant correlations with one another, was also evaluated by examining variable inflation factors (VIF) in the collinearity statistics.

3.2.7.4 Validation

The regression model obtained from the training cohort was then evaluated in the testing cohort. This was carried out by comparing the scores produced by the multiple regression model (the Nottingham Trauma Frailty Index NTFI) with the CFS scores using Bland-Altman plots and analysis (176). The normality of the difference between the NTFI and the CFS was assessed using a Gaussian histogram, as required for Bland-Altman plots. Then, a one-sample t-test was conducted to see whether there

was a statistically significant difference between zero and the mean difference observed between the two instruments. A scatter plot was then generated, with the X-axis representing the average of the two measurements and the Y-axis representing the discrepancy between the paired measurements (176). Additional validations were conducted, including a linear regression analysis to assess the existence of proportional bias and determine the amount of agreement between the model's difference and the mean. Furthermore, box-whisker plots, scatter plots, and linear regression plots were executed to visually validate the effectiveness of the NTFI.

3.3 Results

3.3.1 Results after visual inspection and data completeness

Following the visual inspection of the distributions, 14/27 variables had no evident connection with CFS and were thus not investigated. Two variables (lactate and calcium level) were previously excluded from the analysis due to >20% missing data. Six variables with abnormalities of less than 10% and no obvious link to CFS were eliminated: alcohol use, osteoporosis, Alzheimer's disease, potassium level, platelet count, and visual acuity (see Table 3-4).

Variable			Frequency	Percent
Osteoporosis	No		987	93.6
	Yes		67	6.4
		Total	1054	100.0
Alcohol Excess	No		1002	95.1
	Yes		52	4.9
		Total	1054	100.0

Alzheimer		No		1018	96.6
		Yes		36	3.4
			Total	1054	100.0
Visual Acuity		Abnormal		95	9.0
		Normal		959	91.0
			Total	1054	100.0
Potassium level		Normal		849	80.6
		Abnormal		81	7.7
			Total	930	88.2
	Missing		System	124	11.8
			Total	1054	100.0
Platelets count		Normal		930	88.2
		Abnormal		69	6.5
			Total	999	94.8
	Missing		System	55	5.2
			Total	1054	100.0

Table 3- 4: Excluded variables after visual inspection for abnormal cases on the training dataset

Furthermore, six binary and classified continuous variables were visualised in box-whiskers graphs and eliminated because they did not provide a significant difference in the distributions and medians of CFS across groups: hypertension, diabetes, living alone, sodium, creatinine, and white cell count. Table (3-5) and Figure (3-9) illustrate the eliminated variables after visualising the cases using box-whiskers graphs in connection to CFS.

	Variable	Cases	Valid	
			N	Percent
Clinical frailty scale	**Hypertension**	No	472	100.0%
		Yes	582	100.0%
	Diabetes	No	867	100.0%
		Yes	187	100.0%
	Sodium level	Abnormal	398	100.0%
		Normal	602	100.0%
	Living alone	No	754	100.0%
		Yes	300	100.0%
	White cell count	normal	463	100.0%
		abnormal	539	100.0%
	Creatinine	normal	487	100.0%
		abnormal	502	100.0%

Table 3- 5: Cases of excluded variables using Box-Whiskers graphs on the training dataset.

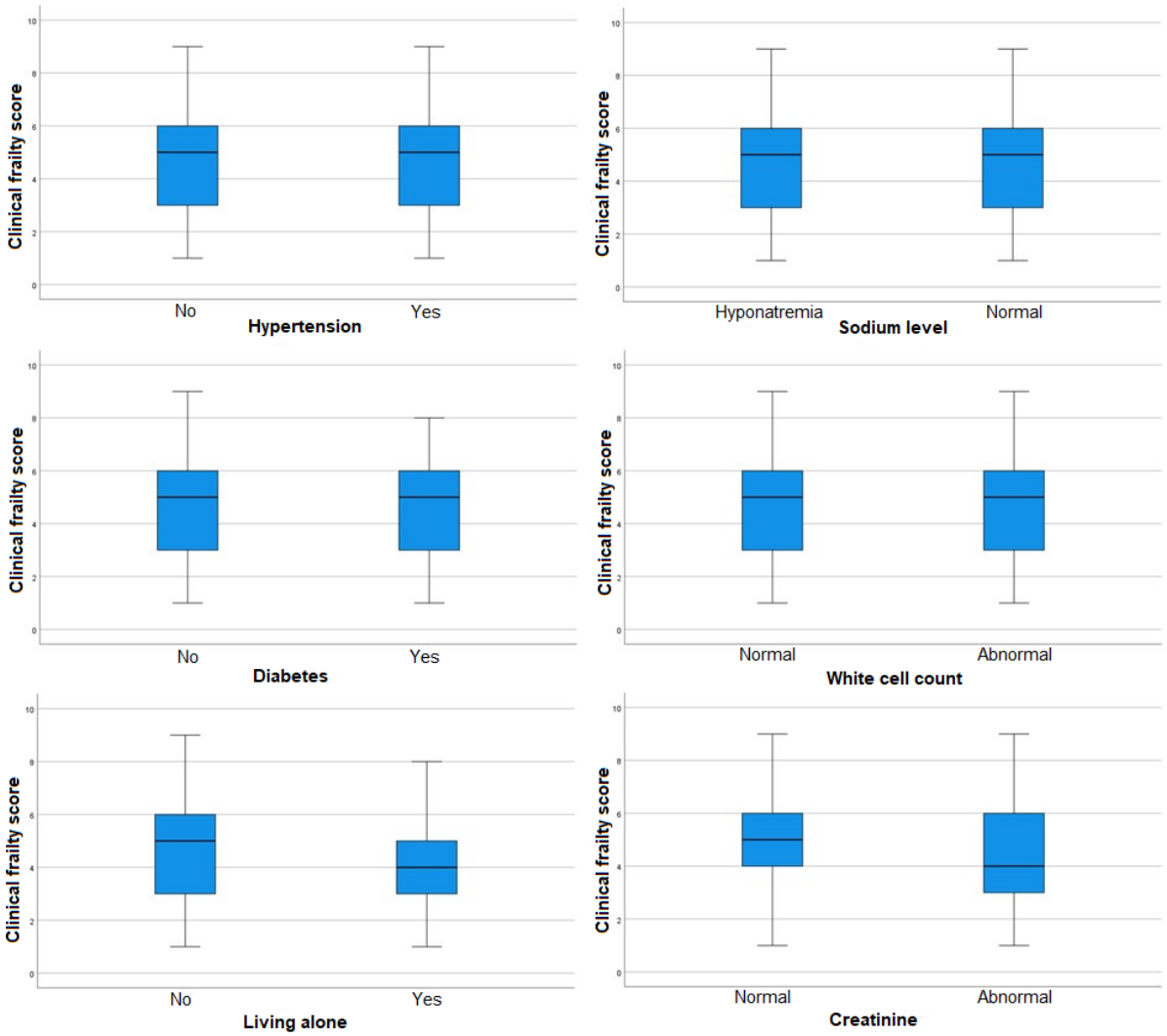


Figure 3- 9: A collection of box-whiskers graphs for excluded variables.

Consequently, univariate analyses were conducted on the remaining 13 variables (age, gender, pre-admission mobility, mechanism of injury, urea (U), abbreviated mental test (AMT), haemoglobin (Hb), glomerular filtration rate (GFR), atrial fibrillation, dementia, residential care home resident, nursing home resident, malignancy) that were eligible for univariate analysis (see Table 3-6).

Variable	Categories		N	%
Gender	Female		308	29.2%
	Male		746	70.8%
		Total	1054	100%
Pre-admission mobility	Needs assistance		665	63.1
	Freely mobile		325	30.8
		Total	990	93.9%
Mechanism of Injury	Falls from standing height		988	93.7%
	Others		65	6.2%
		Total	1053	99.9
Age		Total	1054	100%
Urea (U)		Total	988	93.7%
AMT		Total	998	94.6%
Haemoglobin (Hb)		Total	1012	96%
Glomerular filtration rate (GFR)		Total	942	89.4%
Atrial Fibrillation		Yes	194	18.4%
		No	860	81.6%
Dementia		Yes	290	27.5%
		No	764	72.5%
Residential home resident		Yes	180	17.1%
		No	874	82.9%
Nursing home resident		Yes	100	9.5%
		No	954	90.5%
Malignancy		Yes	207	19.6%
		No	847	80.4%

Table 3- 6: Eligible variables for univariate analysis using the training dataset

3.3.2 Results after univariate analysis of eligible variables with CFS

The eligible 13 variables for univariate analysis were each further assessed based on variable type. A description of the characteristics of patients in the training and testing (validation) groups is provided in (Table 3-7).

Characteristic	Training Group	Testing Group
Number of cases	1054	1054
Age [mean (range)], years	83.58 (65 to105)	83.60 (65 to105)
CFS (mean, SD)	4.56 (1.671)	4.56 (1.686)
AMT [Median (IQR)]	8 (5)	8 (6)
Haemoglobin [Median (IQR)], g/L	123 [111-134]	122 [112-133]
Urea [Median (IQR)], mmol/L	7.1 [5.5-9.2]	6.8 [5.6-8.9]
Pre-admission mobility assistance (n, %)	665 (63.1)	673 (60.4)
MOI: Falls from standing height (n, %)	988 (93.7)	990 (93.9)
Female sex (n, %)	746 (70.8)	743 (70.5)
Atrial fibrillation (n, %)	194 (18.4)	234 (22.2)
Dementia (n, %)	290 (27.5)	286 (27.1)
Residential home resident (n, %)	180 (17.1)	200 (19)
Nursing home resident (n, %)	100 (9.5)	109 (10.3)
Malignancy (n, %)	207 (19.6)	196 (18.6)
Glomerular filtration rate [Median (IQR)], ml/min	71 [51-85]	71 [54-85]

SD, standard deviation; CFS, clinical frailty scale; MOI, mechanism of injury; IQR, interquartile range

Table 3- 7: Characteristics of patients in the training and testing groups

The independent t-test was used for binary variables such as gender, mechanism of injury, atrial fibrillation, dementia, living in a nursing home, malignancy, pre-admission mobility, and residential home residents (Table 3-8). The results were statistically significant with (Cohen's d >0.2), except for the malignancy variable, where the effect size was Cohen's d = -0.17. Thus, malignancy was eliminated as a possible variable suited for multiple regression.

	Yes		NO		t-test	Cohen's *d*	P value (two-tailed)
	M	SD	M	SD			
Female sex	4.69	1.65	4.25	1.69	3.91	0.27	<0.001
Atrial fibrillation	4.89	1.526	4.49	1.695	-3.018	-0.24	0.003
Dementia	5.90	1.508	4.05	1.508	-18.487	-1.28	<0.001
Malignancy	4.79	1.533	4.50	1.700	-2.228	-0.17	0.026
Residential home resident	6.14	1.204	4.24	1.566	-15.391	-1.26	<0.001
Nursing home resident	6.15	1.226	4.39	1.624	-10.500	-1.10	<0.001
Falls from standing height	4.63	1.639	3.54	1.821	-4.690	-0.66	<0.001
Pre-admission mobility assistance	4.94	1.493	3.51	1.701	-13.115	-0.92	<0.001

*. Dependant variable: Clinical frailty scale. M=mean, SD= standard deviation.

Table 3- 8: The independent samples t-test results for eligible categorical (binary) variables

For continuous variables including age, urea, haemoglobin, AMT, and GFR, Pearson's correlation coefficient (r) was used to determine the relationships with CFS (Table 3-9). AMT ($r = -0.585$, $p < 0.001$), haemoglobin level ($r = -0.253$, $p < 0.001$), and GFR ($r = -0.208$, $p < 0.001$) had significant negative correlations with CFS, showing that a rise in CFS is related to a drop in those measures. Two variables, urea ($r = 0.106$, $p < 0.001$) and age ($r = 0.346$, $p < 0.001$), showed significant positive associations with CFS, indicating that a rise in CFS is connected with an increase in urea and age (see Table 3-9). However, urea was eliminated at this stage due to its very low correlation (<0.2) with CFS (177). Thus, the remaining variables (age, gender, pre-admission mobility, mechanism of injury, AMT, Hb, eGFR, atrial fibrillation, dementia, residential home resident, and nursing home resident) were eligible for multiple regression analysis.

Independent Variables	Pearson Correlation (r)	95% Confidence interval	Relationship‡	Sig. (2-tailed)	Direction of Relationship
Age, years	0.35†	[0.30, 0.40]	Moderate	<.001	Positive
Urea, mmol/L	0.11†	[0.04, 0.17]	Weak	<.001	Positive
Haemoglobin, g/L	- 0.25†	[-0.31, -0.19]	Moderate	<.001	Negative
GFR, ml/min	- 0.21†	[-0.27, -0.15]	Moderate	<.001	Negative
AMT (0-10)	- 0.59†	[-0.62, -0.54]	Strong	<.001	Negative

*Dependant variable: Clinical Frailty Scale.
†Correlation is significant at the 0.01 level (two-tailed).
‡ Weak: 0.01 to 0.20; moderate: 0.20 to 0.50; strong: 0.50 or larger.
AMT, Abbreviated Mental Test; GFR, glomerular filtration rate.

Table 3- 9: Pearson correlation for eligible continuous variables

3.3.3 Results after multiple regression analysis

In the training sample, there were **926** complete records available for regression analysis, whereas the testing sample had **948**. After cleansing, screening, visualising, and identifying associations in the suitable univariate predicators, the predictive model was constructed. Four variables (atrial fibrillation, dementia, residential home resident, and nursing home resident) were eliminated from the model because the overall regression coefficient constant (Beta) and individual coefficients were insignificant (P>0.05). Two additional variables, eGFR and gender, had significant overall model coefficients, but their individual coefficients were non-significant (see Table 3-10). Five variables remained significant for inclusion in the model: age, AMT, haemoglobin, MOI, and pre-admission mobility (Table 3-11).

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	6.360	.759		8.375	<.001
	Age	.020	.006	.092	3.311	<.001
	MOI	.455	.207	.054	2.195	.028
	Haemoglobin	-.011	.002	-.110	-4.258	<.001
	AMT	-.229	.012	-.492	-19.322	<.001
	Pre-admission mobility	-1.147	.090	-.321	-12.677	<.001
	eGFR	-.002	.002	-.024	-.872	.384
	Gender	.134	.092	.036	1.456	.146

a. Dependent Variable: Clinical frailty scale

Table 3- 10: multiple regression analysis for eligible variables

Multiple regression analysis was conducted and demonstrated a statistically significant ($p<0.05$) relationship between: age, MOI, pre-admission mobility, haemoglobin, and AMT (see Figure 3-10). A significant regression equation was found ($F(5,920) = 176.739$, $p<0.001$). The regression coefficient [B= 6.383, 95% CI (5.028, 7.740) P<0.001], with $R^2= 0.490$, suggests that the given variables explain 49% of the variance (Table 3-11). The predicted frailty score is equal to 6.383 + 0.021 (Age) - 1.100 (pre-admission mobility) + 0.445 (MOI) - 0.234 (AMT) - 0.011 (haemoglobin), where age included only patients 65 years and older, pre-admission mobility is coded as 1 = Needs assistance, 2 = Freely mobile without aids, MOI is coded as 1 = other, 2 = Falls from standing height, haemoglobin is measured in g/L, and AMT is a 10-point scale.

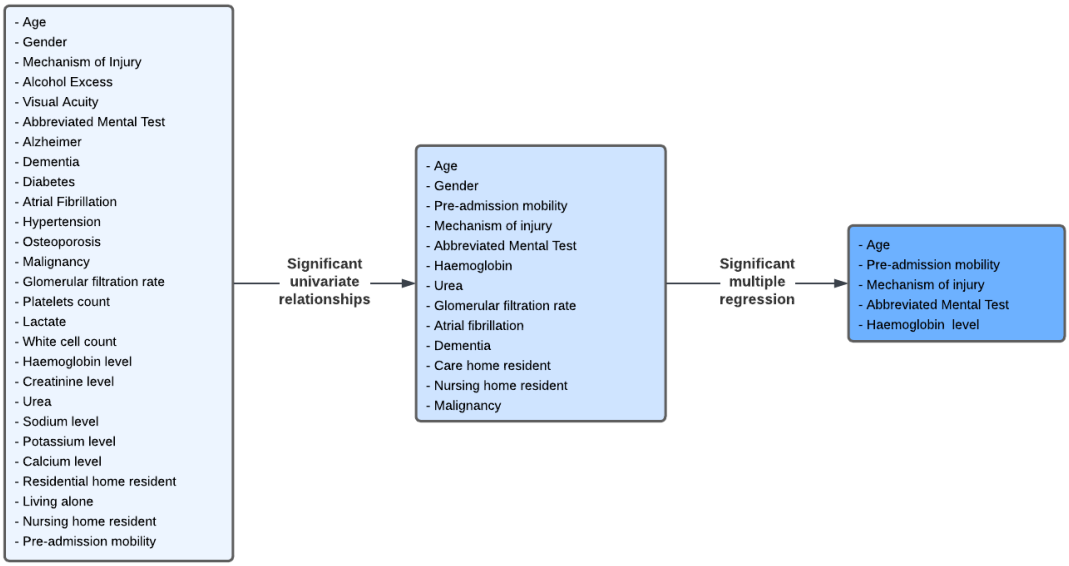


Figure 3- 10: Variables selection processes

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.700[a]	.490	.487	1.193

Predictors: (Constant), HB, MOI, AMT, Pre-admission-mobility, Age

ANOVA [a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1256.912	5	251.382	176.739	<.001[b]
	Residual	1308.553	920	1.422		
	Total	2565.465	925			

a. Dependent Variable: Clinical frailty scale

b. Predictors: (Constant), HB, MOI, AMT, Pre-admission-mobility, Age

Coefficients [a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.	95.0% Confidence Interval for B Lower Bound	95.0% Confidence Interval for B Upper Bound	Collinearity Statistics Tolerance	Collinearity Statistics VIF
1	(Constant)	6.383	.691		9.233	<.001	5.026	7.740		
	AMT	-.234	.011	-.501	-20.418	<.001	-.257	-.212	.919	1.088
	Hb	-.011	.002	-.119	-4.919	<.001	-.016	-.007	.953	1.050
	Age	.021	.005	.102	4.056	<.001	.011	.032	.885	1.130
	MOI	.445	.204	.052	2.187	.029	.046	.845	.991	1.009
	Pre-admission mobility	-1.100	.087	-.309	-12.640	<.001	-1.270	-.929	.927	1.079

a. Dependent Variable: Clinical frailty scale

Table 3- 11: The final significant predictors following multiple regression analysis using training dataset

3.3.3.1 Age

On the univariate analysis, age was significantly associated with CFS ($r = 0.346$, $p < 0.001$), testing age as a continuous variable. In addition, age was a significant predictor in the multiple regression analysis, with an unstandardized coefficient equal to 0.021, 95% CI (0.011, 0.032), $p < 0.001$, indicating that for each increase in age, the predicted frailty increases by 0.021. It is apparent that this variable has a low effect on the entire model, but it may be considered a continuous variable. If age was dichotomised into groups, the impact is expected to be greater in certain age groups, particularly the oldest persons (+80 years old), since the distribution of age was greater in the oldest groups (see Figure 3-11). However, the linear relationship between age and CFS underlines the importance of age in measuring overall frailty. Therefore, chronological age seems to be an essential factor in identifying the degree of frailty in patients with major trauma.

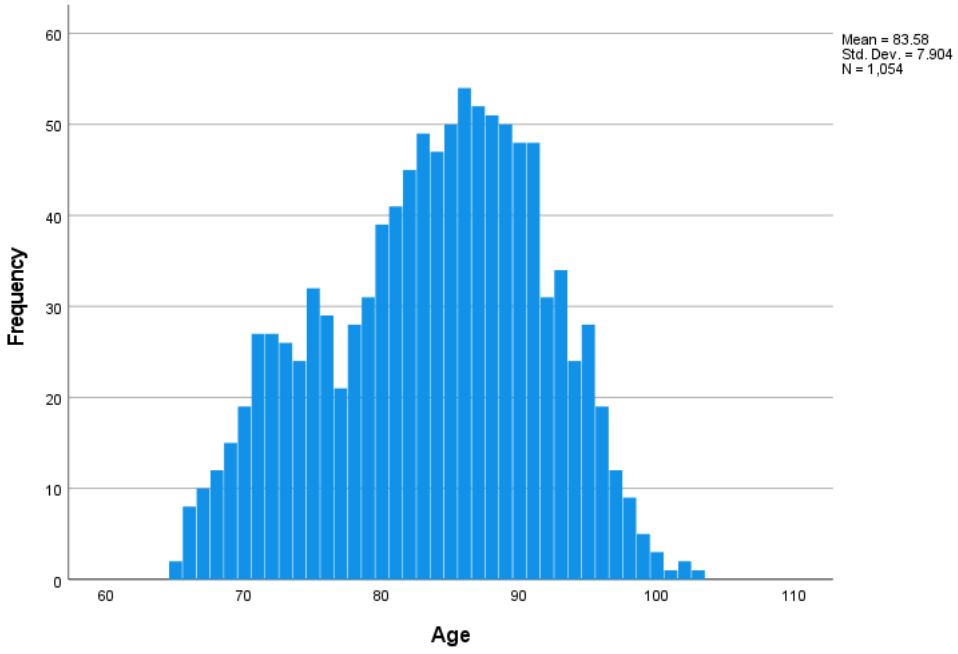


Figure 3- 11: Age distribution on the training dataset

3.3.3.2 Pre-admission mobility status

Mobility status has a crucial role in assessing frailty in older people, especially when using the CFS tool. The definition of pre-admission mobility status was determined by the presence or absence of mobility aids. Patients who need assistance from aids or a frame have a greater likelihood of becoming frail. Pre-admission mobility had the greatest effect on the model, with an unstandardised coefficient of -1.100, 95% CI (-1.270, -0.929), p <0.001. This demonstrates that pre-admission mobility status is a crucial determinant in identifying frailty in older trauma patients.

3.3.3.3 Mechanism of injury

Falls from standing height have been associated with poor outcomes among trauma patients over 65 years old (38, 44, 178-180). Nearly 94% of patients in this variable

had falls from standing height as their MOI, whereas only 6% had falls from height, road traffic accidents, no MOI, or others (see Table 3-12). This has resulted in the reclassification of this variable as a binary variable with two categories: falls from standing height or others. Falls from standing height were a significant predictor of frailty, with an unstandardized coefficient of 0.445, 95% CI (0.046, 0.845), *p* =0.029, demonstrating that the risk of falling from standing height increased with the frailty of older people. Therefore, robust older individuals who fall from standing height are likely to sustain no injuries, and frailty may be the leading cause of adverse outcomes in this age group.

MOI

	Frequency	Percent	Valid Percent	Cumulative Percent
5. Other	12	1.1	1.1	1.1
4. No injury	14	1.3	1.3	2.4
3. RTC	12	1.1	1.1	3.5
2. Fall from height	28	2.7	2.7	6.2
1. Fall from standing height	988	93.8	93.8	100.0
Total	1054	100.0	100.0	

Table 3- 12: MOI distribution on the training dataset

3.3.3.4 Abbreviated mental test (AMT)

The abbreviated mental test (AMT) was developed by Hodkinson in 1972 in order to assess memory and orientation in older people (181). The test now widely used to assess cognition on hospital admission. The Nottingham Hip Fracture Score identified AMT as a significant predictor of morbidity and mortality in fractures of the neck of the femur (128). In addition, AMT was an important factor in the overall frailty model, with

an unstandardized coefficient of -0.234, 95% CI (-0.257, -0.212) p <0.001, indicating that for each one-point decrease in AMT, the predicted frailty increases. Additionally, this test may be considered a reliable measure of pre-existing cognitive impairment, a condition that is often overlooked by current assessment methods, or the frailty response per se, including the onset of delirium, or both.

3.3.3.5 Haemoglobin level

Anaemia and frailty are both prevalent in geriatric people and have been related to similar negative health outcomes (182). Numerous studies have emphasised the need to assess frailty in older anaemic patients in order to determine the possible adverse consequences related to the co-occurrence of both conditions (183-186). There is no contemporary evidence to describe the association between haemoglobin and frailty in major trauma in older patients. By this model, the identified relationship between frailty and anaemia in older trauma patients would help to highlight the importance of haemoglobin levels in frail older trauma patients. On the univariate analysis, haemoglobin has shown a significant relationship with CFS ($r = -0.253$, $p < 0.001$). Additionally, haemoglobin was a significant measure in the multiple regression analysis, with an unstandardized coefficient equal to -0.011, 95% CI (-0.016, -0.007), $p < 0.001$, indicating that for each one-point decrease in haemoglobin, the predicted frailty increases. The fact that haemoglobin was the sole significant biological variable in the model demonstrates the importance of biological variables in diagnosing frailty. This association may have originated from a pre-injury multi-organ impairment, a post-injury response to the challenge, or both, requiring more research. However, this model demonstrated a significant association between low haemoglobin concentration and an increase in the predicted frailty, indicating that severe cases with high

haemoglobin (polycythaemia) cannot be diagnosed properly using this model. However, no instances exceeded +185 g/L in the dataset, and the majority of cases were less than 160 g/L, indicating that polycythaemia may not be a prevalent condition in this population (see Figure 3-12).

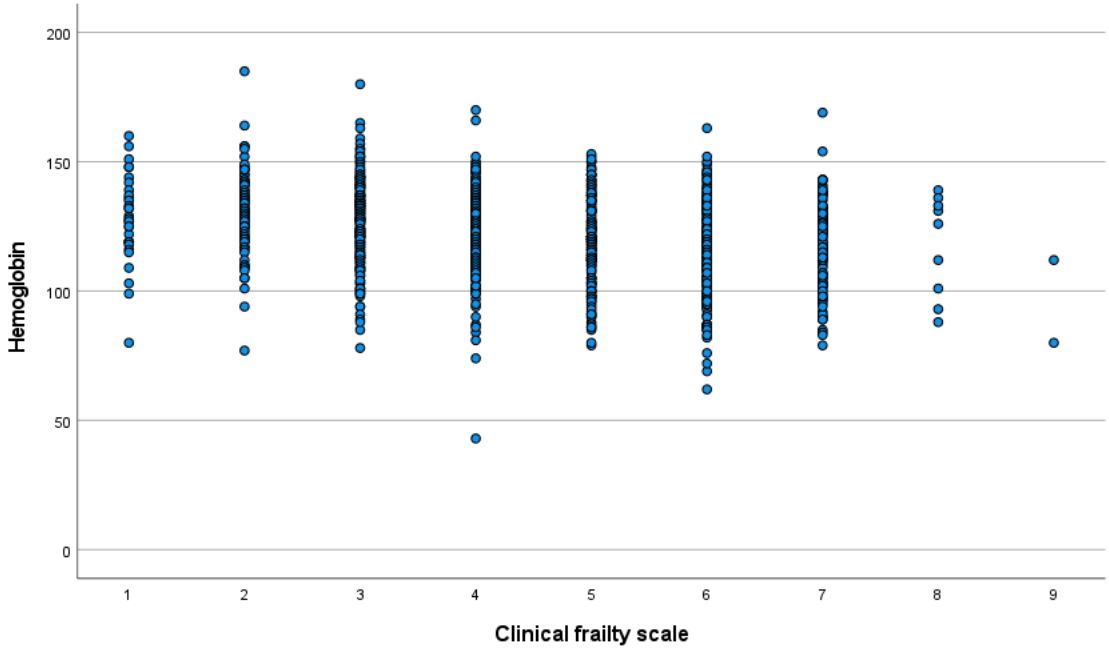


Figure 3- 12: A scatterplots of haemoglobin level versus CFS on the training dataset

3.3.3.6 Excluded variables after the multiple regression analysis.

Two variables were found to be significant in univariate analysis, but their significance was lost when multiple regression analysis was applied. Despite the fact that these variables (eGFR and gender) were excluded from the overall regression, a number of important aspects regarding their relationship to frailty and the major trauma population could be considered.

3.3.3.6.1 Glomerular filtration rate (eGFR).

GFR is one of the most practical laboratory tests for detecting renal function and diagnosing kidney disease in its most curable early stages (187). Numerous studies have shown a correlation between frailty and renal function decline (188-190). Numerous studies have also indicated that decreased renal function, as measured by GFR, is related to morbidity and death in older adults (191), as well as the incidence of frailty (192). However, no studies were identified that examined the relationship between a low GFR and frailty in individuals with major trauma. Throughout the development of this model, the univariate analysis revealed a strong association between GFR and CFS ($r = -0.208$, $p < 0.001$), demonstrating the significance of the relationship between the two variables. The below bar graph shows the importance of this variable in older trauma patients with frailty, which may require further investigation (see figure 3-13).

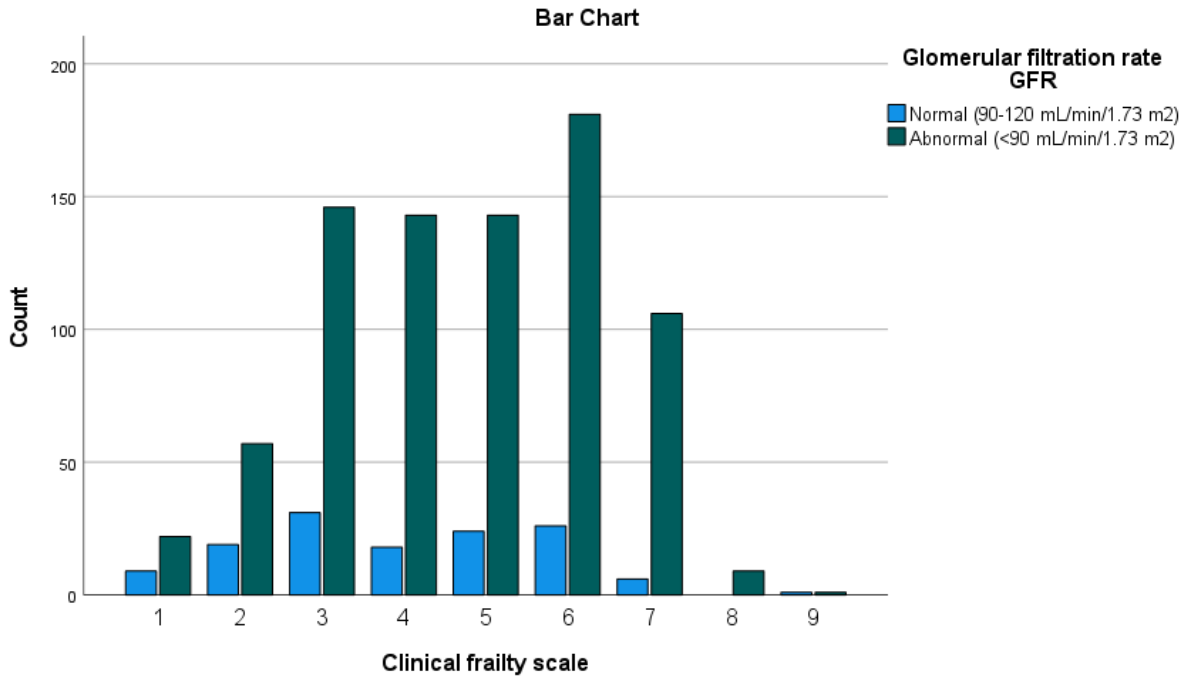


Figure 3- 13: Normal vs abnormal glomerular filtration rate (GFR) association with frailty on the training dataset

3.3.3.6.2 Gender

Numerous studies (193-195) have investigated the influence of gender on outcomes after major trauma, but none have targeted frailty or older individuals. In the dataset, the mean age of the patients was 83 years (SD 7.9), and 746 (70.8%) of the patients were female. On the univariate analysis, gender was shown to have a significant difference with CFS: *t* (561.100) = - 3.909, *p* <0.001, with a mean CFS of 4.69 in female patients and 4.25 in male patients, showing that females were more frail (see Table 3-13). However, it is important to note that the sample size consisted of 70% females. The modest difference seen between the means of CFS and gender does not primarily suggest a higher frailty level associated with females compared to males. This finding might be attributed to the fact that the included patients were mostly female, which influenced the comparison. In the multiple regression analysis, however, gender was not a significant factor, with unstandardised coefficients of 0.134, p = 0.146.

	Gender	N	Mean	Std. Deviation	Std. Error Mean
Clinical frailty scale	Male	308	4.25	1.687	.096
	Female	746	4.69	1.649	.060

Table 3- 13: Gender group statistics versus frailty

3.3.4 Model specification

3.3.4.1 The computed formula from the model

This prediction model was named the Nottingham Trauma Frailty Index (NTFI). The regression equation (F (5,920) = 176.74, p < 0.001, regression coefficient B = 6.383,

(95% CI 5.028 to 7.740); $p < 0.001$, R2 = 0.49) was utilised to construct a projected frailty score (NTFI) using the following equation:

NTFI = 6.383 + 0.021 (Age) - 1.100 (pre-admission mobility) + 0.445 (MOI) - 0.234 (Abbreviated mental Test) - 0.011 (Haemoglobin)

The criteria for each variable in this model require specific numerical inputs (see Table 3-14).

Variable	Values	Type
Age	65 and over	Continuous
Abbreviated mental Test (AMT)	0 -10	Continuous
Haemoglobin (Hb)	g/L	Continuous
Pre-admission mobility	1- Needs assistance 2- Freely mobile without aids	Binary
Mechanism of injury (MOI)	1- Other mechanism of injuries 2- Falls from standing height	Binary

Table 3- 14: Statistical requirements for the NTFI equation

3.3.4 Model Verification

Verification of a model is the process of confirming that it is implemented correctly in relation to the conceptual model and complies with the required specifications and assumptions for the intended application purpose (196). Providing the steps for creating this model was essential for proving the model's verification and structural integrity. The regression coefficient of the multiple regression [B= 6.383, 95% CI (5.028, 7.740) $P<0.001$], with $R^2 = 0.490$, indicates that the given variables explain 49% of the variance. However, a high R^2 value does not imply that the model fits the data well, highlighting the necessity for model verification and validation in order to offer accurate answers to the clinical questions being investigated (197). In addition, a successful predictive model should not only have the needed goodness of fit and be statistically significant, but it should also produce residuals that meet certain conditions

(198). Therefore, model verification was conducted to verify the performance of the predictive model by analysing the generated residuals. There are several methods for verifying a model, including statistical tests and structured walk-throughs (199). Both were utilised to verify the model and the obtained residuals. The below circle map represents the model's overall verification and validation processes (see Figure 3-14).

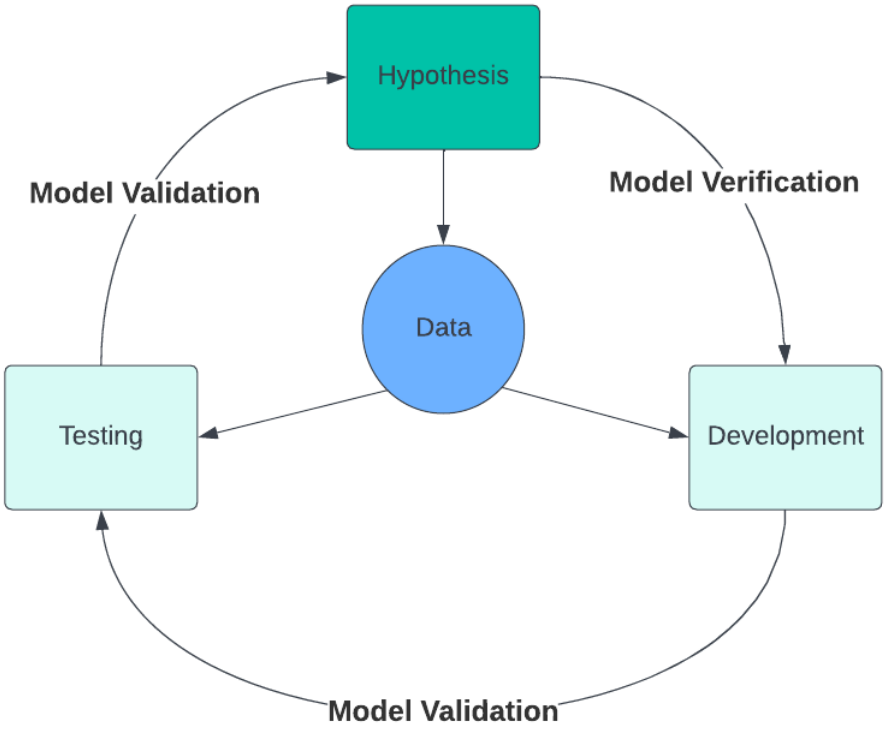


Figure 3- 14: Circular diagram illustrating model verification and validation

3.3.4.1 Check for homoscedasticity

Homoscedastic is a term that refers to the circumstance in which the variance of the residual, or error term, in a regression model is constant, meaning that the error term varies only slightly as the value of the predictor variable varies (200). Alternately, the variance of the data points is approximately the same for all data points. A scatterplot was used to test the homoscedasticity assumption by plotting the predicted values and

residuals (see Figure 3-15). As seen in the graph, the assumption of homoscedasticity was met, as the scatter plot took a (approximately) rectangular shape and scores were concentrated in the centre (around 0) and scattered in a rectangular pattern (201). This verifies that the residuals (the difference between the actual and predicted dependent variables DV scores) and variance of the residuals are identical for all predicted scores (homoscedasticity).

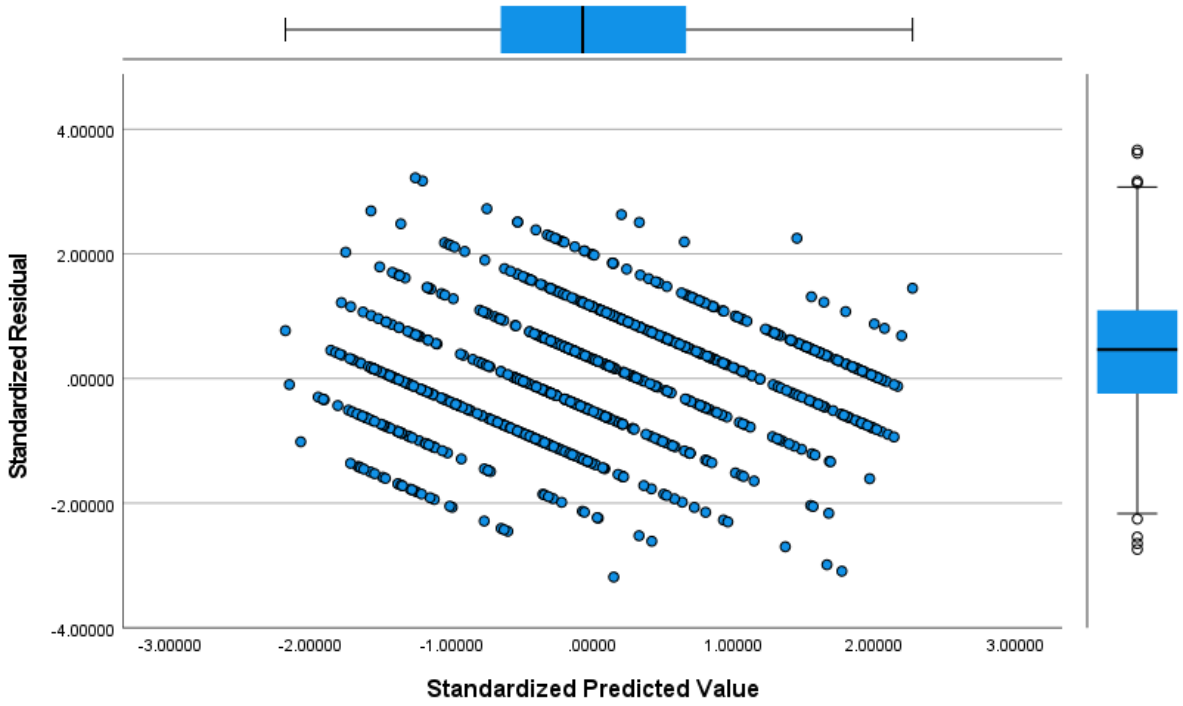


Figure 3- 15: Scatterplots of standardised predicted values versus standardised residual values for homoscedasticity

Additionally, a quantile-quantile (Q-Q) plot of the model's standardised residuals was performed to visually evaluate the model's homoscedasticity and normality assumptions. The standardised residuals from the multiple regression were then calculated and displayed using Q-Q plots, which indicated the homoscedasticity and the normal distribution of standardised residuals (see Figure 3-16).

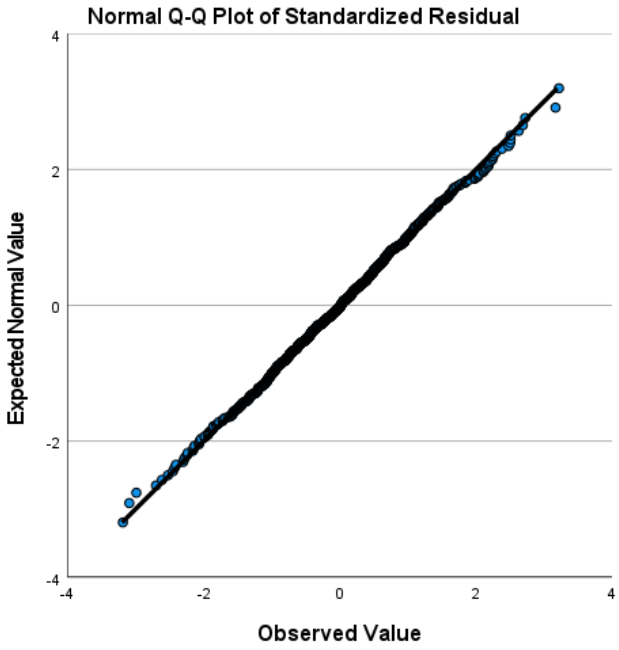


Figure 3- 16: Q-Q plots of standardised residuals of the model

3.3.4.2 Check for multi-collinearity

Multi-collinearity is the condition in which two or more independent variables in a regression model are substantially associated with one another (202). In a regression model, this means that one independent variable may be predicted by another independent variable. This was not the case in this model, as each variable represents a distinct clinical aspect. In addition to this, multi-collinearity was detected by analysing variable inflation factors (VIF) in collinearity statistics results (see Table 3-15). When the VIF is greater than 4 or the tolerance is less than 0.25, multi-collinearity may occur and requires additional examination; when the VIF is greater than 10 or the tolerance is less than 0.1, there is considerable multi-collinearity that must be rectified (203). However, as highlighted in the collinearity statistics columns in Table 3-15, multi-

collinearity was not present, as demonstrated by the table's results. This means that the model's independent variables are not correlated with one another.

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B		Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound	Tolerance	VIF
1	(Constant)	6.383	.691		9.233	<.001	5.026	7.740		
	AMT	-.234	.011	-.501	-20.418	<.001	-.257	-.212	.919	1.088
	Hb	-.011	.002	-.119	-4.919	<.001	-.016	-.007	.953	1.050
	Age	.021	.005	.102	4.056	<.001	.011	.032	.885	1.130
	MOI	.445	.204	.052	2.187	.029	.046	.845	.991	1.009
	Pre-admission mobility	-1.100	.087	-.309	-12.640	<.001	-1.270	-.929	.927	1.079

a. Dependent Variable: Clinical frailty scale

Table 3- 15: Testing for multi-collinearity

3.3.5 Model validation

Model verification and model validation procedures were defined similarly in the literature for multiple regression, causing the two topics to overlap. In this model, verification processes were undertaken on the training dataset, and validation was attributed to the use of the testing dataset in validation tests. However, there are three methods for assessing the validity of regression models: (1) comparison of model predictions and coefficients with the clinical theory; (2) collection of new data to verify model predictions; and (3) data splitting, in which a portion of the available data is reserved to obtain an independent measure of the model's prediction accuracy (204-206).

Checking the model predictions and coefficients

The purpose of comparing predictions with coefficients is to examine the effectiveness of the generated model in predicting the outcome of interest in the testing dataset and

the coefficients in the training dataset (206). This was performed manually using the formula and data, as well as via machine learning using the testing dataset for validation. A significant prediction was achieved relative to coefficients [B= 6.383, 95% CI (5.028, 7.740) P<0.001], with R^2 = 0.49, demonstrating the predictive ability of the model. In addition, statistical tests were conducted to evaluate the accuracy and predictive capabilities of this model in the next sections.

Collection of new data

The acquisition of new datasets to validate a model in health care is often utilised as an independent validation to be performed by a third party after the model has been constructed, verified, and validated (207, 208). Consequently, the reserved dataset (the testing dataset) was used to evaluate the validity of multiple regression in this chapter, while the other outcome-related validation methods will be discovered in the following chapters. Therefore, validation in this chapter was conducted solely to validate the model's robustness (generalizability) to produce accurate predictions in order to have accurate application against clinical outcomes in the testing dataset and external validation dataset.

Data splitting

In addition to the CFS dataset splitting described in (Section 3.2.7.1), the testing dataset was utilised for validation tests to guarantee correct predictions. Initially, the training dataset-generated formula was calculated as a separate variable for validation in the testing dataset. Then, validation tests, such as Bland-Altman plots and linear regression, were used to evaluate the accuracy of the prediction in the testing dataset.

3.3.5.1 Bland-Altman plot for the model on the testing dataset

A Bland-Altman plot is a useful display to evaluate the agreement among two different instruments or two measurement techniques (176). Four types of data misbehaviour can be illustrated by the graph: systematic error, proportional error, inconsistent variability, and excessive or erratic variability (209). The mean difference represents the estimated bias, while the standard deviation of the differences measures the random fluctuations around this mean. The Bland-Altman plot is useful for revealing a relationship between measurement differences and magnitude, searching for systematic bias, and identifying potential outliers. The graph is an XY scatter plot, with the X axis representing the mean of the two measures and the Y axis representing the difference between the two paired measures (176). These were calculated as follows:

- A mean of CFS with the model = (CFS + the model)/2
- The difference between CFS and the model = | the model - CFS |

The normal distribution of the difference is a crucial aspect in producing this graph (see Figure 3-17), which demonstrates the normal distribution as approximately 95% of differences between d-1.96s and d +1.96s.

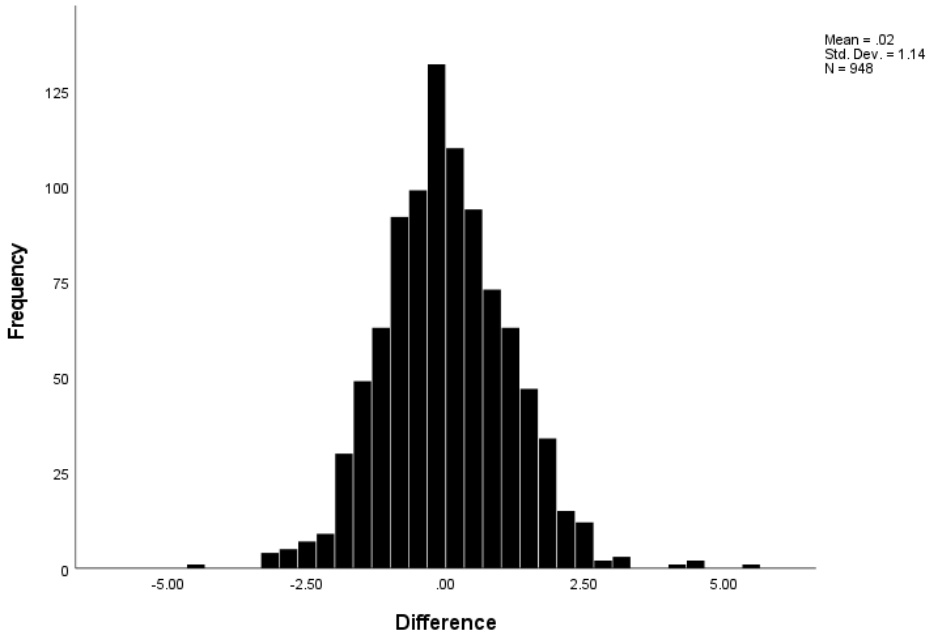


Figure 3- 17: the normal distribution of difference between the model and CFS

After verifying the normal distribution of the differences and calculating the mean of the two instruments, a one-sample t-test was performed to determine whether there was a statistically significant difference between zero and the mean difference of the two instruments, with the results (Table 3-16) showing that there was no statistically significant difference between the measurements.

	N	Mean Difference (M)	SD	t	df	p (One-Sided)	p (Two-Sided)	95% CI for the Mean Difference
The difference of CFS and model	948	.01877	1.13958	.507	947	.306	.612	[-.0539, .0914]

Table 3- 16: One-sample t test to check the difference between the two measurements.

A scatter plot was then performed for the mean and difference of measurements (Figure 3-18). The last step was to apply the lower and upper confidence limit lines to represent data fit and agreement. The calculations were as follows:

- Upper confidence horizontal limit line = mean + 1.96 x (standard deviation) = (0. 0188) + 1.96 x (1.13958) = 2.252377
- Lower confidence horizontal limit line = mean - 1.96 x (standard deviation) = (0. 0188) - 1.96 x (1.13958) = -2.21478

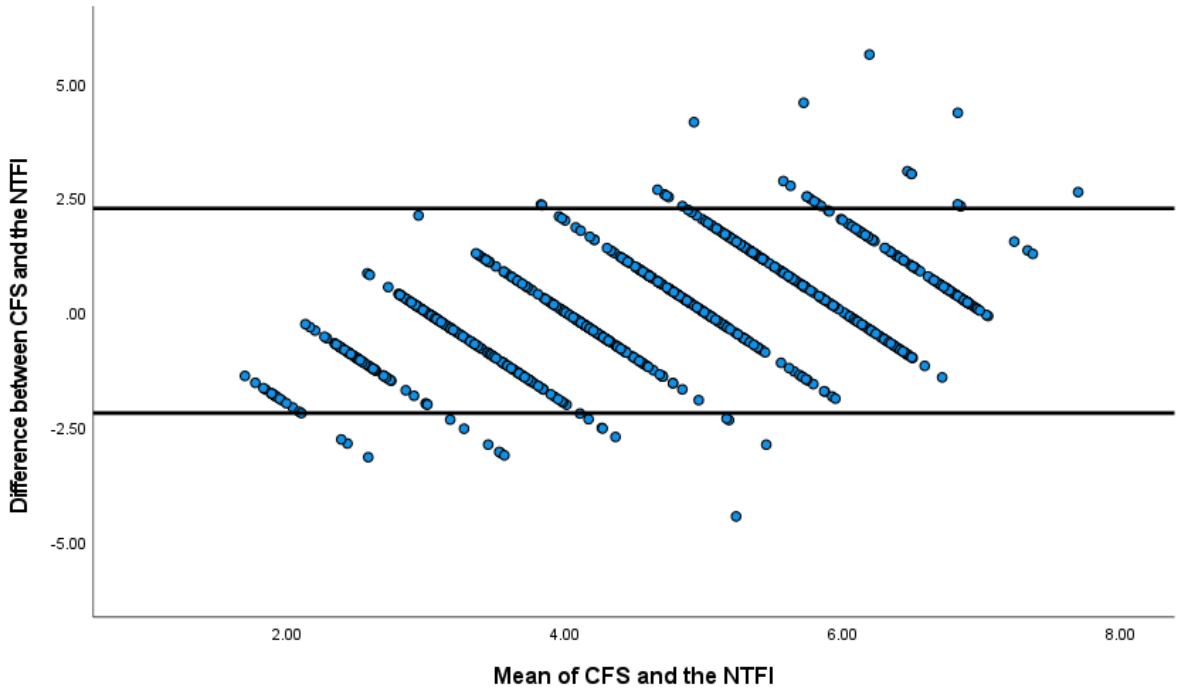


Figure 3- 18: Bland-Altman plots for model validation on the testing dataset

The lines in (Figure 3-18) represent the mean of the difference “the bias” (MD: 0.018), as well as the limits of agreement (95% limits of agreement). As the mean difference is close to zero (MD: 0.018), there is neither a systematic difference nor a fixed bias, which is the error that occurs when the MD is not zero, between the two measures (176). Using N = 948 from the validation (testing) dataset, there was high agreement between measures. The visual representation of the plot demonstrates that fewer points were outside the limits and the range between limits was small, indicating a high level of agreement (210). As the model will undergo additional validations to determine

the cut-off point, no a priori determination was made regarding the acceptable error level.

3.3.5.2 A linear regression between the difference and the mean

In order to check the proportional bias represented in Bland-Altman plots for instances above or below the limit lines, a linear regression was performed to calculate and visualise the level of agreement between the model's difference and mean. The results of the linear regression analysis indicate that the null hypothesis, which states that the average coefficient is equal to zero, was rejected. This suggests the presence of proportional bias, where the difference in magnitude systematically varies with the size of the measurements (see Table 3-17). Because CFS is a scale of (1 - 9) points and the produced model is a scale of (1.90 - 7.47), proportional bias was anticipated, as the numbering styles of the two instruments did not match. In contrast, the P-P plot graph showed the precision of the mean and difference in displaying the magnitude of the linear relationship.

		Unstandardized Coefficients		Standardized Coefficients		
Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	-1.716	.121		-14.143	<.001
	Mean of CFS and the model	.377	.025	.435	14.870	<.001

Note. R= 0.435, R^2= 0.189, Adjusted R^2= 0.189, P<.001
a. Dependent Variable: The difference of CFS and model

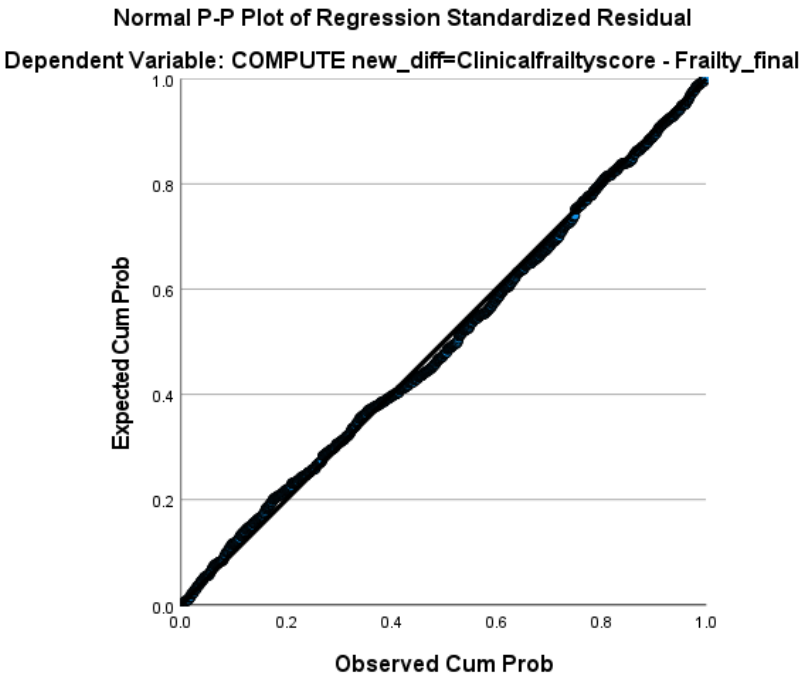


Table 3- 17: Linear regression results for mean and difference on the testing dataset

3.3.5.3 Box-whiskers plots and scatterplots of the model with CFS

To conduct further visual validations of the model, box-whisker plots and scatterplots were generated to illustrate the predictive link between the model and CFS (see Figure 3-19 and 3-20).

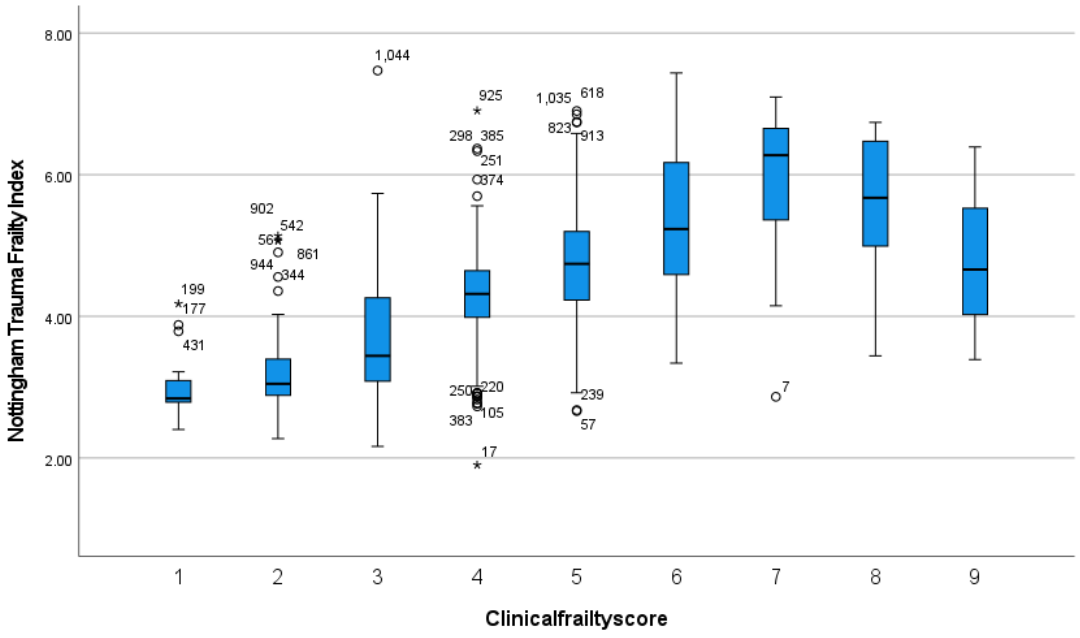


Figure 3- 19: Box-whiskers plots of the model with CFS on the testing dataset

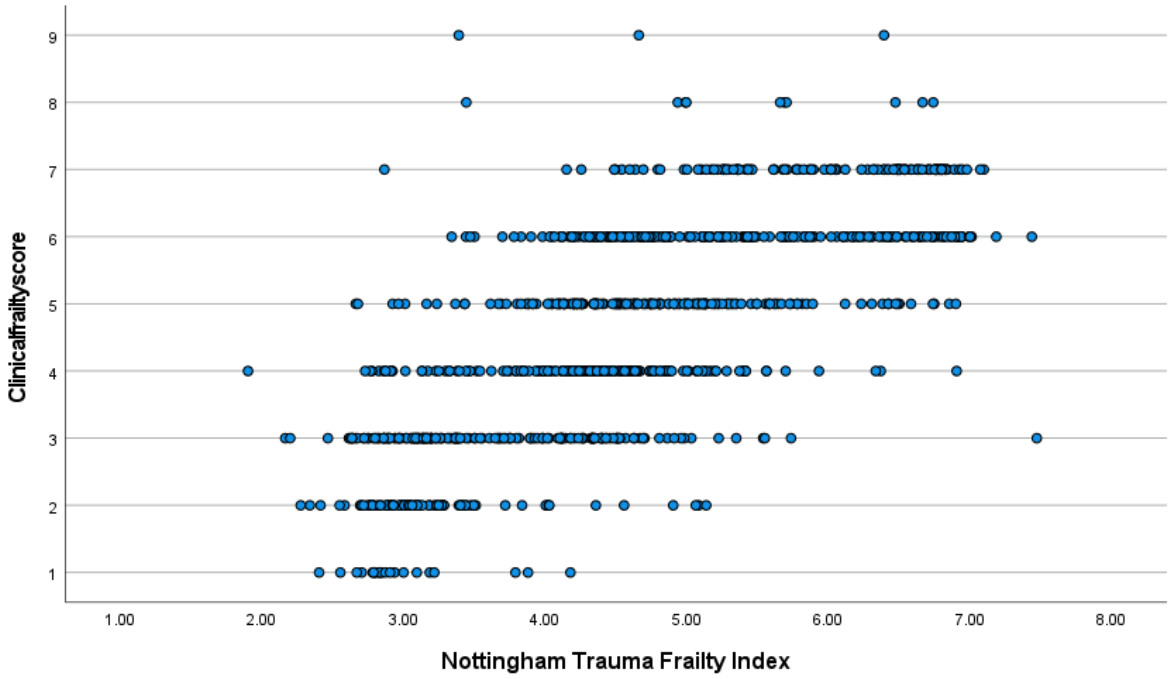


Figure 3- 20: Scatter plots of the model with CFS on the testing dataset

3.3.5.4 A linear regression plots of the model with CFS

The developed model was further tested for linearity with CFS by using regression plots to detect outliers, leverage points, and influential data points(211). However, a consistent linearship association was found, as shown in Figure 3-21.

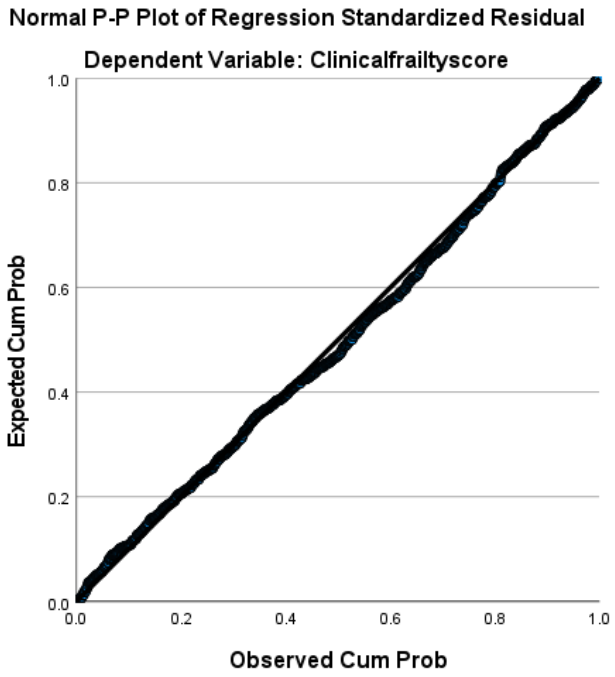


Figure 3- 21: A linear regression plot of the model with CFS using testing dataset

3.3.5.5 Bootstrapping

In regression, bootstrapping is one of the validation techniques that uses random resampling with replacements (212). As CFS was normally distributed and the change in numbering order in CFS could potentially affect the overall result of regression, bootstrapping would not be a reliable test for CFS and could provide inconsequential findings (213). However, the aforementioned validation tests were sufficient to reflect the model's and residuals comprehensive validity.

3.3.6 Minimisation of bias

Bias is a challenging aspect of research. Bias in research is any tendency or divergence from the truth in data collection, data analysis, interpretation, and publishing that might result in erroneous results (214). Bias might occur at any point throughout the research process. In predictive modelling, there are numerous sources of bias that must be acknowledged.

3.3.6.1 Selection bias

Selection bias occurs when individuals join or leave a group in a non-random manner; it may occur in sampling, exposure, or data (215). The process of splitting is one of the most prevalent stages in which selection bias may occur (216). In contrast, this was not the case in this model, since splitting was conducted at random and the sequential order of patients was not filtered, sorted, or arranged in a manner that may have resulted in a selection bias.

Incomplete data may introduce the possibility of selection bias, which, if not addressed, may compromise the accuracy of the model and result in inaccurate predictions (217). This was taken into account while processing cases with incomplete data by list-wise deletion and the removal of variables with more than 20% of missing data. Despite the fact that these applied methods may result in a selection bias, the extensive validation results validated the accuracy and helped to mitigate the risk of selection bias. Consequently, the probability of selection bias may occur at some phases of model development, despite its little impact on model performance.

3.3.6.2 Interpretation bias

The assumption of linearity in multiple linear regression to find relationships with unrecognised factors relevant to CFS might lead to interpretation bias if nonlinear correlation exists (218). However, the inclusion of all variables in univariate analyses to assess correlations without any specifications or literature-based effect on variable selection helped to eliminate the possibility of interpretation bias.

3.3.6.3 Omitted variable bias

In multiple linear regression analysis, omitted variable bias arises when one or more relevant independent variables are omitted from the regression model (219). Some variables, such as lactate, showed a link with frailty but not with trauma involvement in the literature but were omitted from the model due to a lack of data (220, 221). In addition, methods to mitigate omitted variables, such as using a control variable or a proxy variable, cannot be implemented since lactate defines a distinct biological component that cannot be specified by another variable. Therefore, this model may be susceptible to omitted variable bias in relation to lactate, as well as other omitted variables that were not collected in the dataset. This emphasises the need for further research to investigate the association between lactate and frailty in major trauma, as well as to identify other unrecognised routinely collected variables that may be predictive of frailty in trauma.

3.3.6.4 Proportional bias

A proportional bias arises when one instrument provides values that are proportionally more or less than those from the other instrument, based on the level of the variable

being measured. This was evident in the Bland and Altman plots (Figure 3-18) and the mean with difference in linear regression (Table 3-17). A recalculation of the natural logarithms of the two measures was performed, followed by redrawing the Bland-Altman plots. This was done in order to remove any proportional bias. However, the results of this analysis were not significant. This establishes that the different scaling techniques used in CFS and the NTFI had an impact on how Bland-Altman plots and linear regression were represented, resulting in the emergence of proportional bias. In addition, the measurement of variables often involves some level of error, and both the analytical imprecision of CFS and the NTFI contribute to variations in the differences (176). Consequently, there is a possibility of introducing proportionate bias when comparing the two instruments for validation. However, this bias did not have a significant impact on the measurement since the bulk of the data fell within the bias limits shown by the Bland-Altman plots (Figure 3-18).

3.4 Discussion

This chapter describes the development and validation of a novel predictive scoring model to predict frailty in patients with major trauma using routinely collected data. The primary purpose of the model's development was to produce an objective, clinically applicable tool based on easily measured physiological and functional parameters. For this reason, a number of potential co-variables were excluded. This does restrict the breadth of measures that are available to go into the model; however, it broadens the clinical relevance and ease of use of this frailty model. To illustrate, the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity POSSUM scoring system, which utilises 12 physiological and 6 operative

variables, requires a computer and is therefore not typically utilised outside the ICU (222). In contrast, the Nottingham Hip Fracture Score (NHFS) has fewer variables, is more widely used, and is objective (128). Another example relating to frailty evaluation is the CFS. While simple to use, it is subjective and requires training, as well as being less effective in predicting and discriminating between outcomes in higher CFS categories defined as frail individuals (135). Whereas this model consists of five variables, objective, easy to use, does not need training, less prone to bias, capable of predicting outcomes, and is based on physiological and functional characteristics.

Identified predictors (age, abbreviated mental test AMT, falls from standing height, haemoglobin, and pre-admission mobility status) determine essential factors related to the identification of frailty in older trauma patients. Current frailty instruments used to indicate frailty in trauma patients differ, with some including factors related to some dimensions of frailty (27) or measuring co-morbidity (112), despite the fact that frailty is not synonymous with co-morbidity. This approach has shown that frailty may manifest in numerous dimensions and has to be identified depending on unique challenges, such as trauma. Furthermore, there is no universal instrument that can be used for all challenges.

The found predictors are evidently functioning as trauma-specific frailty variables in older adults. While age alone may not consistently indicate frailty (106), in trauma patients, it may become a useful predictor of frailty when combined with other variables. Although frailty was found to be a better predictor than age (85), age in this model has a low effect on the overall model compared to other included variables (Beta =.102, $t(947) = 4.056$, $p<0.001$). Hence, although age may play a significant role

in identifying frailty among other predictors in trauma cases, it may not be a dependable factor on its own for predicting the outcomes of older individuals who are frail and have experienced trauma.

Another predictor was the AMT, which is widely used to evaluate a patient's cognition upon hospital admission. The relationship between AMT, mental health issues, delirium, and dementia in old people has been extensively studied (64, 181, 223-226); therefore, the association between AMT and frailty in older trauma patients in this model confirms the significance of this relationship to trauma. Research, such as the conducted systematic review (85), did not uncover relevant papers discussing mental health issues and frailty in trauma patients. In this model, there is a significant association between frailty and AMT, which determines the impact of this variable in acute contexts, such as trauma, and suggests that further investigation may be required to include this outcome in older trauma care.

Falling from standing height is an additional potential variable in this model. Falls from standing height in older people are caused by a disturbed homeostatic balance system, which indicates the existence of numerous system deficiencies and is considered to be known as "frailty syndrome"(41, 42). Frailty was identified as a key determinant that contributed to falls from standing height and poor outcomes in older people (44, 227). This model's identification of the relationship between falls from standing height and frailty confirms that this age group is influenced by frailty and not by age alone. Nearly 95% of patients included in the entire dataset sustained trauma from falls from standing heights. This highlights the importance of falls from standing height for older people who are frail. It emphasises the need for preventative strategies

targeting frailty and raising awareness about falls in order to promote healthy ageing. Addressing this issue is considered to be of the utmost importance due to its strong association with adverse outcomes in this age group.

Mobility status was also one of the predictors, which is not a new factor associated with frailty because it is a component of the two most widely used frailty measurements, the Rockwood clinical frailty scale (CFS) (27) by quantifying fitness, and the Fried et al. frailty phenotype (18) by measuring slowness and low activity. In addition, these two conceptual theories of frailty have been associated with poor outcomes in older trauma patients (110, 228). This establishes that pre-admission mobility status is a crucial predictor in this model, indicating that older patients with mobility issues must be considered at high risk for frailty-related trauma outcomes.
Haemoglobin, on the other hand, was the only biological factor in this model that was associated with the frailty of trauma patients. This association may represent the hematopoietic function associated with the ageing process (229) or the effect of chronic diseases that cause inflammation of red blood cells, resulting in anaemia (230). Malnutrition may also be considered a significant factor associated with ageing that contributes to anaemia (231). Haemoglobin levels are also likely to be trauma-specific since they represent not only basic frailty impairments, such as the degree of pre-morbid anaemia and malnutrition, but also blood loss caused by injury. These potential causes of anaemia or changes in haemoglobin level in older individuals confirm the face validity of this variable's significance in this model.

This chapter has introduced a novel multidimensional measure for frailty in trauma patients that includes functional impairments, important biological, and clinical

variables. The following clinical case demonstrates the use of the Nottingham Trauma Frailty Index (NTFI) (see Figure 3-22).

- Age 86
- AMT 9
- Haemoglobin level 89 g/L
- MOI; Falls from standing height
- Pre-admission mobility : Needs assistance

NTFI = 6.383 + 0.021(Age) - 1.100 (pre-admission mobility) + 0.445 (MOI) – 0.234 (AMT) – 0.011 (Haemoglobin)]

= 6.383 + 0.021(86) - 1.100 (1) + 0.445 (2) – 0.234 (9) – 0.011 (89)

NTFI = 4.894

Figure 3- 22: Clinical example of the Nottingham Trauma Frailty Index (NTFI)

Numerous sources of bias can arise in predictive modelling. Data splitting is a common stage where selection bias can occur, which was minimised by randomly and proportionally splitting the data (50/50) (216). Incomplete data, another source of bias that could result in selection bias, impact the accuracy of the model, and lead to incorrect predictions that could affect the model's representativeness and generalizability (217), was addressed by list-wise deletion for cases with missing data. If data are not missing at random, there is a chance that a bias will be introduced into the predictive model using this method. However, the significant Bland-Altman mean difference (bias) and linear regression validation results confirmed the model's accuracy and mitigated this bias. The omitted variable bias may also arise for the missing variables (219) (lactate and calcium levels), which may require further investigation as they were found to be associated with poor outcomes among older individuals but not with frailty (163-169). However, these variables would add more predictors of frailty in trauma if they were related without changing the model's conclusion. Another possible bias is the interpretation bias that may result from the assumption of a linear relationship to identify relationships with unrecognised variables

(218), which was eliminated by including all variables in univariate correlation analyses without any specifications or literature-based effect on variable selection. Other biases, such as proportional bias in Bland-Altman results, were not a substantial source of variation since the majority of the data were within the bias limits shown by Bland-Altman plots (176). Other biases may still exist or emerge in different settings, which may require further research to test the validity, generalizability, and applicability of this predictive model in predictions. The accuracy of this model's prediction based on the available validation tests confirms its ability to predict frailty in major trauma, but it has not yet been validated for clinical outcomes, which might require application of the model to other datasets in this instance.

In this chapter, we focused on patients who were assessed using the CFS as this our ground truth measurement. While this strategy may introduce selection bias by removing patients who have not completed CFS assessments, the utilisation of a large dataset helps to alleviate this problem. The high sample size improves the robustness of our findings and their generalisability within the population being examined. However, we recognise that some patient groups may still be under-represented. Future study should strive to involve a wider patient group in order to confirm and expand these findings. The use CFS as the sole indicator of frailty in this model has a number of strengths and limitations, including the introduction of observation biases. CFS was employed in this model as both a classifier of frailty status and a benchmark tool, with each score representing the amount of frailty based on the parameters. The CFS is widely regarded as a well-validated scale that provides clinicians with a summary tool for assessing frailty and fitness based on their clinical judgement and patient evaluation. The majority of studies discussing trauma and frailty utilised the

CFS (104, 107-109, 111) due to its efficiency, since it just takes a few minutes and a short clinical history to complete. However, there are other factors that clearly illustrate the inappropriateness of CFS in trauma contexts. CFS is a subjective diagnostic tool that depends on the judgement of the clinician. It is vulnerable to being affected by the clinician's experience, bias, or preference (232). Due to the subjective nature of CFS, the scoring may be affected by the level of training of clinicians and the influence of external factors such as fatigue, medication, and trauma. Hence, the NTFI would effectively address these concerns by providing an objective assessment based on patients' physiological characteristics, which is not influenced by clinical considerations. Therefore, the use of objective measures in NTFI is anticipated to provide superior outcomes in clinical settings and demonstrate reduced vulnerability to biases and concerns associated with intra- and inter-observer dependability (134).

Since biases may affect the tool's interpretability and generalisation, NTFI creation followed a strategy to minimise biases, with assumptions for each method. These assumptions—methodological (233), statistical (234), and theoretical (235)—ensure the model's validity and dependability. Although statistical assumptions may interact with theoretical assumptions, such as in the screening of candidate variables, some of which may or may not have a clear previous relationship with frailty in the literature, statistical assumptions were used to assess their inclusion to avoid inaccurate conclusions. Although this may weaken theoretical assumptions over statistical assumptions, the final five variables showed important face validity with theoretical linkages in trauma frailty settings, validating these measures' theoretical assumptions (236). The model may benefit from other routinely collected data items not included in screening from the three trauma datasets. However, the model measured frailty and

predicted trauma-related frailty outcomes with fewer variables, reducing the risk of overfitting (237).

The model's generalizability may be limited by its development and confirmation using data from one institution. Large sample sizes in development and validation allowed for more patient demographic diversity and generalizability. NTFI had two successful validations, but more external validation may be needed to improve its usability and generalizability across contexts and populations and reveal the model's resilience and performance. Traumatic Brain Injury (TBI) and burns were not in the development datasets. Given that the development of NTFI limited to severely injured individuals admitted for orthopaedic surgery, additional validation involving patients with TBIs is necessary. Validation with TBI patients may be effective, but cognitive health changes must be considered because TBI may impair orientation, which could lead to inaccurate AMT estimates and misleading NTFI results. Despite burns being less common in older people (29) and less likely to be associated with cognitive impairments that could impede NTFI use, the NTFI appears appropriate for validation in this demographic. Validating NTFI for TBI or burns would increase its suitability for assessing trauma frailty across demographics and contexts.

The elimination of subjectivity from a scale has the potential advantage that increased granularity and reliance on physiological parameters relating to frailty will enable other uses of the score, such as the prediction of complications or other outcomes. However, there may be instances in which objective metrics cannot be obtained owing to the complexity of the injury or a lack of data, in which case the clinician's observations serve as the foundation for decision-making. Thus, the NTFI might be a purposely subjective evaluation, needing a careful balance between clinical judgement and

objective measures (238)—both of which are relevant to the NTFI tool since both are necessary for use.

An important clinical implication of this model is that the NTFI will eliminate subjectivity and provide an objective frailty measure for trauma patients with accurate multidimensional frailty in trauma diagnosis. This chapter has demonstrated that the NTFI is a reliable instrument that accurately predicts the ordinal scale of the CFS in acute trauma from routine data. The NTFI could be incorporated into the emergency department to assess patients' frailty, or it could be modified to accommodate trauma surgery admissions for older trauma patients. However, future validations should utilise larger and more diverse samples to replicate and expand the applicability of this model to a variety of trauma settings. In addition, additional validation is required to determine the cut-off point for poor outcomes in a wider trauma population using this model. Additionally, additional potential predictors of frailty could be investigated to improve this model's ability to detect frailty in patients with major trauma.

3.5 Conclusion

The Nottingham Trauma Frailty Index (NTFI) has proven to be a valid instrument for determining frailty in severely injured patients. This index would provide a practical and clinically relevant assessment for frailty, as well as a guide for trauma management measures. However, more study is needed to determine its usefulness in predicting clinical outcomes and its application to a larger population of trauma patients. As a result, the following chapter will study the NTFI's efficacy in predicting clinical outcomes in a larger trauma patient group, with the goal of proving its robustness and generalisability.

Chapter 4: Is the Nottingham Trauma Frailty Index (NTFI) relationship to Clinical Outcomes generalisable to a wider trauma population?

4.1 Introduction

Healthcare models are widely used to predict disease incidence, forecast outcomes, help choose treatments, and characterise disease processes. They assist healthcare workers in making well-informed choices to enhance patient care. The risk prediction model is a widely used methodology in healthcare settings. It is designed to predict the risk of a clinical condition based on a set of variables, such as lung cancer risk prediction (239-242). Predicting clinical outcomes and discharge destinations is another important application of predictive models in health care. The prediction of clinical outcomes following trauma is a critical component in the care of older trauma patients (69). Early recognition of clinical outcomes using predictive models and other resources for older trauma patients with frailty will permit timely and appropriate interventions and referrals to optimise recovery and functional status, thereby enhancing the quality of care and decreasing their morbidity and mortality.

Model validation is a crucial process that confirms the model's ability to measure, predict, and fulfil its intended purposes (243). It is an important step that follows model development and confirmation of prediction accuracy. As previously stated, the train/test-split methodology was used to develop, validate, and evaluate the accuracy of the model's predictions and coefficients for the Nottingham Trauma Frailty Index (NTFI). The Bland-Altman results (mean difference = 0.018) established the capability

of NTFI to be used in additional validation to ensure the model's ability to predict clinical outcomes using available datasets prior to model deployment. This phase of validation will help determine the relationship between NTFI and clinical outcomes. An internal and external validation method will be used to validate the model on a wider population. Using the testing dataset, internal validation will determine the predictive ability of the model with respect to clinical outcomes. In addition, a non-Clinical Frailty Scale (CFS) dataset will be used for external validation to ensure the model's capability and performance when applied to non-measured frailty datasets. External validation of NTFI will assist in testing how well the model performs with new data that were not used to build the model, as well as assessing the generalizability and reliability of a model across populations and settings.

The purpose of this chapter is to establish if, in addition to predicting clinical frailty, there is a valid relationship between NTFI and clinical outcomes.

4.1.1 The research questions.

This chapter will investigate the relationship between NTFI and clinical outcomes using two different approaches. The NTFI for the two datasets will be generated, and the relationship between the NTFI and outcomes will be used in both internal and external validation processes. The research question is:

Is the NTFI validly related to clinical outcomes and discharge destinations in a novel internal and external dataset?

4.1.2 Objectives

1- Exploring the relationship of NTFI with clinical outcomes and discharge destinations.
2- Visualise the relationship between NTFI and each clinical outcome to ascertain which is the most affected.
3- Validate NTFI in an out-of-sample data set in order to establish its applicability and validity in a wider population of trauma patients.

4.2 Methods

There were 7330 patients aged 65 and older. Two thousand one hundred eight patients were used in the formulation and development of the NTFI as a training sample of 1054 and a testing sample of 1054. NTFI was developed using a training dataset and validated using a testing dataset, which confirmed its predictive ability, as determined by Bland-Altman. The goal of this chapter is to verify the usage of the NTFI tool in relation to clinical outcomes and discharge destinations, since the validation in the previous chapter has been verified. There are two sorts of model validation samples that may use this method: in-sample validation and out-of-sample validation (243). Before attempting to use the model with an external dataset, it is recommended that it be validated using the same data as an internal validation (244). The NTFI was therefore validated using:

1. The internal validation sample (testing dataset) was defined previously.
2. A wider dataset from the Nottingham trauma registry (the external validation sample). This dataset included trauma patients aged 65 or older who were

admitted to Queens Medical Centre, Nottingham, UK, between October 2015 and July 2020 but who did not have a completed clinical frailty scale (CFS).

NTFI was then dual-validated against both datasets to determine its predictive capability and generalizability in terms of discharge destinations and clinical outcomes. The purpose of this chapter is to determine the function of the NTFI in identifying frail patients and relating their frailty to known clinical outcomes. The internal validation (testing dataset) included a sample of individuals who had both CFS and NTFI measurements available. In contrast, the external validation included a larger cohort for which NTFI measurements were available; however, the CFS for these patients was not evaluated (see Figure 4-1). The external validation cohort was thus utilised to measure frailty using the NTFI in patients who were eligible for inclusion and then to measure clinical outcome relationships for these patients.

A wide variety of clinical outcomes were examined and evaluated for their relevance to frailty in older trauma patients to be used as validation measures, including hard outcomes such as discharge destinations, while in other cases (such as complications), composite outcomes were developed for the purposes of this validation. The composite outcome measures allow broad inclusion of sporadically occurring complications and maintain clinical relevance to patients (245). The composite outcome measures consisted of the frequently used outcomes for trauma patients, with adjustments made to account for the impact of frailty. These are defined in the section below. Box-whisker, one-way ANOVA, and Pearson's correlation test for continuous outcomes were used to graphically depict the relationships between the model and its outcomes. Results were reported in accordance with the transparent reporting of a multivariable prediction model for prediction model validation (TRIPOD) (146). An approval has been obtained from the Hospital Audit Committee for data

collection and analysis of the audit (approval number 21-040C). Data was transferred to the SPSS statistics package (version 28.0.0.0) for analysis (148).

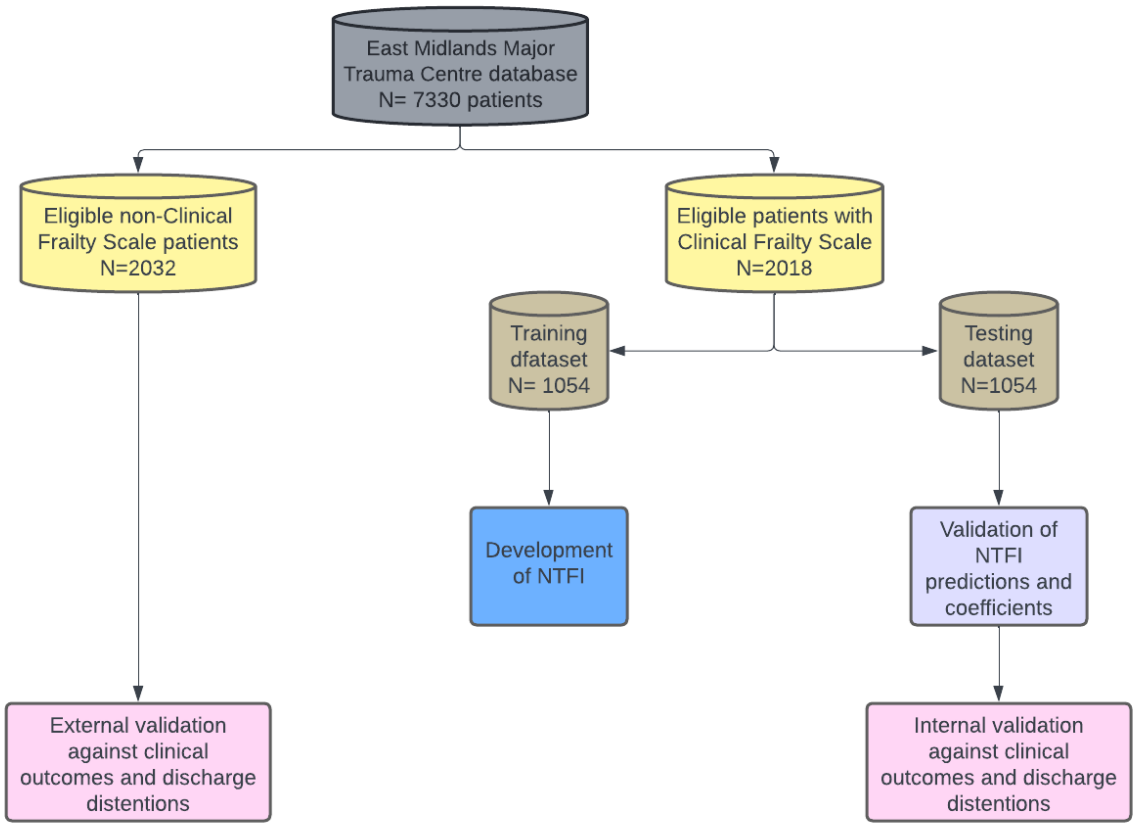


Figure 4- 1: A flowchart of samples used in validation.

4.2.1 Source of data

As stated in the preceding chapter, an anonymised dataset derived from the Nottingham Trauma Registry, combined data from three routinely collected clinical patient groups—fragility fractures, hip fractures, and adult trauma—admitted to the East Midlands Major Trauma Centre at the Queen's Medical Centre, Nottingham, UK, between 1 October 2015 and 31 July 2020. There were 7441 adult fractures; 6002 were fragility fractures, 3801 of which were hip fractures. On the basis of CFS status,

the received database was randomly divided into two primary datasets (patients with completed CFS and patients without CFS), with patients with CFS separated into training and testing datasets. In this chapter, testing and non-CFS datasets were used for both internal and external validation procedures.

4.2.2 Participants

Two validation cohorts were utilised, with the internal validation utilising the testing dataset and the external validation utilising the non-CFS dataset. There are no differences in eligibility requirements between internal and external validation cohorts in order to standardise validation processes and eliminate potential biases in participant selection. Records were selected for patients using the following eligibility criteria:

- Age 65 and above
- Trauma as the primary complaint
- Nottingham trauma frailty index (NTFI) variables are available.

4.2.3 Outcomes

Research on frailty in older trauma patients utilises various clinical outcomes. Mortality (46, 104, 110), length of stay (44, 106-108) and complications (46, 104, 111, 112) are the most frequently measured outcomes for older trauma patients with frailty. Other less frequent outcomes include delirium (107, 246), readmission (112, 247) and discharge to a rehabilitation unit or nursing home (46, 107). Despite the fact that activities of daily living (ADL) are a crucial endpoint for older discharged patients to

indicate their functional condition, relatively few researchers have examined the dependence level of older trauma patients after discharge.

To obtain a more comprehensive assessment of the efficacy of frailty in older trauma patients (245), an examination of complications and adverse events, as well as the change in dependency level, was required. Therefore, it was imperative to develop composite measures to evaluate some outcomes, such as the increase in dependency level, in order to analyse them against NTFI.

Composite outcomes are a consolidated metric in a clinical trial or research that combines many individual outcomes into a single endpoint (248). This technique is used to evaluate the comprehensive impact of an intervention on several facets of a condition or illness. While composite outcomes are often employed in randomised trials, they may also be used in other contexts due to their association with increased statistical efficiency. Therefore, composite outcomes were used to generate and assess in-hospital complications and the increase in dependency level, while discharge destinations and length of stay were available in the datasets. Therefore, the following outcomes were measured in this chapter:

- Total in-hospital complications
- Length of stay (LOS)
- Discharge destinations
- Mortality at discharge
- Increase in dependency level

The following is a description of these outcomes, including a brief introduction to each outcome, its relevance to the population, and the methods used to measure each outcome.

4.2.3.1 Total in-hospital complications

Older trauma patients with frailty are more likely to develop complications in the hospital, which may affect older people's quality of life after discharge. Complications are one of the most common findings in older patients with frailty after trauma. These complications can result in prolonged hospital stays, readmission, and mortality (105, 106, 249). Infections (46, 105-107), pneumonia (44, 46, 106, 107), and urinary tract infections (UTI) (44, 106) are some of the most common in-hospital complications for older trauma patients with frailty. This necessitates measuring this outcome for this population in order to highlight the relationship between this outcome and frail older individuals with trauma, allowing for better tracking of patient progression and treatment.

In both validation datasets, 12 complications variables were accessible, including cerebrovascular accident (CVA), blood transfusion, urinary tract infection (UTI), renal failure, myocardial infarction (MI) or acute coronary syndrome (ACS), clostridium difficile (CDiff), pneumonia, failure of fixation, deep vein thrombosis (DVT), trauma admissions dislocations, compartment syndrome, and pressure ulcers. Only complications variables with >1% of occurrences (more frequent than 1:100 occurrences) in the sample were included in the total number of in-hospital complications, while those with <1% were excluded to ensure that the included complications variables are relevant to the population and represent the actual complications for older people.

Initial frequentist exploratory analysis found these were infrequent individually, although commonly, patients suffered one or more complications. It was therefore necessary to develop a composite outcome to measure the total in-hospital complications. The composite outcome for total in-hospital complications was created

to summarise the number of complications that occurred during hospitalisation following trauma. Total in-hospital complications were calculated by combining the number of eligible complications for patients into a single numerical variable, as the presence of a single complication results in a value of one for the total in-hospital complications. The use of total in-hospital complications as a singular variable enabled the evaluation of the overall risk of complications in this population, as older, frail trauma patients have a greater risk for multiple complications. Consequently, this outcome was hypothesised to reveal the degree of association between NTFI and multiple complications in frail older trauma patients.

4.2.3.2 Length of stay (LOS)

The length of stay (LOS) for older trauma patients is longer than for younger patients (250). Frailty is one of the most important factors that could contribute to a longer LOS (85). In addition to frailty, factors such as the development of complications or mobility issues, the need for surgery, or a prolonged period of recovery may also be associated with it (251, 252). This indicates that frailty and other factors related to frailty may lead to prolonged hospital stays and impact the discharge plan for older trauma patients. Therefore, the purpose of measuring LOS in this chapter was to establish the role of frailty in relation to LOS in older trauma patients and evaluate the association between NTFI and LOS.

Total LOS was computed for all patients based on the number of days a patient spends in the hospital from the date of admission to the date of discharge.

$$\text{LOS} = (\text{date of discharge} - \text{date of admission})$$

The LOS was then encoded and converted to a numeric variable for both patient cohorts.

4.2.3.3 Discharge destinations

Compared to younger patients, older patients are less likely to be discharged to their original place of residence after trauma. The difference between initial and discharge locations may not be explained by age, and other factors may be associated with discharge destinations. According to the conducted systematic review, after a major trauma, frail older patients are unlikely to be discharged to their homes or usual residences (85). Mortality was also found to be higher in older trauma patients with frailty compared to non-frail patients. The discharge destinations of older trauma patients appear to be significantly influenced by frailty. As a result, discharge destinations were compared to NTFI in this chapter to demonstrate whether increasing NTFI can lead to worse discharge destinations or not.

Discharge destinations were categorised as mortality at discharge, nursing home, residential care, rehabilitation unit, acute hospital, and home. Destinations were available in both cohorts and separated and coded for statistical analysis to distinguish between destinations in visualisation graphs.

4.2.3.4 The increase in dependency level

Frailty and disability are distinct concepts, with disability referring to the loss of function and frailty indicating instability and a risk of function loss (253). The primary distinction between frailty and disability is that frailty is a condition of increased vulnerability, whereas disability is a limitation in ability. There is an implication that frailty (vulnerability) can result in disability, but not all frail individuals become disabled. While ADL are the daily activities that individuals must perform to take care of themselves.

Nonetheless, there is a correlation between the decline of ADL and frailty in older people (254). The relationship between older individuals with frailty and the deterioration of ADL following discharge was not thoroughly examined in studies involving trauma. However, this relationship was found to be significant. As an illustration, Rickard et al. (2020) discovered that 42.9% of discharged trauma patients had increased care needs compared to 27.3% of non-frail patients (59). Consequently, suffering an injury is anticipated to affect and reduce independence in ADL, as well as worsen frailty status in this population after discharge. The concept of frailty also implies a failure to recover from injury. Therefore. A measure of dependency level change should correspond to a valid frailty scale. As a result, a composite outcome for the increase in dependency level was developed. This composite outcome was derived using two variables: pre-admission residences and discharge destinations. The two variables were used to determine a global measure of change in independence after trauma in order to determine whether or not older patients were sent to unfavourable destinations requiring additional care, rehabilitation, or long-term care, such as nursing care. The association was evaluated against the NTFI to determine the relationship with the increase in dependency level variable, where each number of this composite outcome represented the degree of dependence and high numbers indicated greater dependency.

Calculations were performed to determine whether patients' admission residences changed after discharge to unfavourable destinations requiring additional care, as well as their relationship to NTFI. If there was no change in discharge destinations or if they improved, this was counted as 0 because this outcome was designed to assess only the increase in dependency level. The objective is to measure the increase in dependency level rather than assigning numbers to fixed discharge destinations, and

to allow this outcome to be used in future studies that may have varying discharge dispositions. As a result, the increase in dependency was counted based on the availability of each dataset's discharge destinations, and numbers were not standardised to be the same in both cohorts as discharge destinations differ. Discharge to a residential home, for instance, was available in the external cohort but not in the internal cohort, resulting in different numbers for this outcome across datasets. The creation and calculation of the increase in dependency level outcome is shown in Table (4-1).

Internal cohort			External cohort		
Pre-admission residence	**Discharge destination**	**Increase in dependency level value**	**Pre-admission residence**	**Discharge destination**	**Increase in dependency level value**
Home	Others not listed	0	Home	Others not listed	0
Home	Home	0	Home	Home	0
Home	Acute hospital	1	Home	Acute hospital	1
Home	Rehabilitation unit	2	Home	Rehabilitation unit	2
Home	Nursing care	3	Home	Residential home	3
Home	Death	4	Home	Nursing care	4
			Home	Death	5
Care home resident	Others not listed	0	Care home resident	Others not listed	0
Care home resident	Home	0	Care home resident	Home	0
Care home resident	Acute hospital	None was found	Care home resident	Acute hospital	None was found
Care home resident	Rehabilitation unit	0	Care home resident	Rehabilitation unit	0
Care home resident	Residential home	None was found	Care home resident	Residential home	0
Care home resident	Nursing care	1	Care home resident	Nursing care	1
Care home resident	Death	2	Care home resident	Death	2
Nursing care resident	Others not listed	0	Nursing care resident	Others not listed	0
Nursing care resident	Home	0	Nursing care resident	Home	0
Nursing care resident	Acute hospital	None was found	Nursing care resident	Acute hospital	None was found
Nursing care resident	Rehabilitation unit	0	Nursing care resident	Rehabilitation unit	0
Nursing care resident	Residential home	None was found	Nursing care resident	Residential home	0
Nursing care resident	Nursing care	0	Nursing care resident	Nursing care	0
Nursing care resident	Death	None was found	Nursing care resident	Death	1

Table 4- 1: The development of the increase in dependency level outcome

4.2.4 Predictors

The Nottingham trauma frailty index (NTFI) was the primary predictor for the validation. The NTFI was validated in a previous chapter for use in prediction and coefficients, establishing this instrument's applicability in trauma settings for frail older individuals. It is reasonable to expect that, as frailty measures vulnerability, an increasing value of a valid frailty measure will be associated with an increasing frequency of adverse outcomes. Therefore, the purpose of this instrument in this chapter is to validate the NTFI relationship to clinical outcomes and discharge destinations in order to achieve the intended objectives of this tool. The NTFI has five variables that must be measured, and failure to do so may result in the case being ruled ineligible, as specified in the eligibility criteria. These variables are age, the Abbreviated Mental Test (AMT), pre-admission mobility status, the mechanism of injury, and haemoglobin level. Each variable was calculated for each case in both datasets, and all variables were summed into a single variable (NTFI) using the following formula:

NTFI = 6.383 + 0.021 (Age) - 1.100 (pre-admission mobility) + 0.445 (MOI) - 0.234 (AMT) - 0.011 (haemoglobin), where:

- Pre-admission mobility is coded as 1 = needs assistance, 2 = freely mobile without aids.
- MOI (mechanism of injury) is coded as 1 = other MOI, 2 = falls from standing height.
- AMT is a 10-point Abbreviated Mental Test Score.
- Haemoglobin is measured in g/L.

The NTFI was then calculated for cases in both datasets in preparation for comparison with clinical outcomes and discharge destinations. The included cases were converted

into a distinct numeric variable in preparation for evaluation against outcomes. Both datasets were prepared for statistical analysis using NTFI as the dependent variable compared to the available outcomes.

4.2.4 Sample size

Two samples (clinical cohorts) were used to accurately validate the performance and generalizability of the NTFI in relation to clinical outcomes and discharge destinations. In the previous chapter, the testing cohort was used for prediction verification and validation; in this chapter, it was used for an internal validation of NTFI against clinical outcomes. This dataset contained 1054 patients, including 948 patients in which all NTFI variables are available. Although the internal validation sample was sufficient to determine the satisfactory performance of NTFI, an external validation sample was used to validate NTFI's generalisability outside of the development cohort. In this case, a dual measure of NTFI and CFS was not required. We externally validate the NTFI in out-of-sample data against clinical outcomes to facilitate a better demonstration of NTFI prediction, validate its applicability in different trauma patients, and confirm its ability to predict outcomes in new datasets (255). It also demonstrates the need of updating or customising a model in order to improve its predictive performance in specific contexts or subgroups. Therefore, the second validation dataset included 2032 patients with new data for trauma patients admitted to Queens Medical Centre, Nottingham, UK, aged 65 years and older and not previously included in model development or testing. The NTFI for these patients was then calculated for external validation against clinical outcomes. As a result, two cohorts were established to validate the relationship between NTFI and the four clinical outcomes, which were

organised into distinct variables in both internal and external cohorts for patients with NTFI calculated in order to apply statistical analyses.

4.2.5 Missing data

Missing data is common in predictive model creation and validation, and machine learning algorithms that rely on complete data are the techniques most impacted by missing data (158, 159). In the previous chapter, a complete case analysis was used to handle missing NTFI data in the internal validation cohort (testing cohort). In this chapter, with the inclusion of additional data, no missing NTFI data were found in the external validation cohort. Both the internal and external validation cohorts had complete data for clinical outcomes and discharge destinations. However, there were exceptions: 20 patients in the internal cohort and four patients in the external cohort had missing length of stay outcome data. As missing data was at random, missing values were not imputed, and a complete case analysis was conducted (160). Other patients from both cohorts had complete data for NTFI, clinical outcomes, and discharge destinations, and no further missing data were identified.

4.2.6 Statistical analysis methods

Before conducting analyses, the NTFI variable was calculated for both internal and external validation cohorts to ensure the completeness of the data for clinical outcome analyses. In addition, clinical outcomes, discharge destinations, and composite outcomes were coded, prepared, and labelled for statistical analysis. As the primary objective of this chapter was to determine whether NTFI was validly associated with clinical outcomes and discharge destinations, a visual inspection

was conducted for each clinical outcome and discharge destination against NTFI to accurately represent the association. Due to the nature of outcome differences, dataset outcomes were independently analysed using statistical methods that were appropriate for the data and outcomes.

Internal validation sample

After generating NTFI for the patients in the internal validation cohort, the outcomes were prepared for analysis. For the total in-hospital complications outcome, the numbers ranged from 0 to 4, with each number representing the number of complications that occurred, up to a maximum of 4. In-hospital complications outcome was compared to NTFI using cross-tabulation descriptive analysis, one-way ANOVA, and box-and-whisker plots. Cross-tabulation was performed to visualise the association between NTFI and in-hospital complications, whereas box-whisker was used to graphically depict this relationship. The one-way ANOVA was performed to compare the means between groups and determine the significant difference in means between complications groups with NTFI. Cross-tabulation and box-whisker plots and one-way ANOVA were utilised to analyse the outcomes of discharge destinations and the increase in dependency level with the same hypotheses of in-hospital complications outcome. The Pearson correlation coefficient was used to assess the strength of the relationship between NTFI and LOS.

External validation sample

NTFI was calculated and transferred as a numeric variable for eligible patients. The measured outcomes were similar to those of the internal validation cohort. Only the discharge destination outcome was different due to the inclusion of other destinations

that were not part of the internal validation cohort, such as residential home care. This has resulted in the addition of this variable to the discharge destination outcome and the modification of the rate of increase in the dependency level outcome in the external validation cohort from 0 to 4 to 0 to 5 in some instances. The statistical analyses used for the external validation cohort were the same as those used for the internal validation cohort, as the data and outcomes were identical and there was no significant difference in terms of data type and outcomes.

4.2.7 Internal validation cohort vs. External validation cohort

As both datasets were obtained from the Nottingham hospital registry, there were no significant differences between them in terms of data structure or measured patient outcomes. In both samples, patients admitted to the orthopaedics and trauma departments had trauma as their primary complaint and were 65 years of age or older. In terms of eligibility criteria and validation procedures, both cohorts were:

- Patients who are at least 65 years old.
- Individuals were admitted for orthopaedic trauma surgery.
- Complete data to compute the NTFI.

The selection of patients for both samples was based on the same eligibility criteria for both groups in order to include patients in analyses and validations.

4.3 Results

948 patients from the internal cohort and 2032 patients from the external cohort were included in the analysis to validate the relationship with NTFI. In both cohorts, the median age was approximately the same (Table 4-2), and females comprised nearly

70% of the samples. Falling from standing height was the primary mechanism of injury in both samples for the majority of patients. The mean of NTFI was slightly greater in the internal sample (4.59), compared to the external cohort (4.49).

	Internal cohort	External cohort
Number of patients	948	2032
Age [median (IQR)]	85 (11)	84 (12)
Gender		
Female (n, %)	665 (70.1%)	1453 (71.5%)
NTFI [mean (SD)]	4.59 (1.19)	4.49 (1.14)
AMT [median (IQR)]	8 (6)	9 (5)
Hb [median (IQR)]	122 (21)	124 (24)
Pre-admission mobility status		
Needs assistance (n, %)	599 (63.2)	1300 (64%)
MOI		
Falls from standing height (n, %)	906 (95.6%)	1924 (94.7%)

CFS, clinical frailty scale; AMT, Abbreviated Mental Test; Hb, Haemoglobin level g/L; NTFI, Nottingham trauma frailty index; MOI, mechanism of injury

Table 4- 2 Characteristics of patients in the internal and external groups

4.3.1 Total in-hospital complications and NTFI

Standardised complications data was recorded prospectively on a daily basis by trained clinical auditors in both cohorts. The dataset included data on 12 standardised in-hospital complications: cerebrovascular accident (CVA), blood transfusion, urinary tract infection (UTI), renal failure, myocardial infarction (MI) or acute coronary syndrome (ACS), clostridium difficile (CDiff), pneumonia, failure of fixation, deep vein thrombosis (DVT), trauma admissions dislocations, compartment syndrome, and pressure ulcers. Following descriptive analysis, the only valid in-hospital complications with cases of >1% were pneumonia, UTI, blood transfusion, and renal failure (see Table 4-3). These complications were significantly more common than other

complications, determining the relationship of these complications to older people in both cohorts. Blood transfusion was the most common complication in both groups, indicating post-injury or post-surgical anaemia in frail older people with trauma (internal 22.2% vs. external 23.4%). Pneumonia was another complication that occurred in 9.3% of the internal cohort and 12.2% of the external cohort. The presence of pneumonia in this outcome in older trauma patients with frailty appears to be a good representation of the weakened immune system that older people are likely to have due to frailty. Renal failure was another complication in this population, affecting 12.8% of the internal cohort and 13.8% of the external cohort. In addition, 6.5% of the internal cohort and 10% of the external cohort had UTIs. As UTI and renal failure were two of the most prevalent complications in this population, it appears that problems with renal function are one of the most common complications that older trauma patients may experience. This also determined the association of the estimated glomerular filtration rate (eGFR) variable, which was one of the significant variables in constructing the NTFI in the univariate analysis (r = -.208, P <.001), but was eliminated following non-significant multiple regression. Therefore, the occurrence of renal function issues, pneumonia, and the need for blood transfusion in older people represents a significant complication that can arise in trauma patients with frailty.

		Internal cohort		External cohort	
		Count	N %	Count	N %
UTI	Yes	62	6.5%	204	10.0%
	No	886	93.5%	1828	90.0%
	Total	948	100.0%	2032	100.0%
Failure of fixation	Yes	1	0.1%	1	0%
	No	947	99.9%	2031	100%
	Total	948	100.0%	2032	100.0%
CVA	Yes	4	0.4%	11	0.5%
	No	944	99.6%	2021	99.5%
	Total	948	100.0%	2032	100.0%
MI or ACS	Yes	5	0.5%	25	1.2%
	No	943	99.7%	2007	98.8%
	Total	948	100.0%	2032	100.0%
DVT	Yes	3	0.3%	3	0.1%
	No	945	99.7%	2029	99.9%
	Total	948	100.0%	2032	100.0%
Trauma admission dislocations	Yes	7	0.7%	9	0.4%
	No	941	99.3%	2023	99.6%
	Total	948	100.0%	2032	100.0%
Blood transfusion	Yes	210	22.2%	475	23.4%
	No	738	77.8%	1557	76.6%
	Total	948	100.0%	2032	100.0%
Compartment syndrome	No	948	100.0%	2032	100.0%
	Total	948	100.0%	2032	100.0%
Renal Failure	Yes	121	12.8%	281	13.8%
	No	827	87.2%	1751	86.2%
	Total	948	100.0%	2032	100.0%
CDiff	Yes	1	0.1%	3	0.1%
	No	947	99.9%	2029	99.9%
	Total	948	100.0%	2032	100.0%
Pressure ulcers	Yes	7	0.7%	21	1.0%
	No	941	99.3%	2011	99.0%
	Total	948	100.0%	2032	100.0%
Pneumonia	Yes	88	9.3%	247	12.2%
	No	860	90.3%	1785	87.8%
	Total	948	100.0%	2032	100.0%

Table 4- 3: Descriptive analyses of all in-hospital complications available.

After assuming the relationship between these four complications (UTI, renal failure, pneumonia, and blood transfusion), the total in-hospital complications outcome was calculated by adding each complication counted in one variable, with a maximum of four complications. In order to investigate the distribution of in-hospital complications, a cross-tabulation against NTFI was created to show the number of patients with each number of complications. (See Table 4-4).

	In-hospital complications	**Internal cohort**		**External cohort**		Total	
		N	Percent	N	Percent	N	Percent
Nottingham Trauma Frailty Index	0.00	591	62.3%	1177	57.9%	1768	59.3%
	1.00	252	26.6%	567	27.9%	819	27.5%
	2.00	87	9.2%	230	11.3%	317	10.6%
	3.00	17	1.8%	52	2.6%	69	2.3%
	4.00	1	0.1%	6	0.3%	7	0.2%
	Total	948	100.0%	2032	100.0%	2980	100.0%

Table 4- 4: Descriptive distribution of in-hospital complications within outcome

Both datasets had similar descriptive distributions, as shown in Table (4-4). According to the findings, approximately half of the patients had no complications, while one-third had one. The proportion of patients who had two or more complications was around 10%, with a low number of patients having three or more complications. This also indicates that in-hospital complications occurred in half of both datasets. These findings are consistent with the distribution of complications in the original data, implying that the NTFI was successful in capturing the underlying patterns and relationships among the variables. The results also show that the NTFI is robust and generalizable, as it performed similarly across two datasets.

Distributions were visualised with box and whisker plots for in-hospital compilations with NTFI in both cohorts. Box-whisker plots were generated with medians, data range, and distribution of complications for clinically relevant different patient groups (e.g, frailty level). This gives an overview of the NTFI association with complications. Differences in terms of central tendency, variation, and distribution were also explored. Box-whisker graphs for both datasets are depicted in Figures (4-2) and (4-3).

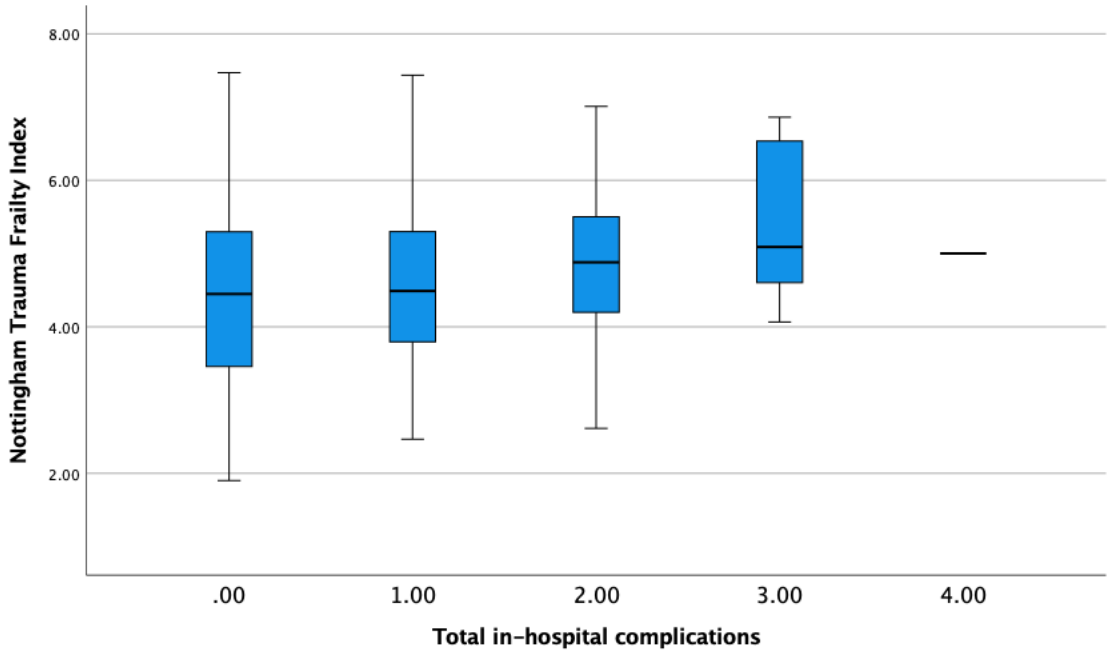


Figure 4- 2: Box-whisker plots for NTFI against in-hospital complications in the internal cohort.

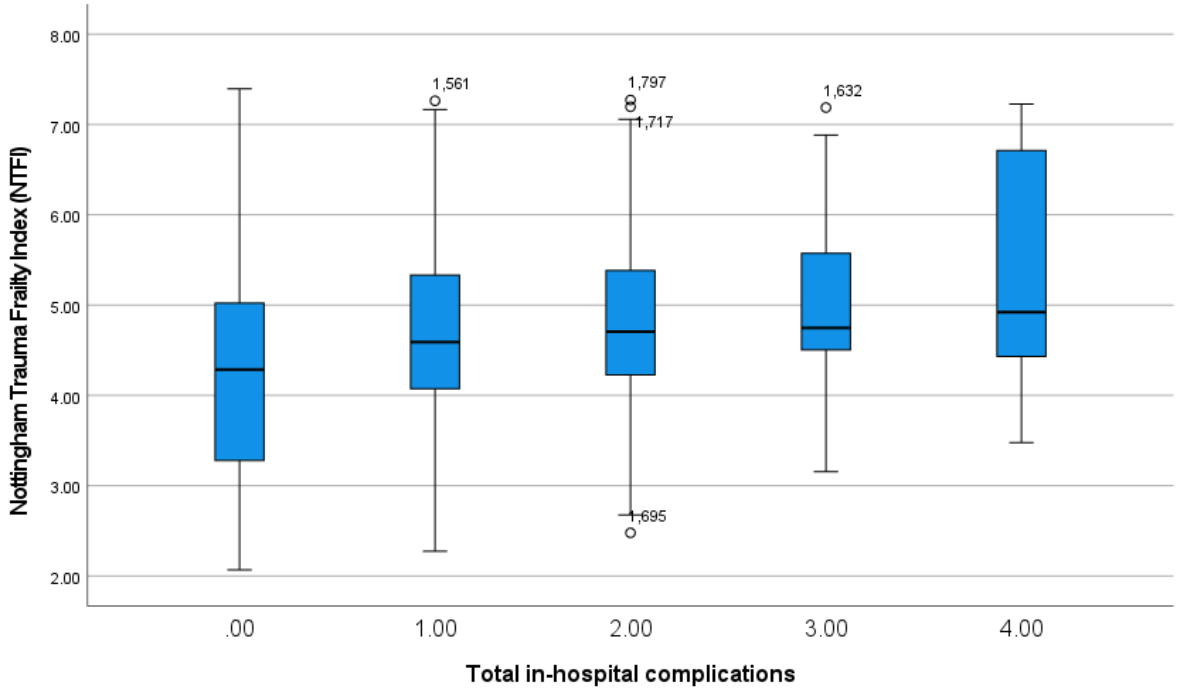


Figure 4- 3: Box-whisker plots for NTFI against in-hospital complications in the external cohort.

Figures (4-2) and (4-3) demonstrate the relationship between NTFI and total in-hospital complications for both groups using box-whisker plots. The graphs show the NTFI scores on the y-axis and the number of complications on the x-axis, which ranges from 0 to 4 on the x-axis. Both figures show that the median NTFI score rises as the number of complications increases, showing that patients with more complications are frailer than those with fewer or no complications. The interquartile range quantifies the variability of NTFI scores around the median and rises with the number of complications, implying that patients with more complications have greater variance in frailty. The figures also show the minimum and maximum NTFI values for each set of complications, excluding outliers. They also indicate that the NTFI score rises with the number of complications, reaching 6.5 for patients with three (internal validation cohort) or four (external validation cohort) complications. This suggests that individuals who are severely frail have a greater number of complications. Because there was just

one patient in the internal cohort for a total of four in-hospital complications, no analysis could be performed in this category. However, in the external cohort, patients with four in-hospital complications, the NTFI was approximately 7, indicating the severity of NTFI in this group. The figures reveal that NTFI is associated with total in-hospital complications and that NTFI increases notably among individuals with higher in-hospital complications.

The findings revealed a visual relationship between NTFI and total in-hospital complications, indicating that greater NTFI levels were linked with more complications. A statistical investigation was necessary to determine the significance of this link. The association between NTFI and total in-hospital complications was assessed using a one-way ANOVA. The findings of the one-way ANOVA for the internal cohort are shown in Table (4-5), while those for the external cohort are shown in Table (4-6).

Internal cohort

Nottingham Trauma Frailty Index (NTFI)

					95% Confidence Interval for Mean			
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	F(4,943)	Sig.
0.00	591	4.5185	1.21162	.04984	4.4206	4.6163	4.083	.003
1.00	252	4.6195	1.15504	.07276	4.4762	4.7628		
2.00	87	4.8773	1.02116	.10948	4.6596	5.0949		
3.00	17	5.4328	1.02328	.24818	4.9067	5.9589		
4.00	1	5.0030	.	.	.	.		
Total	948	4.5952	1.18512	.03849	4.5196	4.6707		

Table 4- 5: One-way ANOVA for total in-hospital complications and NTFI in the internal cohort

External cohort

Nottingham Trauma Frailty Index (NTFI)

					95% Confidence Interval for Mean			
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	F(4,2027)	Sig.
0.00	1177	4.3088	1.14997	.03352	4.2430	4.3745	20.282	<.001
1.00	567	4.6989	1.08487	.04556	4.6095	4.7884		
2.00	230	4.7999	1.04303	.06878	4.6643	4.9354		
3.00	52	4.9657	.92006	.12759	4.7096	5.2219		
4.00	6	5.2818	1.42741	.58274	3.7839	6.7798		
Total	2032	4.4929	1.13683	.02522	4.4434	4.5424		

Table 4- 6:One-way ANOVA for total in-hospital complications and NTFI in the external cohort

A one-way analysis of variance (ANOVA) was then performed to determine the relationship between the NTFI and the four distinct categories of total in-hospital complications. The NTFI had varying means across these complication groups, with an apparent increase as the number of complications escalated in both samples. Both internal and external samples yielded significant results from the one-way ANOVA analysis ($F(4,943) = 4.084$, $p = 0.03$) for the internal sample and the external sample ($F(4,2027) = 20.284$, $p < 0.001$). This indicates that the mean NTFI varied considerably between the four complications groups in both samples. Additionally, the mean NTFI increased as the number of complications increased, indicating that frailer patients had more complications.

NTFI has demonstrated a significant association with an increase in total in-hospital complications in both the internal and external cohorts. Visual inspection, descriptive analysis, and one-way ANOVA revealed a significant relationship between this outcome and NTFI. This demonstrates that an increase in NTFI is reliably related to an increase in complications and that NTFI can be used to measure this outcome in older trauma patients.

4.3.2 Length of stay and NTFI.

The internal cohort included 928 patients with LOS outcome data, while the external cohort included 2028 patients. To quantify and describe the basic characteristics and outliers of the datasets for this outcome, a descriptive analysis was performed for both cohorts. Despite the fact that data in both cohorts were not normally distributed, means and standard deviations were calculated to measure central tendency, which provides an indication of the average value of the data (see Table 4-7).

Length of stay (LOS)

		Internal cohort	**External cohort**
N	Valid	928	2028
	Missing	20	4
Mean		17.79	18.20
95% confidence interval for Mean	Lower Bound	16.97	17.63
	Upper Bound	18.61	18.78
Median		14.00	14.00
Std. Deviation		12.71	13.25
Range		149	130
Interquartile range		10	10
Minimum, Maximum		0, 149	0,130

Table 4- 7: Descriptive analyses for Length of Stay in both cohorts.

Table (4-7) reveals that the data trend for the internal cohort was located between (16.98 and 18.61) and was similar for the external cohorts (17.63 and 18.78), with a median of 14 and an interquartile range of 10 determining data concentration at these points. Cross-tabulation of means was used to compare the means of the two cohorts in order to determine the descriptive characteristics of NTFI upon LOS. This enabled a comprehension of the differences in this outcome between samples (see Table 4-8).

Nottingham Trauma Frailty Index (NTFI)

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
LOS (internal cohort)	928	4.6027	1.18263	.03882	4.5265	4.6789	1.90	7.47
LOS (external cohort)	2028	4.4941	1.13614	.02523	4.4446	4.5435	2.07	7.40

Table 4- 8: cross-tabulation between LOS and NTFI to compare the mean in both cohorts.

Table (4-8) displays the mean values of NTFI in both cohorts against LOS (internal: 4.60 versus external: 4.49). There were no significant differences between cohorts in determining the NTFI cut-off point for LOS based on means and confidence intervals for mean values. This reduced variation and similarity between the two cohorts may suggest the robustness and sensitivity of NTFI in relation to LOS outcomes. After identifying the data descriptors for both cohorts, scatter plots were generated for both cohorts so that the relationship could be visually inspected prior to conducting the analyses (see Figures 4-4 and 4-5).

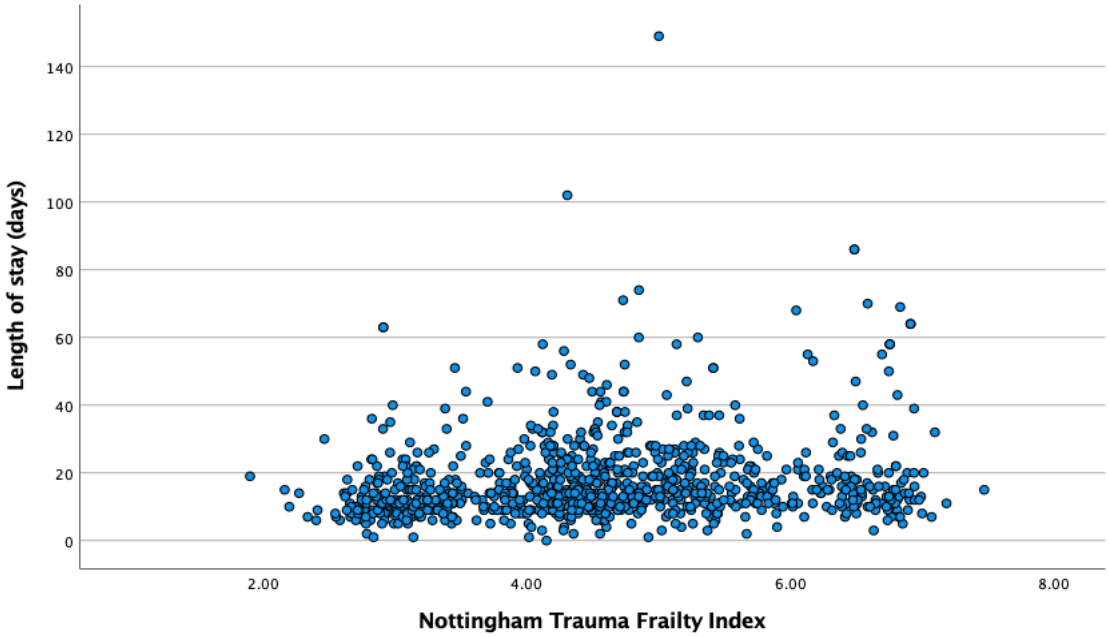


Figure 4- 4: A scatter plot for LOS and NTFI in the internal cohort

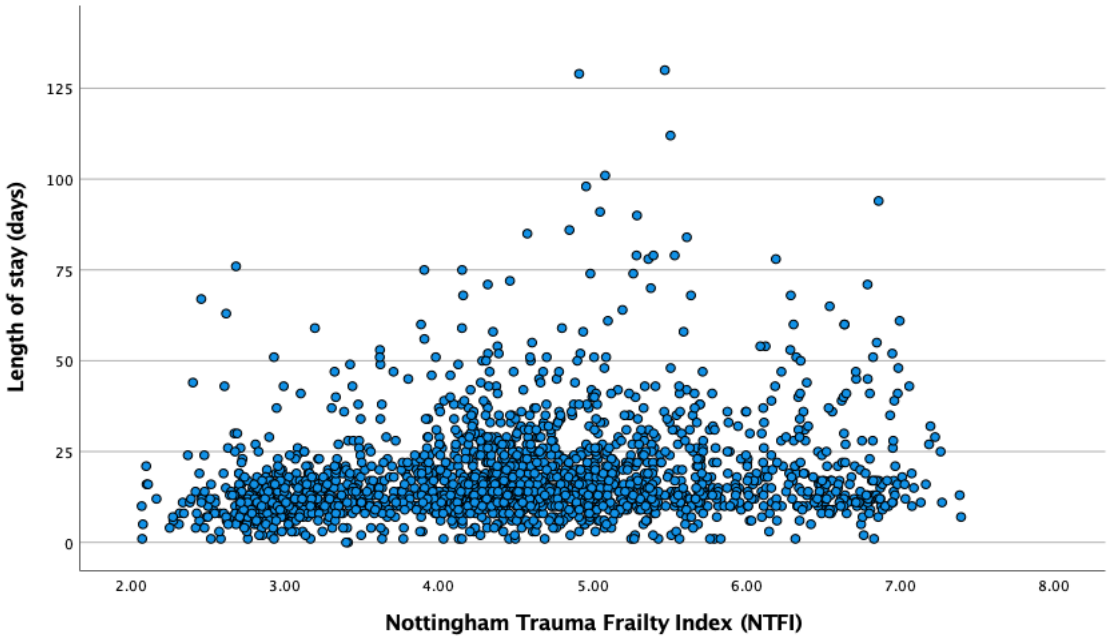


Figure 4- 5: A scatter plots for LOS and NTFI in the external cohort

A visual inspection of the scatter graphs (Figures 4-5 and 4-6) depicting the relationship between LOS and NTFI reveals that there is no clear linear relationship between the two variables. The absence of a discernible pattern in a scatter plot does

not, however, rule out the possibility of a correlation. Taken in the clinical setting (when considering the complications data suggesting a strong relationship between NTFI and complications), this lack of meaningful correlation can be explained in a number of ways. In the trauma setting, patients sometimes die, and their length of stay will be recorded until their death. Whilst it would be ideal to be able to review death data, many patients in the UK do not have a post-mortem, and as such, a reliable cause of death is impossible to establish. There is also a paradox with highly dependent patients who may be admitted from a nursing home who can be rapidly discharged home to their pre-existing care, thereby reducing the length of stay where the less frail may live independently and need the provision of additional support, delaying discharge. These and other explanations may contribute to the only modest correlation between LOS and NTFI.

However, based on the data, the relationship between NTFI and LOS appears to be consistent, with a slight increase among those with high NTFI. This establishes the importance of a statistically significant correlation coefficient test that indicates the existence of a relationship that may not be readily apparent from a visual inspection alone. For a deeper understanding of the complex relationship between NTFI and LOS in these datasets, additional statistical rigour was required.

The Pearson correlation coefficient (r) test was then employed to provide statistically significant correlation evidence that NTFI is associated with LOS differences. This test can also quantify the relationship by providing a precise assessment of the degree of relationship between NTFI and length of stay in both cohorts (see Table 4-9).

		Pearson Correlation	Sig. (2-tailed)	95% Confidence Intervals (2-tailed)[a]	
				Lower	Upper
Internal cohort	Nottingham Trauma Frailty Index - Length of stay (days)	.172	<.001	.108	.233
External cohort	Nottingham Trauma Frailty Index - Length of stay (days)	.203	<.001	.161	.244

a: Estimation is based on Fisher's r-to-z transformation.

Table 4- 9: Pearson correlation coefficient (r) for NTFI and LOS in both cohorts

The Pearson correlation coefficients (r) obtained for the two cohorts examining the relationship between NTFI and length of stay (LOS) are as follows: in the internal cohort, the observed correlation coefficient of r = 0.172, p<.001, and in the external cohort, a correlation coefficient of r = 0.203, p<.001. These findings reveal a statistically significant positive linear relationship between NTFI and the length of stay for both the internal and external cohorts. The positive sign of the correlation coefficients indicates that the length of hospital stays tends to increase as NTFI scores increase.

4.3.3 Discharge destinations and NTFI

Both cohorts had discharge destination data widely available, with the internal cohort including 948 patients with discharge destination outcome data and the external cohort including 2032 patients. Home, acute hospital, rehabilitation unit, residential care home, nursing care, mortality, and others were among the recorded discharge destinations. The primary descriptive analyses were performed on both cohorts to describe the characteristics of discharge destinations outcomes and quantify the number of patients in each destination (see Table 4-10).

	Internal cohort		External cohort		Total	
	N	Percent	N	Percent	N	Percent
Others	65	6.9%	235	11.6%	300	10.1%
Own home/sheltered housing	401	42.3%	965	47.5%	1366	45.8%
Acute hospital	20	2.1%	28	1.4%	48	1.6%
Rehabilitation unit	232	24.5%	303	14.9%	535	18.0%
Residential care home	0	0%	170	8.4%	170	5.7%
Nursing care	169	17.8%	178	8.8%	347	11.6%
Dead	61	6.4%	153	7.5%	214	7.2%
Total	948	100%	2032	100%	2980	100%

Table 4- 10:Descriptive analyses for discharge destinations in both cohorts

Comparing the internal cohort with the external cohort, Table (4-10) reveals that there were similarities and differences in certain destinations. Importantly, in both cohorts, less than half of the patients were discharged to their own homes, indicating that a significant proportion of patients required alternative care arrangements. Notably, 24.5% of patients in the internal cohort were referred to a rehabilitation unit, compared to 14.9% of patients in the external cohort. In the internal cohort, there were no discharges to residential care homes, and 17.8% of patients transitioned to nursing care. Comparatively, the external cohort had a greater proportion of patients transitioning to residential care homes 8.4% and fewer patients discharged to nursing care 8.8% than the internal cohort. Both cohorts had low mortality (internal: 6.4% vs. external: 7.5%), indicating that older trauma patients may be more prone to complications and significant long-term challenges and morbidity, but their clinical presentation might not always result in immediate mortality. In order to visualise these

data with NTFI, box-whisker graphs were generated for both cohorts (see Figure 4- 6 and 4-7).

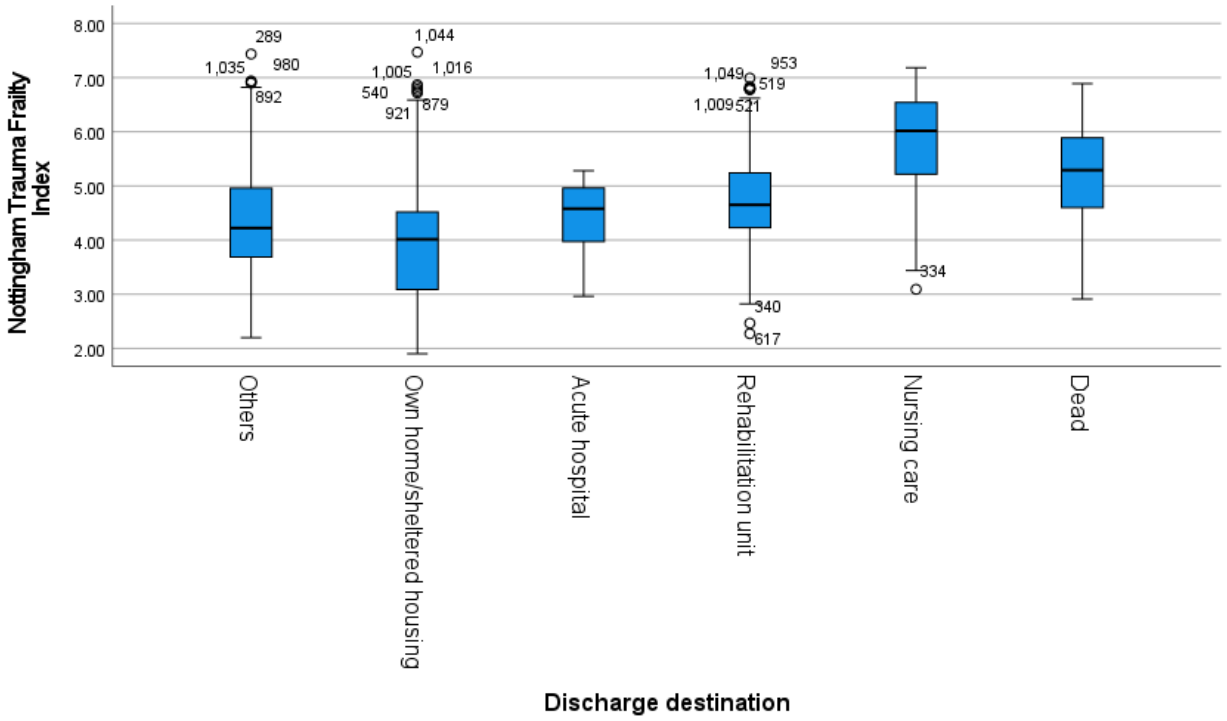


Figure 4- 6: Box-Whisker plots for discharge destinations and NTFI for the internal cohort

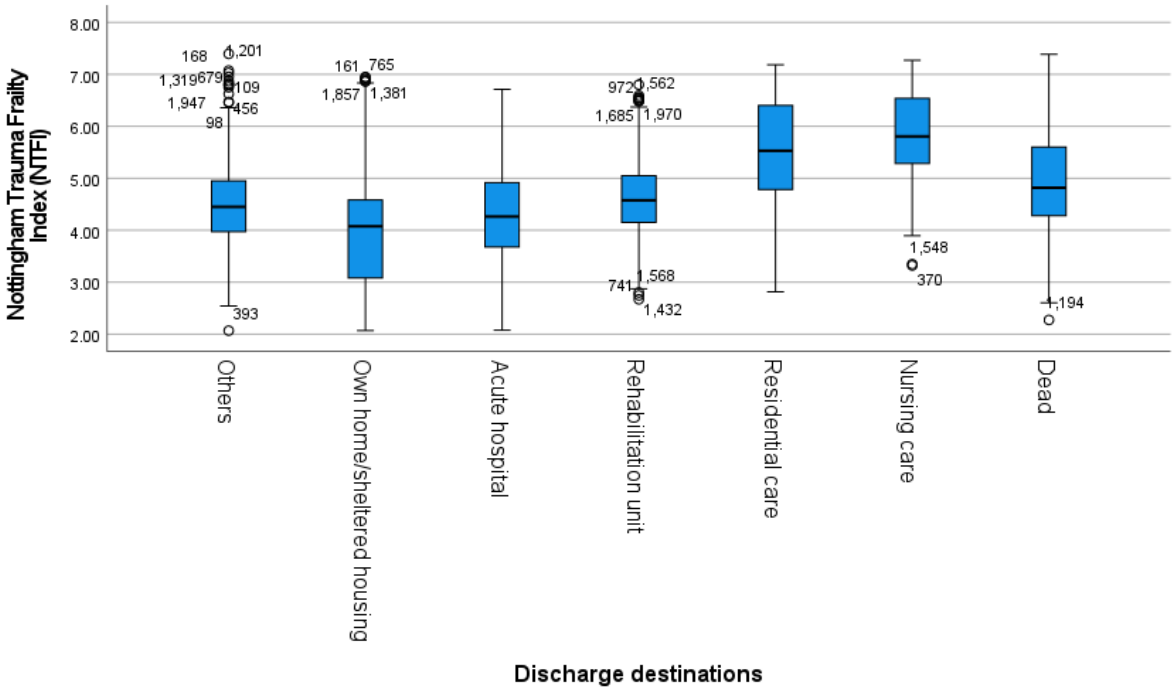


Figure 4- 7: Box-Whisker plots for discharge destinations and NTFI for the external cohort

Box-whisker plots in figures (4-6) and (4-7) reveal a consistent rise in both figures in relation to the NTFI score at discharge destinations. In the internal cohort, the box-and-whisker plot reveals a median NTFI of 4 for home-discharged patients, with an interquartile range (IQR) extending from 3.1 (Q1) to 4.5 (Q3) and only 6 outliers. The same interpretation was discovered for home-discharged patients in the external cohort, demonstrating the convergent validity of NTFI to evaluate this aspect of the outcome. Internal cohort NTFI median slightly higher than external cohort NTFI median (internal: 4.6 vs. external: 4.3), with lower (Q1) in external cohort 3.7 vs. internal 4 and same (Q3) in both cohorts for acute hospital discharge. The greater range of the IQR in the external cohort suggests that patients with a lower NTFI could also be discharged to an acute hospital. This can be understood by networked care, which is common in the UK, where patients will be discharged to a local hospital following treatment in the trauma centre. Except for outliers, rehabilitation unit discharge rates were consistent across cohorts, with a median of 4.5 and a similar IQR. For patients discharged to nursing care, medinas varied between cohorts (internal: 6, externa: 5.8), whereas IQRs were the same in both cohorts (5.2-6.5), indicating that patients may have a higher NTFI but within the same NTFI range. Mortality medians in the two cohorts differed marginally (internal: 5.3, external: 4.9), with no outliers (internal: 4.6-5.9, external: 4.3-5.8). Compared to nursing care destination, a lower NTFI for mortality may indicate an earlier death caused by a high injury severity score, in which trauma has a greater impact than frailty. However, mortality exhibited a higher NTFI compared to the remaining destinations, excluding nursing care, indicating the validity of NTFI for predicting discharge destination outcomes. A potential explanation for this is that severely frail patients may die before

they are admitted. Furthermore, the orthopaedics dataset does not include patients receiving end-of-life care. Furthermore, trauma is classified as an acute diagnosis. Consequently, patients who are admitted with trauma are not admitted based on their cumulative deficit but rather due to a sudden and acute event. Making mortality rates more reflective of community-wide mortality as well as the burden of injury and surgery.

However, the constant similarity across datasets in both figures for discharge destinations shows that the NTFI is robust and not dependent on the individual dataset utilised. A further one-way ANOVA was performed to determine the means of the various destinations in relation to NTFI and to determine whether there are significant distinctions between the means (see Tables (4-11) and (4-12).

Internal cohort

Nottingham Trauma Frailty Index (NTFI)

					95% Confidence Interval for Mean			
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	F(5,942)	Sig.
Others	65	4.3958	1.17181	.14535	4.1054	4.6861	98.323	<.001
Own home/sheltered housing	401	3.9417	.98062	.04897	3.8455	4.0380		
Acute hospital	20	4.3823	.68270	.15266	4.0628	4.7018		
Rehabilitation unit	232	4.7412	.91516	.06008	4.6228	4.8596		
Nursing care	169	5.8140	.90204	.06939	5.6770	5.9510		
Dead	61	5.2406	1.01991	.13059	4.9793	5.5018		
Total	948	4.5952	1.18512	.03849	4.5196	4.6707		

Table 4- 11: One-way ANOVA for discharge destinations and NTFI in the internal cohort

External cohort

Nottingham Trauma Frailty Index (NTFI)

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean Lower Bound	95% Confidence Interval for Mean Upper Bound	F(6,2025)	Sig.
Others	235	4.4863	.96619	.06303	4.3621	4.6105	143.644	<.001
Own home/sheltered housing	965	3.9740	.97908	.03152	3.9121	4.0358		
Acute hospital	28	4.3068	1.09490	.20692	3.8822	4.7313		
Rehabilitation unit	303	4.5902	.82425	.04735	4.4970	4.6834		
Residential care	170	5.5101	1.01751	.07804	5.3560	5.6641		
Nursing care	178	5.8185	.81879	.06137	5.6973	5.9396		
Dead	153	4.9451	1.04971	.08486	4.7774	5.1127		
Total	2032	4.4929	1.13683	.02522	4.4434	4.5424		

Table 4- 12: One-way ANOVA for discharge destinations and NTFI in the external cohort

On both the internal and external cohorts, a one-way analysis of variance (ANOVA) was then performed to ascertain the relationship between the NTFI and the discharge destinations and to assess whether there is a significant difference between the means of the discharge destinations being compared. The NTFI was found to have varying means across these discharge destinations, with an evident increase as discharge to adverse or more specialised destinations increased in both datasets. The one-way ANOVA analysis produced significant results for both internal and external samples. $F(5,942) = 98.32$, $p < 0.001$ for the internal cohort, whereas $F(6,2025) = 143.64$, $p < 0.001$ for the external cohort. This indicates that the mean NTFI varied significantly between discharge destination groups in both cohorts, with the exception of mortality, where the mean was marginally lower. In addition, the mean NTFI increased as patients were discharged to unfavourable destinations, suggesting that frailer patients are more likely to be discharged to unfavourable destinations.

Both the internal and external cohorts exhibited a significant association between NTFI and an increase in discharges to unfavourable destinations. The results of descriptive analyses, Box-Whisker plots, and a one-way ANOVA revealed a significant correlation between discharge destination outcome and NTFI. This demonstrates that a rise in NTFI is dependably associated with a patient's discharge to a poor destination.

4.3.4 The increase in dependency level and NTFI

A full numerical scale was constructed for both cohorts after completing calculations between the two included variables to create this composite outcome, using pre-admission residences with discharge destinations (see above Table 4-1). Each domestic destination was allocated to a numerical scale, and the change in dependency was calculated. There were three pre-admission residences available for this outcome: home, care home resident, and nursing home resident. For both cohorts, calculations were performed separately for each pre-admission residence. A descriptive analysis was performed to summarise the characteristics of each dwelling in each cohort in connection to the increase in dependency level outcome (Table 4-13).

Preadmission residence	The increase in dependency level		Internal cohort		External cohort	
			N	Percent	N	Percent
Home	.00		445	59.1%	1166	65.3%
	1.00		20	2.7%	28	1.6%
	2.00		219	29.1%	293	16.4%
	3.00		26	3.5%	114	6.4%
	4.00		43	5.7%	53	3.0%
	5.00		0	0	132	7.4%
		Total	753	100.0%	1786	100.0%
Care Home Resident	.00		32	16.8%	81	49.7%
	1.00		141	73.8%	69	42.3%
	2.00		18	9.4%	13	8.0%
		Total	191	100.0%	163	100.0%
Nursing Care	.00		4	100.0%	75	90.4%
	1.00		0	0	8	9.6%
		Total	4	100.0%	83	100%

Table 4- 13: Descriptive analyses for the increase in dependency level outcome in both cohorts

Table (4-13) displays the number of patients in each increase in dependency level depending on their pre-admission residences, as each increase determines the amount of care required for patients. In the internal cohort, 41% of patients did not return home as their final destination, with the majority at two of the increases in dependency level outcome by 29.1%. In the external cohort, 34.7% of patients for this residence were not sent home, and the increase in dependency level was likewise highest at number two (16.4%). This demonstrates that approximately half of the patients admitted from their homes were not returned home, and the majority had an increase in dependency level of at least two. For patients admitted from residential care homes, 83.2% in the internal cohort and 50.3% in the external cohort were not improved or returned to care homes, indicating a higher risk of complications and increased care need for patients admitted from care homes. Community nursing care

homes are the highest level of community nursing care; as expected, there was no significant increase in dependency levels across both cohorts due to a ceiling effect. Box-whisker plot graphs were generated for both cohorts to depict the association of an increase in dependency level outcome with the use of NTFI (see Figure (4-8) and (4-9).

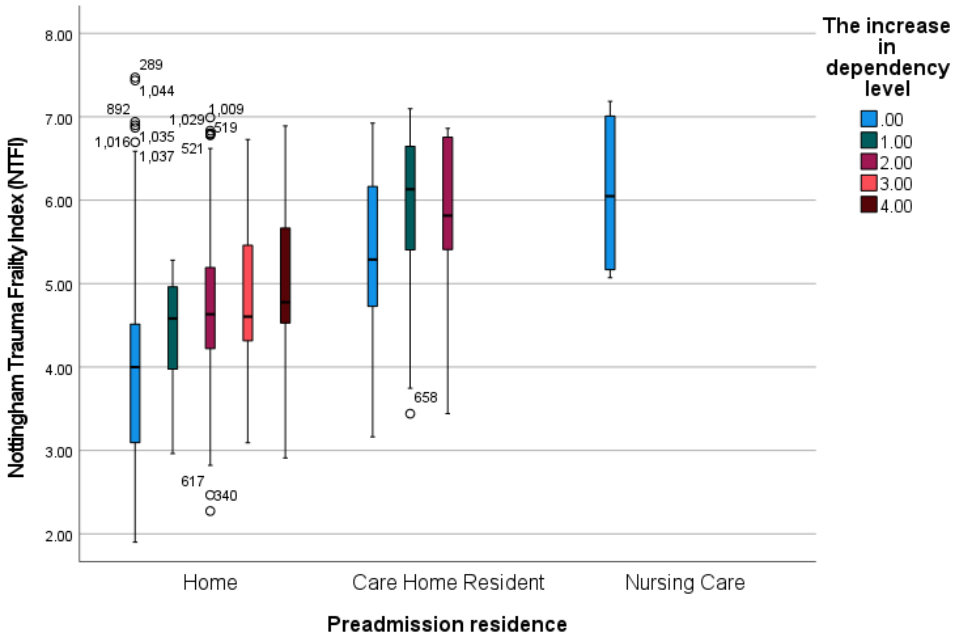


Figure 4- 8: Box-whisker plots for the increase in dependency level outcome with NTFI in the internal cohort

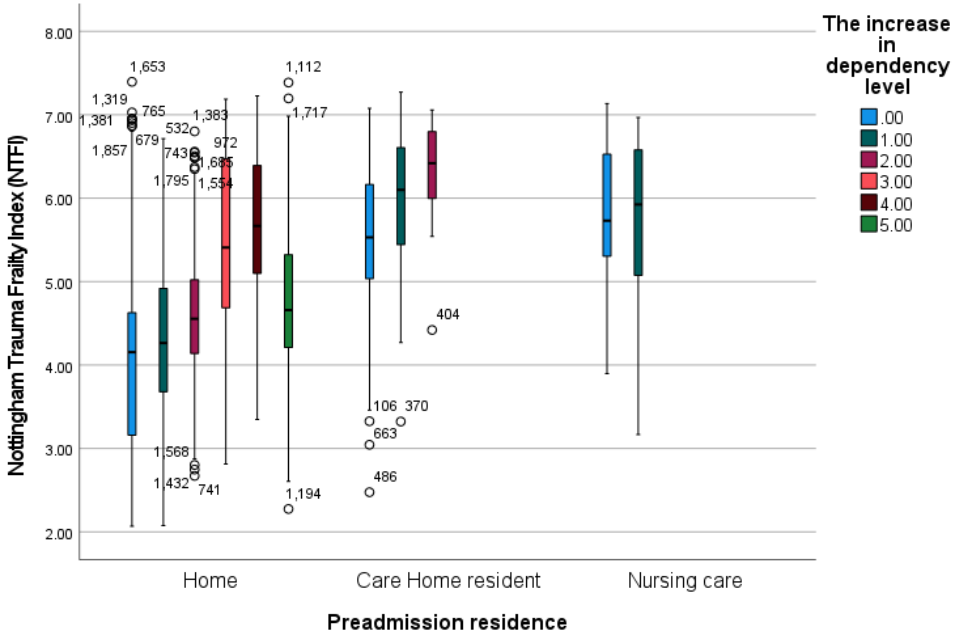


Figure 4- 9: Box-whisker plots for the increase in dependency level outcome with NTFI in the external cohort

Figures (4-8) and (4-9) show that NTFI increased with dependency level in each pre-admission residence group and that higher NTFI was visually associated with an increase in dependency level. In the internal cohort, patients were admitted from homes, NTFI medians and (IQRs) for the increase in dependency levels (0-4) were as follows: 4 (3-4.5), 4.5 (3.9-4.9), 4.6 (4.3-5.3), 4.5 (4.4-5.6), and 4.9 (4.8-5.8) represent the consistent increase across all four levels of NTFI, with a few outliers. While in the external cohort for the same residence, NTFI medians and IQRs for dependency levels 0, 1, and 2 were comparable, those for levels 3 and 4 were slightly higher [level 3: 5.5(4.6-6.5) and level 4: 5.7(5.2-6.4)], respectively. Patients with a score of 5 died during the care episode in the external cohort of patients admitted from the home group; the median and (IQR) for the NTFI were low 4.6(4.3-5.4), which indicates that inpatient mortality is not entirely linked to the NTFI. Patients in both cohorts had higher NTFI medians for care home residents compared to home, demonstrating the ability of the NTFI score to differentiate between care home and home patients. At levels 0 and 1 of care home residents, the medians and (IQRs) were the same for both cohorts [level 0: internal 5.3 (4.7-6.2), external 5.4 (5.1-6.2)] and [level 1: internal 6.2 (5.4-6.6), external 6.2 (5.5-6.6)]. While the IQRs were higher for both cohorts at level 2 compared to levels 0 and 1, the internal cohort had a lower median [level 2: internal 5.8 (5.4-6.8), external 6.5 (6.0-6.8)]. For nursing home residents, only level zero was represented in the internal cohort with a median of 6.1 and an IQR (5.3-7.00), while external cohorts represented levels 0 and 1 [level 0: 5.7 (5.4-6.6), level1: 5.9 (5.1-6.7)]. Both cohorts showed higher NTFI and a consistent increase in medians for patients admitted from nursing homes.

In summary, a noticeable increase in medians across three pre-admission residences was observed, along with an increase in dependency levels, indicating that patients

admitted from homes are likely to have a lower NTFI than those admitted to care homes or nursing homes. Additionally, the significant determination of NTFI for these patients admitted from different residences with an increase in dependency levels determines the ability of NTFI to predict frailer patients and the relationship between each residence's increase in dependency levels. Additional one-way ANOVA tests were conducted to determine whether there is a significant difference between the means of the increase in dependency level in NTFI being compared (see tables 4-14 and 4-15).

Internal cohort

Nottingham Trauma Frailty Index (NTFI)

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		F(4,943)	Sig.
					Lower Bound	Upper Bound		
0.00	481	4.0524	1.04805	.04779	3.9585	4.1463	97.200	<.001
1.00	161	5.7902	.92784	.07312	5.6458	5.9346		
2.00	237	4.7896	.96082	.06241	4.6666	4.9126		
3.00	26	4.8356	.92518	.18144	4.4619	5.2093		
4.00	43	4.9748	.94535	.14416	4.6839	5.2657		
Total	948	4.5952	1.18512	.03849	4.5196	4.6707		

Table 4- 14:One-way ANOVA for the increase in dependency level and NTFI in the internal cohort

External cohort

Nottingham Trauma Frailty Index (NTFI)

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		F(5,2026)	Sig.
					Lower Bound	Upper Bound		
0.00	1274	4.1714	1.05903	.02967	4.1132	4.2296	98.460	<.001
1.00	36	4.6079	1.25219	.20870	4.1843	5.0316		
2.00	341	4.7022	.89772	.04861	4.6066	4.7978		
3.00	183	5.6498	1.00424	.07424	5.5034	5.7963		
4.00	66	5.7886	.89403	.11005	5.5688	6.0084		
5.00	132	4.7720	.95549	.08317	4.6075	4.9366		
Total	2032	4.4929	1.13683	.02522	4.4434	4.5424		

Table 4- 15:One-way ANOVA for the increase in dependency level and NTFI in the external cohort

On both the internal and external cohorts, a one-way ANOVA was conducted to evaluate the relationship between the NTFI and the increase in dependency level outcome and to determine if there is a significant difference between the means of the increase in dependency levels being measured. The increase in dependency level was not associated with the pre-admission residences in the on-way ANOVA, and analyses were conducted using the levels of increase in dependency from each residence. This was performed in order to validate the overall outcome and ascertain the univariate association between NTFI and an increase in dependency levels. The

NTFI was discovered to have varying means across the increase in dependency levels, with an obvious increase in both cohorts. For both internal and external cohorts, the one-way ANOVA analysis yielded significant results. $F(4,943) = 97.20$, $p < 0.001$ for the internal cohort, whereas $F(5,2026) = 98.46$, $p < 0.001$ for the external cohort. This indicates that the mean NTFI differed considerably between increasing levels of dependency in both cohorts, with the exception of level 5 in the external cohort, where the mean was slightly lower. This indicates that frailer patients are more likely to experience an increase in dependency level and can be identified by a greater NTFI.

In both internal and external cohorts, a significant association between NTFI and an increase in dependency level outcome was seen. This is consistent with the concept of frailty and indicates NTFI is a measure of vulnerability. Descriptive analyses, Box-Whisker plots, and a one-way ANOVA revealed a significant correlation between increase in dependency level outcome and NTFI. This demonstrates that an increase in NTFI is reliably associated with an increase in a patient's level of dependency.

4.3.5 Model performance

All four measured outcomes (in-hospital complications, length of stay, discharge destinations, and increase in dependency level) yielded significant results. The relationship between these outcomes and NTFI appeared to be positive based on descriptive analyses and visualisations conducted prior to the one-way ANOVA. In the in-hospital complication outcome, NTFI ranged between 4.51-5.00 in the internal cohort and 4.30-5.28 in the external cohort, with narrow confidence intervals (CIs) across all complications. The results of the two cohorts determined the reliability of the NTFI to identify frailty in patients with a greater number of complications. Scatter plots

did not reveal an apparent relationship between NTFI and LOS; however, Pearson's correlation test revealed a positive relationship between NTFI and LOS for both cohorts, with marginally similar means for both cohorts (internal: 4.60 vs. external: 4.49) and a significant P value <0.001, with narrow confidence intervals (CIs). A striking result for the discharge destination outcome was that half of the patients in both groups were not returned home. Furthermore, an increase in NTFI was related to more unfavourable destinations in both groups. The one-way ANOVA for this outcome likewise revealed that nearly identical NTFI means were detected for both cohorts, with the same consistent increase for each adverse destination, ranging from 3.94 to 5.24 in the internal cohort and 3.97 to 4.95 in the external, with P<0.001. The same was seen for dependency level increase and NTFI, with a similar increase in NTFI with dependency level increase results in both cohorts. As a consequence, similarities in NTFI values with narrow confidence intervals across assessed outcomes in both cohorts demonstrate the NTFI's robustness of performance in detecting frail patients and capacity to predict outcomes for older people with trauma.

4.4 Discussion

Two validations of the NTFI and its relationships with different clinical outcomes were performed in this chapter. The objective was to investigate the relationship between the developed NTFI and outcomes by analysing the visual graphs of outcomes in order to study the distributions of NTFI on outcomes prior to the application of statistical methods. Additionally, statistical methodologies were used to establish NTFI's predictive ability for measuring frailty in older trauma patients. Visual inspections of the four outcomes demonstrated that NTFI was rising with unfavourable outcomes,

indicating that greater NTFI is validly associated with negative outcomes. $F(5,942) = 98.32$, $p < 0.001$ for the internal cohort, while $F(6,2025) = 143.64$, $p < 0.001$ for the external cohort, indicating the greater variances of means between complications numbers across both cohorts. The results of the one-way ANOVA demonstrate the reliability of NTFI as a predictor of complications, with substantial variation observed between the various levels of complications. This demonstrates the NTFI's ability to differentiate between frail individuals and the number of complications. The LOS outcome was unable to demonstrate the pattern of relationship between NTFI and LOS since the relationship was not clearly represented in scatter plots. However, Pearson's correlation coefficients of both cohorts revealed a linear relationship between LOS and NTFI (internal cohort, $r = 0.172$, $p<.001$, and external cohort, $r = 0.203$, $p<.001$), indicating that an increase in NTFI was associated with longer hospital stays in both cohorts. Some missing values were observed for this outcome; however, the data in this clinical registry were presumed to be missing completely at random (MCAR), so a complete case analysis would not be expected to introduce systematic bias (256). In both cohorts, discharge destinations were substantially associated with NTFI, with low NTFI means observed in mortality cases. This is because all trauma patients in both cohorts were included to visualise the actual association of discharge destinations based on NTFI, without trauma severity classifications or early death exclusion. Further validation may be necessary to categorise patients based on injury severity against NTFI, with the exclusion of early mortality patients who are at high risk of death owing to trauma severity (55). This was subsequently discovered in the formulation of the composite outcome for the increase in dependency level outcome when patients at higher levels were impacted by outcome misclassification, resulting in low NTFI at those levels (257). However, an increase in dependency level was

validly associated with NTFI in determining the increase in specialised care needs among included patients.

The measured clinical outcomes were significantly appraised by NTFI, with a high significant p value of $P<0.001$, implying the robustness of NTFI in discriminating between less favourable results within each outcome. As a result, NTFI has validly defined poor outcomes in both cohorts with high NTFI values and similar means, indicating the prediction capacity and the approximation threshold for the majority of included outcomes.

This is the first validation of a frailty index for trauma patients using routinely collected clinical data, to the best of our knowledge. In addition to being user-friendly, automated, and based on routinely available physiological and historical patient data that does not require staff training to use, NTFI distinguishes effectively between poor outcomes and frailty levels. In this chapter, two separate validations were conducted to establish the strong predictive capabilities of NTFI in determining outcomes and its association with adverse outcomes. Despite the fact that NTFI has demonstrated findings that allow it to be independently validated and implemented in other institutions, additional validation may be required to investigate its performance in other registries, centres, or countries.

One limitation of the validations in this chapter was the reliance on a database from a single centre for both internal and external validation. This approach may have resulted in similarities in patient characteristics, influencing generalizability. Although NTFI has shown significant prediction coefficients that validate the use of the tool upon outcomes, independent validation may be needed in other centres to validate the applicability and generalizability of the results to diverse patient populations. Another limitation could be the use of total in-hospital complications as a single outcome, which

may not account for the severity of each complication. However, the goal was to use NTFI to evaluate the association of the overall risk of complications in older trauma patients. Furthermore, both discharge destinations and increase in dependency level outcomes were influenced by outcome misclassification, which resulted in a low NTFI representation of mortality patients. This is due to the complete representation of patients, as the objective was to visualise and not evaluate the function of NTFI on those patients, which may assist minimise survivorship bias when only including survivors (258). However, the consistent rise in each pre-admission residence with the other increase in dependency levels outcome and discharge destinations determines the role of NTFI in accurately detecting frailty for these patients without the confounding factors. As a result, further validations may be required to remove patients who died on admission or within the first 24 hours following admission in order to validly quantify mortality outcomes using NTFI.

The NTFI has shown that the capacity to recognise frailty is validly associated with worse outcomes in older trauma patients. Significant results from both internal and external validations indicate the NTFI's border applicability to identify frailty and poor outcomes. These validations enable the tool to be used in other current clinical and research datasets where frailty was not assessed to investigate the impact of frailty on patients' outcomes. Furthermore, since NTFI is simple to implement and does not need training, it is cost-efficient, and clinical services would not be required educate or assign specialists to use NTFI, and it could be used retrospectively to monitor outcomes. Further research is required to determine the NTFI cut-off point for the development of adverse outcomes in order to identify the development of frailty in adverse outcomes.

4.5 Conclusion

The NTFI has demonstrated its usefulness in diagnosing poor outcomes related to frailty in two independent cohorts, and external validation has encouraged its widespread use. However, setting a precise and diagnostic threshold would improve the precision of clinically relevant frailty identification, proving that the tool accurately finds those who are at high risk of adverse outcomes. This would allow clinicians to better target treatments, perhaps improving the prognosis of older trauma patients through fast interventions that minimise frailty-related complications. A well-defined cut-off would also enhance clinical decision-making by giving clear recommendations for consistent use, facilitating the wider adoption of NTFI across a variety of trauma settings. This crucial task of determining the most appropriate cut-off point will be addressed in the following chapter.

Chapter 5: Stratification of Patient Outcomes Using a Nottingham Trauma Frailty Index (NTFI) Threshold Point for the Development of Adverse Outcomes

5.1 Introduction

Frailty instruments' ability to precisely identify patients who are frail and at high risk of experiencing adverse outcomes is critical. Current frailty tools for identifying frailty are vulnerable to bias introduction in trauma contexts, whether in assessments or statistical classification in research (259). These biases can have a negative impact on the accuracy and effectiveness of these tools. One of the biases that may occur during older patient assessment is performance bias, which can arise when there are systematic differences in training, thereby introducing potential covariates that can influence the observed frailty scores (214). Observer bias (assessor bias) is an additional potential bias that could also be introduced during the assessment or selection of groups in research. Observer bias can occur when health care providers subjectively assess frailty, leading to inadvertent favouritism or preconceived expectations (260). For instance, the clinical frailty scale CFS is used in trauma studies to classify frailty groups, where some have classified it into two (107, 108, 150), or three (59) or four categories (104). The presence of these biases can substantially compromise the reliability and accuracy of evaluating frailty in trauma-related individuals. However, one of the aims of developing NTFI was to mitigate biases displayed by patients or clinicians during frailty assessment in trauma situations. Despite the inherent biases of trauma, NTFI seems to be able to save clinicians time in diagnostic frailty and minimise biases such as observer bias based on initial injury

phases, allowing clinicians to make the optimal clinical decision for the appropriate patients. Furthermore, the objectivity of the NTFI would make it straightforward for clinicians to identify frailty in trauma patients using the five objective physiological and historical patient data that are routinely available.

Previous chapters have validated NTFI in several ways to assure its applicability in a variety of situations and to demonstrate its dependability and clinical utility. Early validation and verification of NTFI were performed to assess the predictive ability and coefficients of NTFI before its application to clinical outcomes. Additional internal validation and external validation (out-of-sample validation) were conducted to investigate and visualise the relationships between selected outcomes and NTFI, as well as to affirm significant associations and generalisability. NTFI was able to represent frailty among outcomes and determine that negative outcomes were associated with high frailty across all available outcomes, with significant correlations. NTFI has also been shown to indicate susceptibility to adverse outcomes, demonstrating this instrument's ability to measure factors relevant to both frailty and the likely occurrence of poor outcomes. On the basis of these foundations, the NTFI has demonstrated discriminatory predictive abilities and significant findings against clinical outcomes, establishing its clinical applicability and relevance in measuring frailty in older trauma patients. However, frailty status varied amongst patients, and the NTFI tool's cut-off point is critical for prognostic value and risk stratification, identifying the most impacted group and assisting clinicians in understanding the potential trajectory of frailty-related trauma to prepare for future care needs. Consequently, the purpose of this chapter is to establish a threshold within the NTFI that indicates a higher risk for the development of adverse outcomes.

The purpose of using clinical outcomes for identification was to accurately differentiate the group of individuals who are at high risk of experiencing frailty consequences from the frailty group using the NTFI. This is in line with the concept of frailty as vulnerability to "challenge" due to age-related multisystem deficits (15, 261). Consequently, the NTFI incorporated two challenges: the trauma challenge, which involved exclusively older trauma patients, and the clinical outcome challenge, which will be used in this chapter to establish the threshold for unfavourable outcomes. NTFI utilised the two challenges to improve the accuracy of identifying individuals who are frail and to precisely determine the beginning of unfavourable outcomes that accurately represent the heightened risks associated with frailty consequences. Hence, the purpose of this chapter is to determine the precise thresholds of NTFI that signify the occurrence of adverse consequences. The objective will be accomplished by examining two distinct groups, one internal and one external, with the aim of determining an optimal threshold that can accurately forecast negative outcomes in older trauma patients.

5.1.2 Research question

This chapter will investigate the diagnostic ability of the NTFI and the optimal cut-off value in relation to clinical outcomes. To determine the NTFI cut-off point in relation to clinical outcomes, the sensitivity versus specificity of the NTFI values will be statistically mapped. Consequently, the research question for this chapter is as follows:

What is the optimal predictive frailty cut-off on the NTFI for the onset of adverse outcomes?

5.1.2 Objectives and hypotheses

1. Investigating the sensitivity and specificity of NTFI in relation to the clinical outcomes of two distinct datasets.
2. Visualising and measuring the relationships between NTFI values and the risks of adverse outcomes across multiple outcomes of two datasets.
3. Determining and validating the optimal NTFI threshold for the development of adverse outcomes.

5.2 Methods

There are a variety of statistical analyses for identifying cut-off points, with distinctions dependent on the nature of the data and the research question. Sensitivity and specificity are the two crucial metrics utilised to determine the cut-off marks. Sensitivity determines the ability of the test to identify patients with an illness, while specificity is the ability of a test to reliably identify individuals without the illness (262). These were utilised in various diagnostic tests for cut-off identification in the medical field. Some of these methods have not been used in previous chapters, including:

- Receiver Operating Characteristic (ROC) Curve Analysis is one of the most accurate statistical tests used to determine the optimal cut-off point by mapping the sensitivity versus 1-specificity for all possible values, where the optimal cut-off point is defined as the point on the ROC curve closest to the (0,1) point (263, 264). The primary outcomes of ROC curve analysis are the diagnostic accuracy of the test and the optimal cut-off value for the test.

- Youden’s index test (264), which can be derived from the analysis of the ROC curve to determine the optimal cut-off point. In the ROC curve, the Youden’s J-index cut-off is depicted by the vertical distance between the diagonal line and the ROC curve. It is an appropriate test if both sensitivity and specificity are equally essential for diagnostic purposes, as it maximises the balance between the two (265). However, it may not be appropriate if diagnostics want to prioritise one over the other, such as when positive cases (sensitivity) are more meaningful than negative cases (specificity) (266).
- The diagnostic odds ratio, which is also utilised in conjunction with the ROC curve to determine an optimal cut-off point by balancing sensitivity and specificity. The diagnostic odds ratio is computed as the ratio of the odds of true positives to the odds of false positives, distinguishing between true positives and false positives (267). It integrates sensitivity and specificity to provide a single metric for evaluating diagnostic performance (267). In the case of normal distributions with equal variances, however, it could lead to cut-off values at the parameter range's boundary and produce unreliable diagnostic results (268). In order to identify accurate diagnostic results, this test can only be applied to data with a non-normal distribution and unequal variances.

On the basis of data, a research question, a graphical representation of an NTFI's performance with measured outcomes, and the fact that maintaining high sensitivities is crucial to the success of a diagnostic test (269), the identification of the cut-off point using the area under the ROC curve analysis was used for NTFI upon outcomes. In addition to identifying the cut-off point, the ROC curve profile estimates the discriminative ability of the NTFI. The area under the ROC curve (AUC) can take on any value between 0 and 1, with an ideal diagnostic test having an AUC of 1 and an

ineffective test having an area of ≤0.5 (270). In the context of test development or validation, it is often seen that the performance of the ROC may exhibit variability when used in various clinical situations. Hence, it is often recommended to average the test's sensitivity and specificity by combining the results of multiple outcomes in order to evaluate the diagnostic test (270). Nevertheless, the intention was to extract two functions from the ROC curve: the AUC that quantifies the overall discriminative capacity of the NTFI, and the best threshold for identifying the onset of adverse outcomes. Given the incapacity to integrate multiple clinical outcomes into a single variable and the hypothesis requirements of the ROC curve, the calculation of ROC curves was conducted individually for each clinical outcome. This approach was used to accurately depict the performance of NTFI and provide more precise cut-off points across the various outcomes. This may result in a lower AUC for NTFI with certain non-severe clinical outcomes, but it will aid in determining the lowest cut-off points for NTFI with these outcomes, as well as the baseline of frailty effects introduction.

The two datasets (internal and external) were then used to evaluate a wider trauma population and represent the diagnostic accuracy of NTFI with precise cut-offs for measured outcomes. Following ROC curve analysis conversion and interpretation requirements, outcomes were prepared as binary outcomes indicating the absence or presence of the measured outcome (271). Then, multiple ROC analyses were conducted within the two datasets for each component of clinical outcomes used against NTFI, and cut-off points were determined for each. Multiple cut-off points were determined based on the outcomes measured for both cohorts. The optimal cut-off point was identified as the lowest predictive NTFI score associated with the occurrence of adverse outcomes in both cohorts. This is due to the fact that the determination of

the cut-off point cannot be based on a single outcome, and the lowest predictive NTFI can predict other outcomes and reduce false negatives, whereas other criteria may not accurately represent adverse outcomes. Other methods, such as the selection of the optimal cut-off point by selecting the most frequent cut-off occurrences, were inapplicable because multiple cut-offs were identified with varying decimal points to depict different situations (272). The weighted mean cut-off point by allocating weight to each ROC curve based on the importance of outcomes was also inappropriate (273), as all adverse outcomes were important and the weight between measured outcomes was equal. Because of the NTFI's clinical relevance and sensitivity to poor outcomes, the lowest NTFI was the most appropriate method for determining the onset and threshold for the development of adverse outcomes (274) (see Figure 5-1).

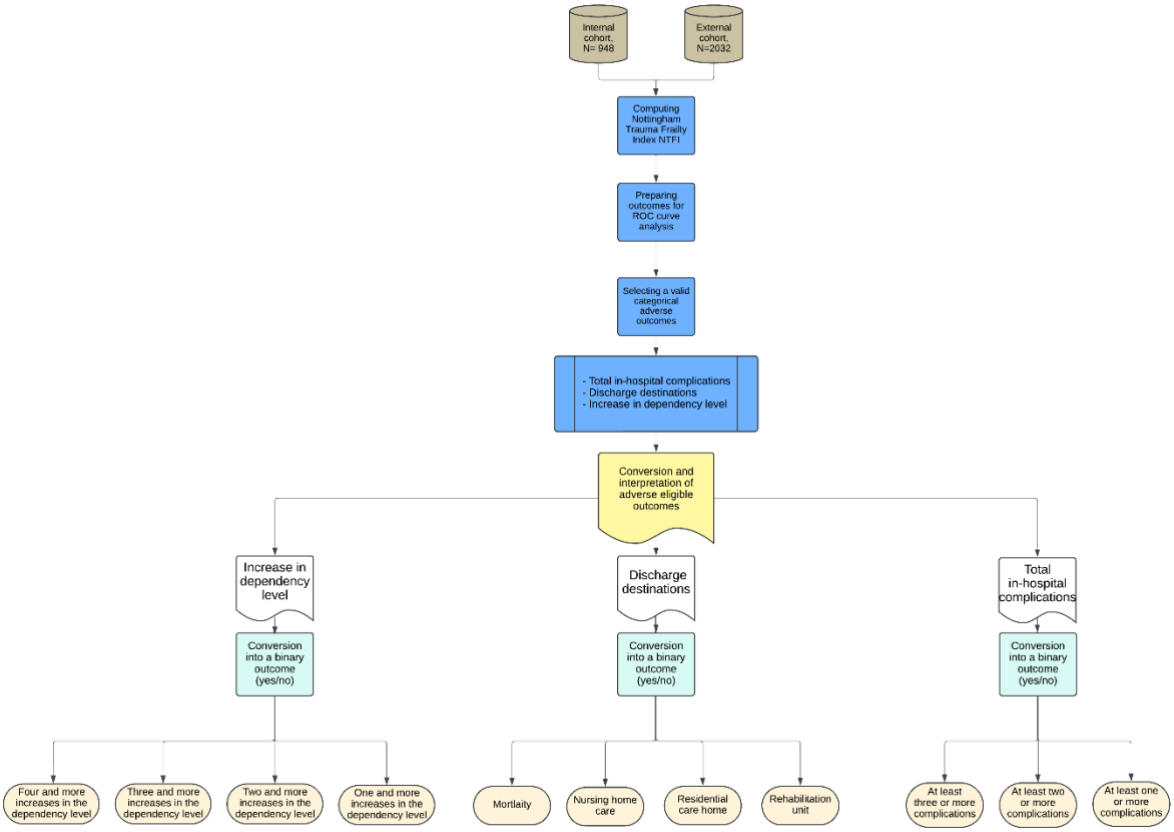


Figure 5- 1: Flowchart depicts the processes of selecting and converting outcomes for ROC analyses.

After identifying the cut-off point, the identified value was used in binary logistic regression against adverse outcomes to determine the significance and predictive ability of NTFI risk stratification. The chapter was reported in accordance with a full series of phases using transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD statement for model validation) (146), in order to ensure that the methodological approach of identifying and validating the cut-off was adequately covered. IBM SPSS Statistics (version 28.0.0.0) was also used to compile and code the data (148).

5.2.1 Source of data

The data source, which was previously described in the previous chapter (Chapter 4). In brief, they are prospectively collected registry data for older trauma patients (>65) who were admitted to level one trauma centre from October 2015 to July 2020. The data were extracted from the Nottingham Trauma Registry, which integrated data from three routinely collected clinical patient groups: fragility fractures, hip fractures, and adult trauma. The two cohorts used in the previous chapter were included in the analyses for this chapter in order to investigate clinical outcomes performance and define cut-off points for NTFI. The testing dataset (internal validation cohort) and out-of-sample dataset (external validation cohort) were utilised for validation and identification. An approval has been previously obtained for data collection and analysis of the audit, and the project approval number is **21-040C.** The same data protection measures were applied in this chapter, following the Caldicott principles, to ensure the anonymity and confidentiality of data as in pervious chapters.

5.2.2 Participants

Two cohorts were used to validate the predictive value of the NTFI against clinical outcomes through internal and external validation processes. The internal validation cohort (testing cohort as previously described), which is the second half of the dataset used for model development and validation of NTFI using the train-test split method described in (Chapter 4, Section 4.2). The external cohort (patients without frailty measure) included patients without frailty who were not involved in the model development and validation. Patients' inclusion in both datasets was subjected to the following eligibility requirements:

- Age of 65 years and older.
- Presenting with a fracture necessitating hospitalisation.
- Variables for the Nottingham Trauma Frailty Index (NTFI) are available.

5.2.3 Outcome

One of the objectives of this chapter was to establish the validity of the predicted frailty as determined by the NTFI outcome across various clinical outcomes. The NTFI was computed and combined into separate variables for each cohort using five variables: age, pre-admission mobility, Abbreviated Mental Test, haemoglobin, and mechanism of injury. The NTFI obtained from cohorts was then used as the dependent variable (outcome) in relation to clinical outcomes via the use of ROC analysis. The cut-off point of NTFI was identified for each prepared outcome category employed in the ROC analysis. The cut-off points of the NTFI for individual categories were then tested against the internal and external sets in order to determine an optimal threshold for the occurrence of adverse outcomes.

The determined optimal cut-off point was then used in a binary logistic regression analysis to assess the predictive efficacy of the optimal NTFI threshold in relation to adverse outcomes, hence validating its prognostic utility.

Consequently, NTFI was employed as an outcome in two different contexts. Mainly, it was employed as a continuous outcome in ROC analyses to validate diagnostic performance and identify potential cut-offs for the development of adverse outcomes. Second, once an optimal threshold was determined, the NTFI was transformed into a binary outcome. This was to validate the predictive ability of the threshold on adverse outcomes through binary logistic regression utilising the threshold.

5.2.4 Predictors

The candidate predictive outcomes were described in (Chapter 4, Section 4.2.3). These were subjected to correlation analysis with NTFI; and all candidates were found to correlate across outcomes, thereby establishing significant univariate associations with NTFI. In this chapter, the diagnostic performance and cut-off point of these outcomes in relation to NTFI were evaluated. This chapter used outcomes to determine the thresholds for the onset of adverse outcomes using NTFI. In ROC analyses, the test variable must be in continuous form, whereas the measured outcomes must be binary. This is a common requirement for ROC-based diagnostic accuracy studies; outcomes must be binary for accurate identification of the presence or absence of the outcome and the cut-off (275). Therefore, the conversion and interpretation of continuous clinical outcomes into dichotomous categories was required to validate certain outcomes, such as increase in dependency level and in-hospital complications. These outcomes were selected as opposed to dichotomising by thresholds, to avoid being potentially misleading metrics (276). Each outcome was

then subdivided into multiple binary outcomes to generate true values that accurately represent the performance of the outcome against NTFI with fewer diagnostic errors (277). The dichotomisation of numerical outcomes took into account the available categories and numerical representations. This is to define cut-offs based on diagnostic performance for each category and to specify the cut-off value (reference value) to distinguish between patients. However, length of stay was not included with the outcomes in this chapter because the data ranged from zero to 149 days, making it challenging to assume dichotomising thresholds and conduct ROC analysis that may be driven by misleading thresholds. The length of stay (LOS) outcome was then excluded from outcomes to avoid diagnostic inaccuracies and loss of estimation efficiency due to dichotomisation (278). Therefore, the remaining outcomes are as follows:

- Total in-hospital complications.
- Discharge destinations.
- Increase in dependency level.

These outcomes were utilised in this chapter against NTFI. Multiple ROC analyses were conducted for each outcome from both internal and external validation cohorts in order to represent NTFI diagnostic performance on outcomes and identify the optimal cut-off point.

5.2.4.1 Total in-hospital complications

In-hospital complications are one of the most important outcomes measured for older trauma patients (279). This is as a result of frailty, which increases the risk of complications due to the compromised physical condition and diminished resilience (280). This establishes that measuring in-hospital complications in this population is

crucial, as it correlates with prolonged hospital stays and quality of life after discharge. Consequently, this outcome is not only a relevant measure for older trauma patients with frailty, but it can also determine the potential risks associated with discharge outcomes. As previously described, total in-hospital complications ranged from 0 to 4 in both cohorts. In the previous chapter, total in-hospital complications were found to be associated with NTFI after developing and analysing a composite outcome consisting of pneumonia, renal failure, UTI, and blood transfusion. This outcome was divided into three categories in this chapter, each of which represents a specific number of complications. The following categories were present:

- At least one or more complications
- At least two or more complications
- At least three or more complications

In the previous chapter, it was determined that the NTFI across each number of complications in total in-hospital complications outcomes increased as the number of complications increased. The purpose of separating total in-hospital complications in this chapter was to satisfy ROC analysis requirements by utilising an appropriate visualisation for the diagnostic performance of NTFI based on the number of complications and not just the total impact. This is to determine and evaluate the possible cut-off points across the various categories of the two cohorts in order to precisely determine the optimal threshold.

5.2.4.2 Discharge destinations

Destination at discharge is one of the less biased outcomes that reveals important elements of care and patient status after treatment (281). Different criteria, including

frailty status, trauma severity, and pre-injury physiological state, might influence the choice of discharge destinations in older trauma patients with frailty. This implies that discharge destinations may or may not be impacted by unrelated patient characteristics and may or may not accurately represent the patient's condition. However, NTFI was significantly associated with unfavourable discharge destinations across both cohorts in the preceding chapter. This establishes that the NTFI was able to precisely determine the discharge destinations for older trauma patients with frailty.

The outcomes of discharge destinations varied between the two cohorts in the previous chapter. In the external cohort, some patients were discharged to a residential care home, whereas there were none of these events in the internal cohort. This underlines the value of external validation of NTFI as various possible discharge destinations for older trauma patients with frailty are identified. With the exception of mortality, the increase in NTFI was associated with adverse destinations in both cohorts in the previous chapter. However, low mortality rates at discharge among older trauma patients with frailty were a common finding in studies of trauma patients (104, 107). It is important to note that the results could be influenced by frailty or other factors such as injury-related aspects, confirming the difference frailty can make to outcomes when combined with trauma, and frailty outcomes such as disability and independence level may be better measured outcomes for those patients. However, the association between mortality and NTFI would not impact the identification of the cut-off point, as the NTFI threshold was chosen based on which category had the lowest NTFI across all selected outcomes. Consequently, discharge destinations from both cohorts were used in conjunction with ROC analyses to identify thresholds for each destination. Death, nursing home care, residential care home, rehabilitation unit, acute hospital,

and home were the available discharge destinations. Those discharged to the following destinations were eligible for inclusion:

- Rehabilitation unit
- Residential care home
- Nursing home care
- Mortality

The analysis and identification of cut-offs did not include patients who were released home or sent to acute hospitals. This decision was made in order to determine the threshold value of NTFI that is associated with the occurrence of adverse outcomes. Including these two destinations, which do not represent adverse outcomes, might potentially result in an inaccurate or biased estimation of the threshold value for adverse outcomes. Hence, an evaluation was conducted on four destinations for the NTFI, taking into consideration the availability of destinations for both cohorts. The analysis eliminated destinations that had no patients.

5.2.4.3 The increase in dependency level

The preceding chapter's definition of increase in dependency level as a composite outcome resulted in a successful assessment of dependency level change among older trauma patients with frailty. A considerable increase in dependency level needs after discharge was established. This was linked to NTFI in both cohorts, indicating that older trauma patients with frailty were more likely to remain dependent after discharge. Approximately half of patients from both cohorts were released to unfavourable destinations in contrast to their pre-admission places of residence,

indicating an increase in dependency level. The substantial results establish the relationship between an increase in dependency level and NTFI, highlighting the importance of including this outcome in investigations to determine the optimal threshold for adverse outcomes. Due to various discharge destinations amongst cohorts, the results ranged in the internal cohort from 0 to 4, and in the external cohort from 0 to 5. As a result, this outcome was assessed using ROC analysis for the internal validation cohort as follows:

- One and more increases in the dependency level
- Two and more increases in the dependency level
- Three and more increases in the dependency level

While for the external validation cohort:

- One and more increases in the dependency level
- Two and more increases in the dependency level
- Three and more increases in the dependency level
- Four and more increases in the dependency level

For cut-off identification, each category was subsequently assessed using ROC analysis. This is intended to explore the performance on various dependency levels in order to appropriately depict the effect of an increase in dependency level on older trauma patients with frailty. This is due to the fact that each increase in dependency level category determines discharge to more adverse destinations that need inquiry and may represent distinct potential NTFI degrees. As a consequence, these groups were numerically separated in order to properly identify the correct probable cut-offs

for the increase in dependency level, which give a comprehensive depiction of the conclusion with precise results.

5.2.5 Sample size

Two cohorts were used, with the aim of conducting two distinct validations. As was stated in the preceding chapter, two samples—internal and external validation cohorts—were utilised exclusively for validation objectives and did not participate in the NTFI development process. The sample size was a convenience sample, utilising all available data from a large dataset. These samples were also employed in this chapter to discover and validate NTFI's predictive value for the development of adverse outcomes. The testing cohort (internal validation cohort), as previously stated, comprised 948 patients who were qualified for validation inclusion. A wider trauma population was present in the second sample. It contains data on 2032 trauma patients from the Nottingham Trauma Registry whose data were excluded from the construction or validation of NTFI due to eligibility criteria in the database. In order to examine the NTFI's reproducibility, generalizability, and threshold identification, it was imperative to employ an external validation cohort to validate the prognostic value of the NTFI in a more extensive trauma population (282). Consequently, two validations utilising internal and external cohorts were performed to determine and validate the optimal threshold for the development of adverse outcomes.

5.2.6 Missing data

Missing data was handled as described in (Chapter 4, Section 4.2.5). There were no missing NTFI patient data in either cohort. In addition, there were no missing clinical

outcomes or discharge destination data in either validation cohort. In both cohorts, therefore, a complete set of data was utilised for ROC analyses, threshold determination, and logistic regression to determine the NTFI predictive value.

5.2.7 Statistical analysis methods

The data pertaining to patients, NTFI variables, and clinical outcomes were appropriately prepared prior to conducting analyses for both cohorts. This included coding and labelling variables, as well as outcomes, in accordance with the specific needs of the data analysis. The NTFI data variables were consistently used in their continuous form across both cohorts. Initially, clinical outcome variables were used as binary outcomes in order to facilitate the fitting of ROC analyses. This included dividing the outcome into categories and then assessing each category. In logistic regression analyses, clinical outcomes were also utilised in the original categorical and continuous forms to validate the identified cut-off point. As a consequence, the two cohorts (internal validation cohort and external validation cohort) were employed in two separate statistical methodologies versus clinical outcomes to satisfy the chapter's goals for identification and validation.

Identification of a cut-off point

ROC curve analyses were used to evaluate binary clinical outcomes, including the occurrence of in-hospital complications, discharge destinations, and increase in dependency level, using the data from the two cohorts with NTFI. Clinical outcomes were converted into a binary form with the intent of accurately capturing each category within the outcomes. ROC curve analyses were conducted to determine the best cut-off point for the development of adverse outcomes by including the outcomes of both

cohorts and the test variable (NTFI). Cut-off points were identified by selecting the point on the ROC curve with the shortest distance from the left-upper corner of the unit square, where sensitivity = 1 and false positive rate = 0 (specificity = 1) (271, 283, 284). As a result, threshold points were first produced, and then selection was performed in accordance with the coordinates of the curve table for each outcome category, with the area under curve AUC larger than 0.5 (285). This technique was utilised with nine different binary outcomes in the internal cohort, resulting in the identification of nine cut-off points. The external validation cohort (which contains more fields) yielded eleven cut-off points using the same approach. The lowest NTFI threshold determined by ROC curves across cohorts was then used as a cut-off point for the development of adverse outcomes validated in logistic regression.

Validating the predictive ability of the optimal cut-off point

A second analysis was undertaken using the NTFI variable, which was dichotomised based on the optimum threshold established using the appropriate cut-off point. This was then further evaluated against clinical outcomes using logistic regression analysis to assess its predictive capacity for adverse outcomes, with variables deemed statistically significant if their p-values were ≤0.05. Adverse outcomes from available measures were chosen as the sole focus of the logistic regression analysis, with the intention of including and considering only the following categories of adverse outcomes:

- The discharge destination was divided into two groups (adverse vs. non-adverse). Only the adverse destinations were used in the regression analysis. The adverse destinations included were consistent with the destinations utilised for ROC curve analyses. These were “discharge to a rehabilitation unit”,

"discharge to a residential care home", "discharge to nursing home care", and mortality.

- The increase in dependency level outcome was employed as a continuous variable, as the increase in number defined a higher degree of despondency level.
- In-hospital complications were also used as a continuous variable against NTFI, since each additional rise in the number of complication events corresponds to a greater number of complications experienced by patients.

These outcomes were paired with the ideally identified NTFI to demonstrate the point's validity in terms of adverse outcome prediction, generalizability, and potential integration into a practical application.

5.3 Results

A total of 948 patients in the internal validation cohort and 2032 patients in the external validation cohort were included in both the ROC analyses and the validation of the optimal threshold. The table depicting the characteristics of patients is shown in (Table 4-2), as stated in the preceding chapter.

5.3.1 Participants

Patients with NTFI calculated and meeting the eligibility criteria for analyses were included in the two cohorts. The cohorts' characteristics were compared as a measure of equivalence. Table (5-1) shows the patient outcomes and clinical outcome characteristics for both cohorts. The median age of patients in both internal and external cohorts was similar (85 vs. 84), and females were more prevalent in both

(70.1% vs. 71.5%). The internal validation cohort's NTFI mean was slightly higher than the external validation cohort (4.59 vs. 4.49). Adverse discharge destinations were substantially greater in the internal validation cohort (39.6% vs. 51.3%). About half of the patients in the internal validation cohort were not discharged to their homes, and more than a third were in the external cohort, indicating the high likelihood of adverse discharge destinations for patients in both cohorts. The mortality rates observed in both cohorts were relatively low, with rates of 6.4% and 7.5%, respectively. It is worth noting that mortality is cumulative and may be more accurately assessed over a longer period of time. On the other hand, there are significant unrelated mortality rates in this population demographic, and measures taken too far into the future are less likely to be causally related. The increase in dependency level was similarly larger in both cohorts, with almost half of the included patients in both cohorts requiring more specialist care or dying after discharge. Furthermore, both cohorts had a high rate of complications, with about 40% of patients in each cohort experiencing complications. The findings show that older trauma patients in the two studied cohorts may not face imminent death as a result, whereas frailty outcomes may have a greater impact on quality of life and dependency level after discharge.

	Internal validation cohort	External validation cohort
Number of patients	948	2032
Age [median (IQR)]	85 (11)	84 (12)
Sex		
Female (n, %)	665 (70.1%)	1453 (71.5%)
NTFI [mean (SD)]	4.59 (1.19)	4.49 (1.14)
Adverse discharge destinations (n,%)	462 (51.3)	804 (39.6%)
Rehabilitation unit (n,%)	232 (24.5%)	303 (14.9%)
Residential home care (n,%)	-	170 (8.4%)
Nursing home care (n,%)	169 (17.8%)	178 (8.8%)
Mortality (n,%)	61 (6.4%)	153 (7.5%)
The increase in dependency level (n,%)	467 (49.3%)	710 (34.9%)
In-hospital complications (n,%)	357 (37.7%)	855 (42.1%)

NTFI, Nottingham trauma frailty index;

Table 5- 1: The clinical outcomes and characteristics of the patients included in the internal and external validation cohorts

5.3.2 Development of the NTFI cut-off point

Nine ROC analysis curves were generated for the different outcome categories in the internal validation cohort, whereas 11 ROC curves were created for the external validation cohort. The interpretation of each ROC curve was conducted on an individual basis in order to determine the optimal threshold for predicting the occurrence of the particular outcome category. A total of twenty ROC curves were generated, each corresponding to a distinct threshold value obtained. The retrieved data from each ROC curve contained the Area Under the Curve (AUC), the confidence interval (CI), and the cut-off point. The cut-off point was determined based on the coordinates table, which provided the sensitivity and specificity values. The cut-off values for the included outcomes were as follows: in-hospital complications (one and more complications, two and more complications, three and more complications),

discharge destinations (rehabilitation unit, residential care home (external cohort only), nursing home care, and mortality), and increase in dependency level (one and more, two and more, three and more, and four and more (external cohort only)).

5.3.2.1 NTFI and in-hospital complications

The ROC analyses of NTFI with in-hospital complications yielded three ROC curves for the internal validation cohort and three curves for the external validation cohort (see Appendices (9 to 14) for details). The findings were consolidated and presented in (Table 5-2). The ROC curve analysis for at least one in-hospital complication and more revealed an AUC value for the internal cohort of 0.55 (95% CI [0.51-.59]) and was comparable to the external cohort AUC of 0.61 (95% CI [0.59-.64]) with both demonstrating similar curve shape and performance that significantly outperformed chance (0.5). In terms of AUCs, the similarities between both cohorts in the first in-hospital complications define the stability of NTFI in identifying low frailty rates, as the discovered cut-offs were the lowest across complications (NTFI: 4.490 internal and NTFI: 4.432 external). For the second phase of complications (at least two or more), the internal and external cohorts had the same AUC of 0.61. This demonstrates that the internal group performed better, whereas the external cohort performed the same with one hospital complication and more. This is not a concern since consistency of AUC with fewer complications does not imply poor performance, as performance is determined by attaining an AUC >0.5. This may occur to some degree when sensitivity increases (true positive rate), but at the cost of specificity (true negative rate), resulting in a balanced trade-off (286). This occurred throughout the early phases of ROC curves with complications in both cohorts, finding that a high NTFI was balanced to

predict instances of two or more complications. This is a reasonable performance identifier, given that not all patients with higher NTFIs experienced two or more complications; in fact, some patients with high NTFIs may have encountered additional complications or other fatal outcomes such as mortality. However, the determined NTFI thresholds were higher in both cohorts when compared to one or more complications groups (4.620 internal and 4.551 external), indicating the influence of complications on NTFI performance. In the group of patients with at least three or more complications, the internal cohort exhibited a high AUC of 0.70 (95% CI [0.60-.80]) and the external cohort revealed a greater AUC of 0.64 (95% CI [0.58-.70]), with both demonstrating comparable curve shapes and performance considerably surpassed by chance (0.5). The identified cut-off values for the development of three complications or more were greater in both cohorts (NTFI: 4.758 internal and NTFI: 4.562 external). It is obvious that NTFI rises with increased complications in both samples, with a higher NTFI determination in the internal cohort across all three complications groups. This might be due to sample variability, as the included patients in the internal cohort had greater NTFI than the external cohort, as the mean NTFI in the internal cohort was 4.59 (SD 1.19) vs. 4.49 (SD 1.14) for the external cohort, or to variations in the prevalence of the outcome between the samples. This, however, illustrates the consequences of using two separate samples for validation and different categories in ROC curves for determining the cut-off point. The determined cut-off values varied from 4.490 to a maximum of 4.758 across all categories in both cohorts. NTFI demonstrated that increases in complications were significantly associated with increases in the NTFI threshold ($p<0.05$), and NTFI is capable of determining patients with greater and lower complications throughout the evaluation of the ROC analyses for six curves.

Cohorts	Number of hospital complications	AUC	P-value	Cut-off point	95%CI	Sensitivity	Specificity
Internal validation cohort	At least one or more complications	.55	.009	4.490	.51-.59	.55	.49
	At least two or more complications	.61	.000	4.620	.56-.66	.61	.44
	At least three or more complications	.70	.004	4.758	.60-.80	.67	.40
External validation cohort	At least one or more complications	.61	.000	4.432	.59-.64	.61	.44
	At least two or more complications	.61	.000	4.551	.58-.64	.61	.43
	At least three or more complications	.64	.000	4.562	.58-.70	.64	.45

Abbreviations: AUC, area under curve; ROC, receiver operating characteristic

Table 5- 2: ROC analysis for in-hospital complications with NTFI in both cohorts

5.3.2.2 NTFI and adverse discharge destinations

The possible discharge destinations included in the ROC analyses varied across cohorts. Discharge destinations for the internal validation cohort comprised discharge to a rehabilitation unit, discharge to nursing home care, and mortality. Discharge destinations for the external cohort were identical to those of the internal cohort, with the addition of discharge to a residential care home (see Table (5-3)). As a result, four ROC curves for the external cohort were generated compared to three for the internal cohort (see Appendices (15 to 21) for details). For patients discharged to rehabilitation units, ROC curves shape performance was poorer at higher thresholds, with some early occurrences of a downward trend in the curves, with attained AUC >0.5 in both cohorts. This shows that patients with high NTFI were less likely to be discharged to a rehabilitation unit, indicating the NTFI's performance validity, and that individuals with more adverse outcomes may have higher NTFI thresholds. This was also verified

by the identified cut-offs, which were the lowest in both cohorts across discharge destinations (NTFI: 4.560 internal and NTFI: 4.496 external). Furthermore, discharge to a rehabilitation unit may or may not be regarded as an adverse destination because discharge to a rehabilitation unit may be for necessary specialised therapy, whereas others may regard discharge to a rehabilitation unit as an intrinsic part of the recovery process after trauma. However, older trauma patients with frailty may be discharged to rehabilitation for deconditioning during hospital stays or treating frailty-related issues for such patients with customised therapy and restoration of functioning (287). Thus, classifying discharge to rehabilitation institutions as entirely adverse in assessing outcomes for frail older trauma patients may oversimplify their complicated recovery routes. In the group of patients discharged to nursing home care, the AUC was 0.85 (95% CI [0.82-.88]) in both cohorts, and the external cohort revealed an AUC of 0.86 (95% CI [0.83-.88]), with both demonstrating perfect accuracy performance with curves closer to the upper left corner. The excellent performance of NTFI with nursing home care discharge confirms both the validity of NTFI as a frailty measure in trauma and the importance of nursing home care discharge as a frailty outcome. The internal cohort had the highest detected cut-off, at 4.849, while the external cohort had the highest, at 5.022. This shows that older trauma patients with frailty are more likely to be discharged to nursing home care with a higher NTFI than other discharge destinations such as mortality, confirming the importance of measuring frailty outcomes for trauma patients and not just mortality as a determinant of adverse destination for these patients. This was additionally observed in patients discharged to a residential care facility in the external cohort, with an AUC of.77 (95% CI [0.83-.88]) and NTFI threshold of 4.765. Both discharge destinations, residential care homes and nursing home care, are meant to provide assistance for those patients in daily life

activities, demonstrating an important shift in dependence in older persons with frailty after trauma. These data demonstrate that frailty outcomes differ from standard trauma outcomes and that older trauma patients with frailty are more likely to be sent to nursing home care and residential care homes with greater frailty. Another possible confirmation for this was the death rates in both cohorts, which were NTFI cut-offs lower than nursing and residential care (NTFI: 4.686 internal and NTFI: 4.528 external), with an AUC of .68 (95% CI [0.62-.74]) for the internal cohort and .63 (95% CI [0.58-.67]). Similar curve shapes were seen in both cohorts, with lower NTFIs identified, indicating that death may not be the preferred destination for older trauma patients. However, NTFI performance with mortality at different time points, such as one-year mortality, may differ, as one-year mortality may give a wider evaluation of frailty consequences and take into account the chronic nature of frailty and progression after discharge (288). As a result, analysis of discharge destinations revealed that older trauma patients with greater NTFI were released to residential care homes and nursing home care, whereas those with lower NTFI died.

Cohorts	Discharge destination	AUC	P-value	Cut-off point	95%CI	Sensitivity	Specificity
Internal validation cohort	Rehabilitation unit	.56	.004	4.560	.53-.60	.56	.45
	Nursing home care	.85	.000	4.849	.82-.88	.85	.28
	Mortality	.68	.000	4.686	.62-.74	.66	.41
External validation cohort	Rehabilitation unit	.54	.016	4.496	.51-.57	.54	.47
	Residential care home	.77	.000	4.765	.74-.81	.77	.34
	Nursing home care	.86	.000	5.022	.83-.88	.85	.24
	Mortality	.63	.000	4.528	.58-.67	.62	.46

Abbreviations: AUC, area under curve; ROC, receiver operating characteristic

Table 5- 3: ROC analysis for discharge destinations with NTFI in both cohorts

5.3.2.3 NTFI and the increase in dependency level

The increase in dependency level outcome was analysed using the available categories, which were three in the internal validation cohort and four in the external validation cohort. The range of dependency level increase was 0-3 in the internal cohort and 0-4 in the external validation cohort, with each number of increases indicating an adverse destination that was not where the patient was prior to admission. The ROC curves for each increase in dependency level with NTFI are provided in appendices (see Appendices 22 to 28) and the results are shown in (Table 5-4). Patients with one or more increases in dependency level had the greatest AUC in the internal validation cohort of .78 (95% CI [0.75-.81]), which was equivalent to the external validation cohort AUC of .72 (95% CI [0.70-.75]), with both displaying similar curve shapes and strong NTFI performance. The internal validation cohort's NTFI cut-off point was 4.345, while the external cohort was 4.399. Similar performance with

somewhat comparable thresholds, indicating that the spread of NTFI thresholds was consistent with the total increase in dependency levels included in this outcome category in both cohorts. However, the ROC analysis for patients with at least two increases in dependency level found an AUC of .60 (95% CI [0.60-.43]) in the internal validation cohort with lower performance with high thresholds, whereas the external validation cohort revealed an AUC of .73 (95% CI [0.71-.75]) with superior performance. This was likewise the case in the three and higher increase in dependency level category, where poor performance of the initial high NTFI thresholds of the ROC curve was shown in the internal validation cohort while better performance was revealed in the external validation cohort. The variation in performance of these categories between cohorts could be attributed to class imbalance as well as the small number of patients in the internal cohort to determine this category of outcome, which resulted in the loss representation of NTFI in other classifiers within the cohort, which was resolved in the wider sample (external cohort) (289, 290). However, AUCs of 0.60 were found for both classifiers (two and more, and three and more) in the internal validation cohort, indicating the NTFI's capacity to rank random positives higher than random negatives 60% of the time. This indicates that the internal validation cohort may have been influenced by the imbalance classification determined by the dominated class (one or more increases in dependency), which has influenced the other classes within the cohort, but NTFI was able to correctly and positively predict based on available patients. An additional category was investigated in the external validation cohort for NTFI with four or more increase in dependency level, yielding an AUC of.74 (95% CI [0.71-.77]), with strong consistent performance. Although sample and class imbalance influenced the outcome of some classifiers, NTFI was significantly associated with an increase in dependency level in both cohorts, with cut-

offs ranging from 4.345 to 4.601. Given that large samples improved stability and generalizability and decreased sampling variability, it is evident that ROCs performed better with larger samples than with smaller samples (291). However, regardless of some curve performance, NTFI ROCs generated AUCs of >.60 across categorises within both cohorts, indicating the higher NTFI's effectiveness in distinguishing between the positive and negative classes. As a result, an increase in dependency level was related to greater NTFI across the board in both cohorts, with thresholds ranging from 4.345 to 4.601 with the greatest dependency level.

Cohorts	Increase in dependency level	AUC	P-value	Cut-off point	95%CI	Sensitivity	Specificity
Internal validation cohort	At least one and more	.78	.000	4.345	.75-.81	.76	.37
	At least two and more	.60	.000	4.547	.56-.63	.60	.43
	At least three and more	.60	.008	4.606	.54-.65	.59	.45
External validation cohort	At least one and more	.72	.000	4.399	.70-.75	.72	.40
	At least two and more	.73	.000	4.404	.71-.75	.73	.41
	At least three and more	.78	.000	4.558	.76-.81	.78	.37
	At least four and more	.74	.000	4.601	.71-.77	.74	.39

Abbreviations: AUC, area under curve; ROC, receiver operating characteristic

Table 5- 4: ROC analysis for increase in dependency level with NTFI in both cohorts

5.3.4 The optimal threshold for the development of adverse outcomes

The NTFI was used on a range of adverse outcomes in order to explore the diagnostic performance of adverse outcomes with the NTFI. NTFI performance has shown AUCs of >0.5 across multiple adverse outcomes, determining its ability to distinguish between positive and negative outcomes. In addition, the AUCs of NTFI performance

were able to quantify (AUC>0.5), and not affected by outcomes that present with a majority high NTFI or only less severe cases caused by classifiers. This shows the stability and validity of NTFI in distinguishing between the severity of outcomes and the severity of frailty. After confirming NTFI ability and identifying that all adverse outcomes were of AUCs>.5, identifications of cut-offs were performed on twenty adverse outcome categories (see Appendices 9 to 28). Threshold point performance was first produced in accordance with the coordinates of the curve table for each outcome category, and then selection was performed for the closest point to the left-corner of the ROC curve, representing the optimal threshold (285). NTFI ranged between 1.90 and 7.47 in the internal validation cohort and 2.07 to 7.40 in the external cohort, while twenty thresholds were identified (see Table 5-5) and ranged between (min: 4.345 to max: 5.022).

Adverse Outcome	Internal validation cohort threshold	External validation cohort threshold
In hospital complications		
At least one and more complications	4.490	4.432
At least two and more complications	4.620	4.551
At least three and more complications	4.758	4.562
Discharge destination		
Rehabilitation unit	4.560	4.496
Residential care home	-	4.765
Nursing home care	4.849	5.022
Mortality	4.686	4.528

Increase in dependency level		
At least one and more	4.345	4.399
At least two and more	4.547	4.404
At least three and more	4.606	4.558
At least four and more	-	4.601

Table 5- 5: A summary of the NTFI cut-off points identified for the development of adverse outcomes in both cohorts.

The finding of twenty adverse outcome cut-off points for the NTFI within a narrow range of 4.345 to 5.022 is a significant development. This close proximity of cut-off points indicates that the NTFI has a high level of sensitivity, indicating its ability to identify minor differences in frailty and trauma severity that are associated with adverse outcomes. The NTFI's capability to more precisely predict and identify adverse outcomes is highlighted by the accuracy of these cut-offs; consequently, the likelihood of misidentifications or errors is reduced. For this reason, the minimum threshold within this range was chosen in order to achieve the greatest possible balance between sensitivity and specificity, thus maintaining a high level of accuracy while reducing the likelihood of false negatives and ensuring that individuals at risk of adverse outcomes are not missed. Therefore, the optimal threshold selected for the development of adverse outcomes was **NTFI ≥ 4.345**. As the intention is to identify a threshold value below which complications or adverse outcomes are unlikely. As this is the minimum identified cut-off, its validity is established as it encompasses a broad range of adverse outcomes that necessitate higher NTFI thresholds. Given that adverse outcomes are the foremost concern for older trauma patients, the stratification of frailty consequences using the specified cut-off is of utmost importance. Determining this optimal threshold not only aids in the prediction of adverse outcomes

but also functions as a potential indicator of the frailty status of these patients, as the emphasis remains on their outcomes. The NTFI threshold, which was established to indicate the onset of adverse outcomes, could also be used to classify frailty for the development of adverse outcomes. Nevertheless, the validity of this cut-off was assessed through validation to ascertain whether it can differentiate between adverse outcomes and whether it can function as an independent predictor for these outcomes. In the subsequent section, patients with NTFI scores exceeding 4.345 were utilised to establish the threshold for adverse outcomes, serving as a reference point for validation.

5.3.5 Model performance

The aim of the model performance in this chapter was to validate the derived threshold for the development of adverse outcomes as a threshold and an independent predictor of adverse outcomes. Validation was performed on the two cohorts using the NTFI ≥ 4.345 classifier against adverse outcomes. Binary logistic regression was performed using the three major adverse outcomes (discharge destinations, increase in dependency level, and in-hospital complications). For the discharge destination outcome, patients were included as binary, with adverse destinations including discharge to rehabilitation unit, discharge to nursing care, and mortality, with discharge to residential home care included in the external validation cohort. Total in-hospital complications and increase in dependency level were utilised as continuous outcomes to examine the prediction power of this cut-off and whether each increase would be connected with NTFI (see Table 5-6 and Table 5-7).

The findings from the internal validation cohort demonstrated significant relationships between the NTFI and the likelihood of the occurrence of four of the five adverse outcomes. This included mortality, discharge to rehabilitation unit, discharge to nursing care home, and increase in dependency level, with the exception of in-hospital complications, which did not reach statistical significance (P = 0.08) in this cohort and had no influence on the overall model. The intercept (constant) was determined to be -0.617 (p<.001), suggesting that when all predictors are zero, the log odds of NTFI ≥ 4.345 (the reference category) decline by -0.617, while the external validation cohort constant is -0.572 (p<.001). The similarity in constants demonstrates the consistent performance of the cut-off NTFI of ≥ 4.345 with adverse outcomes in both cohorts. Among the predictors, mortality had a significant positive connection with the likelihood of having an NTFI ≥ 4.345, with a high odds ratio of 192.61 (95%CI [31.69-1160.65]) in the internal validation cohort and 13.93 (95%CI [4.88-39.97]) in the external cohort. This reveals a substantial positive relationship between mortality and higher NTFI scores, implying that the existence of mortality raises the probability of having NTFI ≥ 4.345 considerably. The large confidence range indicates that the impact was estimated with high accuracy. This demonstrates that mortality may have failed to perform effectively in the overall thresholds using the ROC of NTFI in contrast to NTFI ≥ 4.345, indicating that mortality is best determined at NTFI ≥ 4.345. Similarly, discharge to nursing care home facilities was associated with NTFI ≥ 4.345, with an odds ratio of 83.89 (95% CI [30.76-228.78]) in the internal cohort and 43.60 (95% CI [19.28-98.57]) in the external cohort. This means that those who are released to nursing homes are much more likely to have a higher NTFI score than those who are not. In the external validation cohort, a comparable odds ratio of 19.05 (95% CI [9.58-37.88]) was seen for patients discharged to a residential care home. These results

highlight the significant influence of post-hospitalization care pathways, suggesting that persons who are transferred to nursing care homes or residential care homes may have heightened frailty or need ongoing care, which in turn increases their probability of having a higher NTFI score. Another predictor, in-hospital complications, showed a coefficient of 0.18 with a p-value of 0.075 in the internal cohort, suggesting a tendency towards significance. This indicates a possible link between complications and the probability of having an NTFI ≥ 4.345; however, it did not meet the standard threshold for statistical significance ($p < 0.05$). However, a significant odd ratio was identified in the external validation cohort with 1.53 (95%CI [1.35-1.74], which effectively resolved and ascertained the correlation between the NTFI ≥ 4.345 and in-hospital complications. On the contrary, there was a negative correlation observed between the increase in dependency level outcome and NTFI ≥ 4.345 ($B = -0.87$, $p < .001$) and ($B = -.32$, $p = .002$) in the external validation cohort. The observed negative coefficient resulting from the odds ratios was less than one, suggesting that an increased degree of dependence was associated with a decreased likelihood of attaining an NTFI equal to or greater than 4.345. This may also be the result of multicollinearity that develops as the level of dependency increases in relation to the destinations of discharge. Nevertheless, multicollinearity does not diminish the ability to make predictions; rather, it may solely impact computations pertaining to specific predictors (292). Hence, multicollinearity may or may not impact an increase in dependency level, which may need further validation or unadjusted regression. Notwithstanding the low odds ratios of .418 (95%CI [.270-.647]) for the internal validation cohort and .724 (95%CI[.589-.891]) for the external validation cohort, which suggested an inverse relationship or the impact of multicollinearity, the results revealed that an increase in dependency level

was a significant predictor with a P<0.001 indicating a significant association with NTFI ≥ 4.345.

The results show that NTFI ≥ 4.345 was a significant predictive threshold for adverse outcomes. As indicated by NTFI ≥ 4.345, discharge to rehabilitation unit, discharge to nursing care home, discharge to residential care home, mortality, increase in dependency level, and in-hospital complications were all independently associated with an increased risk of frailty. Its validity in distinguishing between adverse outcomes and with high odds ratios is determined by the importance of NTFI ≥ 4.345 in a broad variety of outcomes. As a consequence, an NTFI of 4.345 or above is a reliable predictor of frailty and adverse outcomes and could potentially be utilised for further validation in older trauma patients.

							95% CI.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
NTFI ≥ 4.345	Constant	-.617	.104	35.417	1	<.001	.540		
	The increase of dependency level	-.873	.223	15.305	1	<.001	.418	.270	.647
	In-hospital complications	.186	.105	3.166	1	.075	1.205	.981	1.479
	Rehabilitation unit	2.919	.463	39.771	1	<.001	18.530	7.479	45.912
	Nursing home care	4.430	.512	74.884	1	<.001	83.892	30.762	228.786
	Mortality	5.261	.916	32.956	1	<.001	192.612	31.964	1160.651

Table 5- 6: Binary logistic regression results for validating NTFI threshold on adverse outcomes in the internal valiadtion cohort

								95% CI.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
NTFI ≥	Constant	-.572	.067	72.750	1	<.001	.564		
4.345	The increase in dependency level	-.323	.106	9.314	1	.002	.724	.589	.891
	Total in-hospital complications	.431	.065	44.487	1	<.001	1.539	1.356	1.748
	Rehabilitation unit	1.417	.244	33.708	1	<.001	4.123	2.556	6.652
	Residential care home	2.947	.351	70.623	1	<.001	19.050	9.581	37.880
	Nursing home care	3.775	.416	82.292	1	<.001	43.604	19.288	98.573
	mortality	2.635	.535	24.233	1	<.001	13.939	4.883	39.795

Table 5- 7:Binary logistic regression results for validating NTFI threshold on adverse outcomes in the external validation cohort

5.4 Discussion

On a linear scale, clinical utility can be improved by identifying relevant 'cut-off' points representing inflection points in the scale. This chapter has identified an optimal NTFI cut-off of NTFI ≥4.345 for the development of multiple adverse outcomes, including discharge destinations, in-hospital complications, and the increase in dependency level. The cut-off NTFI ≥4.345 was also validated and found to be an independent predictor of discharge to rehabilitation, discharge to nursing home care, discharge to residential care home, mortality, in-hospital complications, and increase in dependency level.

In this chapter, we have used different methods to identify and validate candidate cut-off points of the NTFI in order to establish from two different perspectives if there is a simple single value that can have practical application for the NTFI in trauma settings. The validity of the NTFI as a measure for adverse outcomes was assessed in a prior chapter, where it proved to be highly accurate in identifying such outcomes. However, identifying the optimal cut-off point is necessary to stratify the onset of NTFI frailty outcomes in trauma settings. Although frailty could be better defined by only two

groups' frail vs. non-frail groups, frailty stages may be required to determine the severity of frailty in some settings. This may become less important in clinical trauma settings, where the prognostication of patients requiring additional input or at higher risk of poor outcomes is more valuable than the diagnostic range in terms of saving lives.

A thorough analysis of NTFI's impact on adverse outcomes was conducted utilising ROC curves to investigate the diagnostic performance of NTFI in relation to various domains of poor outcomes, as well as establishing optimum threshold distributions on ROC for each specific outcome. This helped to visualise NTFI and evaluate the threshold distributions for different outcomes. Some ROC graphs were not in the intended shape at the initial graph stages, but this determines the ability of NTFI to distinguish between some outcomes where patients had high or low frailty. For example, in the NTFI comparison between patients discharged to rehabilitation and patients discharged to nursing care where patients discharged to nursing care had a higher NTFI. The reason for this is that a few less severe outcomes, characterised by numerous instances of low NTFI, failed to distinguish between the presence and absence of outcomes, as they represented a lower presence of outcomes compared to a higher one. This is because the ROC curve focusses on discrimination, or the capacity to reliably categorise individuals as having the condition or not, while failing to account for the correlation between projected probability and actual outcomes (293). However, the 20 ROC curves that were conducted demonstrated adequate AUC determination of performance and significant discrimination (AUC>0.50). Therefore, the behaviour of ROC curves was assumed to vary between outcomes, where hard outcomes may represent high NTFIs and less severe outcomes with low NTFIs, which might affect graph shape in some circumstances (294).

An accepted method for determining the cut-off points is the method of the closest point to the left-corner. While simple, this dichotomizes the data set arbitrarily, which may result in a significant misclassification rate in certain clinical scenarios (295). In order to minimise this risk, two unrelated datasets were utilised to establish generalisability. Multiple different ROC analyses were developed based upon different adverse outcomes to triangulate a single relevant threshold value and the risk of misclassifications, with the aim of determining the best cut-off values that were related to a broad range of outcomes in different datasets. In addition, the selection of the lowest NTFI generalises the coverage of the potential outcomes while minimising the risk of misclassifications. Other methods are described for selecting the optimal cut-off, such as average sensitivity and positivity or a weighted mean. However, they were not practical in this situation, as a lower than average NTFI may not account for the underlying concept of frailty as the risk of the onset of adverse outcomes varies between specific outcomes. This is supported by the significant regression coefficient of NTFI≥ 4.345 in relation to adverse outcomes. This indicates the threshold has a significant ability to predict adverse outcomes and can accurately identify adverse outcomes in older trauma patients with frailty. Additional assessments of frailty outcomes could be conducted to further validate this threshold and ensure its validity. Specifically, these assessments could focus on frailty outcomes such as an increase in dependency level.

The conversion of continuous data into binary forecasts may have an impact on the cut-off point determination. This would not, however, indicate a clear distinction between the outcomes since each numerical change was reviewed and graded independently. While multiple testing using ROC analysis may introduce a possibility of type 1 error, the statistical significance of the obtained AUC values was strong, since

all p-values were less than or equal to 0.001. Therefore, it may be concluded that type 1 errors are improbable since the null hypotheses were strongly rejected for all examined outcomes. There may be overlap (measurement error) in certain numerical outcomes, such as an increase in dependency level; however, this was done to reduce false outcome prediction and instead depict the entire range of possible outcomes while maintaining the linearity structure of the composite outcome. Although imbalance classification is prevalent on ROC curves, the use of validations with larger patients removed these concerns with outstanding performance in identifying NTFI-accurate predictions for patients with increased dependency level. However, the inverse link between increase in dependency level and NTFI≥4.345 owing to low odds ratios may need additional validation using a dataset aiming to assess increase in dependency level to prevent overlap with discharge destinations that might contribute to multi-collinearity. However, the increase in dependency level in the preceding chapter was verified individually, with patients separated into three households and evaluated against the NTFI. In this chapter, the increase in dependency level was evaluated as a numerical variable without specifying home, care home resident, or nursing care resident in the statistics to visualise and verify the overall outcome performance versus NTFI. As a result, additional confirmation of this outcome is required, taking into account the patients' pre-admission residency.

This is the first validation and identification of the NTFI cut-off for adverse outcomes. The findings are consistent with previous evidence that frailty is an independent predictor of poor outcomes in trauma. This chapter's findings suggest that frailty in trauma patients, as indicated by NTFI≥4.345, is an independent predictor of adverse discharge destinations, increased dependency level, and in-hospital complications. Outcomes examined in older trauma patients are often connected to trauma itself, with

few researchers concentrating on frailty outcomes, which might have a significant influence on older survivors of frailty post-discharge. Although trauma is the greatest cause of mortality in older people, survivors may also be at risk of frailty and its sequelae following discharge. As a result, combining frailty composite outcomes with traditional trauma outcomes, such as mortality, in the evaluation of trauma management for older patients with suspected frailty can help to provide a more complete understanding of the relationship between frailty and trauma outcomes. This technique improves the accuracy of quantifying the effect of trauma on older people while also facilitating the diagnosis and impact of frailty. Additional testing against outcomes compared to other comparable frailty assessments relevant to trauma is necessary to evaluate if the NTFI is superior, inferior, or equivalent to other instruments. Although NTFI objectivity may assist clinicians in measuring frailty in trauma patients, clinician discretion is still required to enable treatment options, and additional measures, such as the Nottingham hip fracture score (NHFS), may be advised to facilitate patient status. Thus, although NTFI may give prospective information regarding a patient's state, it is advised that other related techniques be combined based on the patient's traumas. NTFI, with a meaningful cut-off point of ≥4.345, may help clinicians diagnose frailty and predict adverse outcomes in trauma patients. This tool will give clinicians with a more objective and less subject to assessor bias strategy for rapidly assessing and predicting frailty in trauma settings. This cut-off point may also prompt a clinician to consider referring to a frailty team, as well as discussing prognosis with patients and families and using shared decision-making. Further research might confirm NTFI≥4.345 and examine its prediction potential for long-term adverse outcomes to determine the threshold of long-term performance with adverse outcomes.

Chapter 6: Discussion

6.1 Introduction

This chapter aims to bring together the thesis as a body of work and set into context the overall work and how it relates to both prior work (discussed in Chapter 1) and also to the new papers published in the area since the systematic review was undertaken. The thesis, in addition to systematically reviewing the literature and identifying the implications for the patient of frailty in the setting of trauma, has also defined and validated the NTFI (85, 296). Secondly, the predictive value of the NTFI and its application to the unselected emergency admission pathway deserve further discussion. This chapter sets out to provide a brief summary of the thesis and then further discuss the implications for current and future research and clinical practice. The potential for the application of a validated trauma frailty score for trauma care systems, healthcare professionals, and patients is finally discussed.

6.2 Defining frailty and major trauma.

The addition of a validated frailty scale has some implications for the current understanding of both major trauma and frailty in that setting. These are discussed briefly below.

Major trauma

The term "major trauma" was defined and expanded upon in this thesis. In trauma centres and emergency departments, "major trauma" refers to serious injuries that have been admitted to trauma systems, which have the resources and specialists to

treat the most severe trauma. One of the most used markers for major trauma is the calculated injury severity score (ISS≥15) (31). ISS may help determine injury severity; however, using a single criterion may simplify trauma. The ISS may misclassify older people who need longer recovery after trauma without surpassing the threshold for physiological resilience. It is clear that "major trauma" refers to a general criterion used to triage trauma patients, not patient-specific complicating factors that may alter the trauma prognosis. Thus, all three terms "major trauma," "severe trauma," and "multiple injured trauma" seem to allude to the same definition: serious injuries or a combination of them that might threaten an individual's life or cause considerable disabilities (30, 69). Such injuries require urgent and specialised medical intervention due to their critical nature. ISS remains useful for categorising trauma in younger patients; however, using it alone for triage or prognosis in fragile older patients may miss the targeted individuals for severe trauma treatment. Therefore, trauma severity varies, and the systematic review shows that frail older adults with the same ISS had worse outcomes than non-frail ones.

Many studies found that older major trauma patients were under-triaged and not triaged to major trauma centres, resulting in higher mortality (297-299). The current major trauma triage tool relies on Glasgow coma score (GCS) values of less than 14 to determine patient transfer to MTC, but older major trauma patients often have higher GCS values, worsening the under-triage rate (71-73). Although pre-hospital factors may cause under-triage, this thesis and the literature show that older trauma patients are more likely to be under-triaged and have their injuries underestimated. While frailty evaluations and triage techniques vary, they both lead patients to a suitable hospital for treatment. Thus, older major trauma patients may need modified triage procedures or frailty evaluations and other prediction tools before admission.

Prioritising frailty's influence on major trauma and measuring frailty levels before or after MTC or hospitalisations may help address this problem. This would allow clinicians to tailor treatments to particular people. Since pre-hospital blood testing for haemoglobin levels is not possible, NTFI may not be suitable for deployment there. Additional validation could be conducted for NTFI by excluding haemoglobin and incorporating more variables that are appropriate for pre-hospital settings. Frailty assessments would enhance sensitivity and allow for more accurate trauma severity quantification, making them essential for assessing trauma and predicting outcomes in older adults.

Frailty

There are two primary aspects that are often confused but distinct when it comes to frailty: the definition of frailty and the identification of frailty. Frailty is typically defined as the vulnerability to challenge due to a loss of homeostatic reserve caused by age-related multisystem deficits (261). This definition highlights the effect of the ageing process, which may or may not be connected with chronological age, and that frailty cannot be quantified without a particular challenge, such as trauma; hence, frailty cannot be evaluated using a single measurement since challenges vary. However, although age is not always connected with frailty, it does raise the risk of frailty (300, 301). Identification of frailty was linked to two models: Fried et al., or Rockwood, with the latter being used to devise 'frailty indices' due to its suitability in acute settings compared to Fried et al. The Rockwood concept was the most often used concept in trauma, and the clinical frailty scale was recently the most regularly used instrument. CFS is a simple frailty test for older adults; however, it requires training. CFS predicted well, but it was designed for general care and long-term care, not trauma (27). Despite

its success in trauma, CFS did not improve frailty measurement and prediction in trauma patients. For hip fracture patients, high CFS scores did not predict mortality, and high frailty was associated with plateau performance (135). This is not a weakness of CFS; rather, trauma patients need a particular trauma frailty assessment that accurately represents the effect of frailty on trauma. As a consequence, the term "frailty" encompasses the whole condition and changes that occur in older individuals; however, assessing it differs depending on the challenge.

6.3 Summary of principal findings

6.3.1 The systematic review and meta-analysis

In (Chapter 2) the published findings of the systematic review and meta-analysis are principle that patients with frailty had higher:

- in-hospital mortality rates
- longer hospital stays
- in-hospital complications
- poorer discharge outcomes

Another noteworthy finding was the age-ISS-frailty link to mortality. Only two studies showed a weak link between age and mortality, and only two identified a significant connection between ISS and mortality. However, all six studies connected frailty to mortality. This suggests that frailty should be emphasised above age and ISS, and that frailty is an important classification for older patients in trauma. The findings support the influence of frailty and the relevance of including frailty evaluation in trauma care for older persons.

6.3.2 Development of NTFI

Age is important in understanding frailty (302), but its direct relationship with identifying frailty varies. In our systematic review, two studies found a weak link between age and mortality, but all six showed frailty as a strong predictor of mortality. This suggests that, while age's contribution to frailty may be minimal, it does confirm its potential influence. Furthermore, age had a minor but significant effect on the total NTFI when compared to other variables (Beta =.021, p <.001), supporting its inclusion in the index. The retention of age, despite its small effect, underscores its importance due to its relevance in a large sample size. Thus, the relationship between frailty and age is intricate, and age could be a useful indicator of frailty in trauma contexts.

NTFI has shown significant findings at various construction stages, including verification, validation, adverse outcome assessment, and ROC curve cut-off point validation. This shows the tool's consistency, making it suitable for frailty measurement in older trauma patients. NTFI used clinician-provided data instead of staff-managed research tools. This means trauma clinical settings are more likely to benefit from the results. Thus, NTFI's validity, simplicity, and automation can improve its use in various trauma settings.

CFS is a widely used frailty measure; thus, the tool's use of it to construct NTFI is a strength. When examining trauma outcomes and frailty, the CFS has plateaued (135). This may be due to the tool's intricate classification of traumatic injuries, since fatal trauma does not necessarily indicate frailty. The plateau may be due to a more precise assessment that considers trauma severity and its potential deviation from frailty as the main explanatory factor, rather than frailty alone determining outcomes. The construction of NTFI used CFS as a measure of frailty (a dependent variable) in trauma

patients, not as a predictor of clinical outcomes. This revealed objective associations between numerical findings from the five NTFI variables and the CFS, which measures trauma and frailty integration. The significant variables incorporated into NTFI were clearly acting as trauma-specific frailty variables, proving their clinical validity. Based on clinical data, NTFI can detect frailty in trauma patients in minutes without training or costly resources and predict adverse outcomes (NTFI≥4.345).

6.3.3 NTFI relation to adverse outcomes

The significant visualisation distributions in (Chapter 4) of the associations between adverse outcomes (length of stay, discharge destinations, increase in dependency level, and complications) and the gradual NTFI increase based on outcome determine NTFI's ability to identify adverse outcomes. Significant results were also obtained for each category of poor outcomes. Patients who have died prior to discharge may not have been adequately represented in the discharge destination assessment. Despite this, a progressive rise in the means of NTFI was seen in both cohorts, with the increase linked to higher dependency destinations. This may be understood as trauma is an acute diagnosis that precipitates admission due to an acute incident rather than cumulative deficiencies (frailty). As a result, in certain cases, high intensity trauma may be the major cause of death rather than frailty. The measured clinical outcomes highly related to measured NTFI, with a high significant p value ($P<0.001$), indicating the robustness of NTFI in differentiating between positive and poor results within each category of outcomes.

6.3.4. NTFI threshold identification and validation for adverse outcomes

The next chapter (Chapter 5) assessed the diagnostic value of the NTFI for a range of outcomes using a ROC method. Two methods were used in the chapter: ROC curves to choose a cut-off and logistic regression to confirm it. Twenty adverse outcomes from internal and external cohorts were significant (P<0.05) with AUC≥0.54. NTFI had high sensitivity, with cut-offs for 20 unfavourable outcomes from two cohorts between 4.345 and 5.022. Multiple uses of curves for outcomes categories that overlap may lower AUCs, but this was done to demonstrate NTFI's diagnostic behaviour performance on the diverse included outcomes and determine the appropriate cut-off for adverse trauma frailty outcomes onset. Thus, the NTFI cut-off of ≥4.345 indicates frailty sequences in older trauma patients at high risk of outcomes. This risk stratification cut-off can help predict poor outcomes, guide treatment, and optimise healthcare resources. Both cohorts confirmed this cut-off as a significant predictive threshold for discharge to a rehabilitation unit, nursing home, residential care home, death, dependency increase, and hospital complications. These findings indicated that an NTFI of 4.345 or higher is a reliable predictor of the onset of frailty trauma consequences and could be used to further validate this cut-off as a categorization in older trauma patients.

6.4 Comparison to previous research

6.4.1 The systematic review and meta-analysis

The development of the NTFI has some implications for previous work. It previously described that suffering major trauma may accelerate development of frailty (303).

This asks questions of the use of non-trauma-specific frailty assessments in the trauma setting. Other systematic reviews in the area measured frailty differently but were consistent with our general findings. For example, a systematic review of a large cohort of patients aged 18 and above, with a mean age ranging from 69 to 78, indicated that frailty is strongly linked with death, comorbidity, and adverse discharge destination following multisystem trauma (304). An additional review found that frailty was associated with mortality and that frailty, not age, should be considered when identifying geriatric patients at risk of adverse outcomes, and that trauma systems should incorporate frailty assessment (305). These two reviews add weight to the findings of our systematic review that frailty is an underlying cause of poor outcomes following trauma in older individuals.

6.4.2 Development of NTFI

The emphasis on frailty tools used in trauma was seen in the most recent discovered literature results, which were more concerned with the validity of employed frailty measures in trauma, where none could be trauma specific. A recent systematic review examined trauma frailty assessment reliability and feasibility. For tool feasibility, time, cost, instructions, and user training were considered. The study found 32 trauma frailty assessments, and CFS had the highest feasibility and low reliability (306). Despite its low interrater reliability, CFS may be feasible due to its simple, little training, and bedside use without complex criteria. The CFS is, at its heart, a subjective tool based on clinician assessment. The NTFI is a calculated tool based on objective components (AMT, mobility, Hb, age and mechanism of injury), providing a more replicatable assessment, with the components all known to have little in the way of inter-rater variation.

In addition to the study that identified hip fracture patients with a plateau in CFS prediction performance with high frailty, a recent large multicentre study using CFS on trauma patients found that frailty severity had a lower impact upon injury severity scores (ISS>25) (307). This is consistent with the thesis results, which state that overwhelming trauma may not adequately represent frailty status and that CFS may lose its potential to predict outcomes at high frailty level. However, given the variety of frailty tools, the CFS is widely used, indicating that trauma settings prefer simple instruments that can be administered quickly due to complexity and time. This suggests that protracted geriatrics non-frailty-specific assessments like the comprehensive geriatric assessment CGA may not be suitable for acute trauma. CGA may be difficult to implement in the early stages of trauma due to its time and resource requirements, but it can be used in trauma wards and ICUs to tailor interventions and support to older people's needs, promoting a more successful recovery and improving quality of life (308). Thus, CGA is an all-encompassing approach that goes beyond acute trauma care and frailty, making it essential for late trauma adoption. Similarly, the frailty index (FI) or electronic frailty index (eFI) includes 30 or more deficits that general practitioners report in primary care. Although not designed for trauma settings, these and other GP frailty evaluation tools require a complete patient medical record and may not be available to all trauma patients upon admission. Even if FI or eFI were accessible for trauma patients, measuring the impact of frailty in trauma may not be reliable since they are not built for this challenge. An abbreviation for FI was operationalized to be modified-FI, and the 5-modified FI to be more easier to administer in trauma, with one big research included in the systematic review utilising this instrument that demonstrated a minor impact when compared to other studies across outcomes. This was due to the fact that the 5-modified FI employed four

comorbidity variables, only one of which was functional, which may have resulted in a lower ability to distinguish between frail and non-frail. While frailty and comorbidity are both essential factors in the management of older persons, they are distinct characteristics of health. Frailty is a state of heightened susceptibility, while comorbidity is the existence of many chronic medical conditions. As a result, these approaches may not evaluate frailty, but rather quantify comorbidities against outcomes. Even if comorbidities were linked to adverse outcomes, utilising frailty for primarily comorbidity tools does not accurately reflect the influence of frailty on outcome. This shows that there is a complicated link between comorbidity and frailty in the techniques employed in trauma, which may not reliably measure frailty. This was rectified in the NTFI by assessing factors for frailty to directly evaluate haemostatic vulnerability rather than frailty-trauma outcomes. The variables were then included into the tool and verified against outcomes for greater reliability, with substantial results discovered.

Although further validations of the NTFI may be necessary for long-term outcomes, other multidimensional assessments such as CGA or FI should not be overlooked since they give a thorough evaluation of geriatrics health condition as well as overall quality of life after discharge. In addition, prognostic measures such as the NHFS (128) or other employed strategies such as the best practice tariff BPT for fragility hip fractures (309), which sought to decrease unfavourable outcomes for hip fractures, may give more precise prediction of outcomes linked to the injury. As a result, NTFI alone can be used to measure frailty and predict outcomes in trauma, while acknowledging the importance of existing tools used at various stages of the trauma care pathway to prognosticate specific injuries that may provide more specific injury

outcomes. Future studies might explore how additional tools interact with NTFI in relation to outcomes for certain injuries.

Recently, specialised measures have been created to assess frailty in trauma settings, like the Geriatrics Trauma Frailty Index (GTFI) and the Trauma-Specific Frailty Index (TSFI). The GTFI retrospectively analyses electronic hospital data to identify frailty markers linked to poor prognosis in older trauma patients. The GTFI retrospectively identifies frail individuals based on poor outcomes using ICD-10 diagnosis codes from medical records (26). The issue with this method was observed in a subsequent GTFI research that intended to test the tool agreement with existing frailty sales, which revealed varying consistency when compared to other established trauma-specific frailty indices such as TSFI and FI (310). This heterogeneity in consistency shows that the GTFI may not be well aligned with other frailty measures, thus limiting its value in clinical practice. Using GTFI's similar method, the Hospital Frailty Risk Score (HFRS) was established for acute settings (311). Agreement was examined with non-trauma specific instruments (Fried and Rockwood); however, it was only fair to moderate. This reinforces the importance of creating frailty measurements of haemostatic vulnerability rather than depending entirely on outcomes.

The TSFI is an additional index that was developed from the 50-variable FI. Its purpose was to identify important characteristics that were associated with adverse outcomes in trauma patients. Fifteen indicators were identified across many domains, including comorbidities, cognitive abilities, emotional health, and functional status (25). Nevertheless, 11 out of the total 15 items were derived from subjective patient (or family) reporting, which brings up concerns about the accuracy and dependability of the data (259). Moreover, the restriction of intubated or unconscious patients curtailed

its practicality. These limitations demonstrate the impracticality of the TSFI in trauma situations, emphasising the need for objective frailty assessment techniques.

This reinforces the validity of the NTFI since it contains five objective variables that can be easily evaluated on admission. NTFI does not depend on self-reporting, and the variables included are objectively analysed; nevertheless, certain variables, such as AMT, may need a patient response. Although additional validation using a surrogate measure for cognitive function instead of AMT may be required for unresponsive patients, measuring cognitive function in trauma is a challenging parameter (312), as it requires verbal interaction and responses from the patient, which can be influenced by consciousness level, time constraints, or communication difficulties. However, AMT is a commonly recorded variable that may be available in medical records prior to admission for trauma patients. If not accessible and the patient is in such critical condition that NTFI evaluation cannot be postponed until the patient is stable for assessment, AMT is one of the five variables in the NTFI; hence, the presence of the four may indicate 80% of the trauma-frailty state (see Table 6-1).

NTFI items	Conscious	Unconscious with family (relatives)
Age	Yes	Yes
AMT	Yes	No
Pre-admission mobility status	Yes	Yes
Haemoglobin level	Yes	Yes
Falls from standing height	Yes	Yes
Completeness of the NTFI assessment	100%	80%

Table 6- 1: the percentage of NTFI assessments based on consciousness level.

6.4.3 NTFI relation to adverse outcomes

Frailty outcomes and trauma outcomes are distinct but related concepts in the context of patient medical care. The assessment of outcomes for frailty with trauma has historically concentrated on the immediate consequences of traumatic injuries, such as mortality, morbidity, length of stay in the hospital or intensive care unit, and the need for various forms of organ support (304, 313). While frailty outcomes relate to the consequences of a patient's frailty condition, such as functional decline, impairment, hospitalisations, institutionalisation, worse quality of life, higher death rates, and a lower probability of returning home (314). The systematic review identified some studies that examined the impact of frailty on outcomes such as returning home after trauma. However, no studies were found that measured the changes in activities of daily living (ADL) or cognitive health for older individuals with frailty after trauma. For this reason, NTFI was validated using a broader range of frailty-related trauma outcomes rather than traditional trauma outcomes, resulting in a more accurate representation of the effect of frailty on trauma patients. The increase in the level of dependency was one of the composite outcomes that developed and had a strong correlation with NTFI. A significant rise in dependency level was seen in over 50% of patients in both cohorts when evaluated using NTFI.

Some recent studies have employed outcomes associated with frailty in trauma, such as the requirement for health utilisation of resources (304), readmissions, and fall recurrence (315) or measuring functional recovery (316). Although some of these appear to be non-immediate outcomes requiring follow-up, considering long-term frailty outcomes in trauma patients is critical for understanding the broader impact of the injury, guiding rehabilitation efforts, and optimising long-term outcomes and quality of life (317, 318). As a result, trauma outcomes may demonstrate vital results linked

to frail patients in the near term, but longitudinal monitoring of key frailty outcomes is critical for addressing the unique requirements of trauma patients, particularly older individuals.

6.4.4 NTFI cut-off identification and validation for adverse outcomes

Clinical instrument validation procedures vary. Approaches varied according to instrument usage, clinical setting, and outcomes (319). Several factors contributed to the validation ROC curve selection. One of the key drives was to graphically represent NTFI performance and determine whether high frailty means poor outcomes and low frailty means better outcomes. Multiple outcomes corroborated the findings, with low-impact outcomes having low NTFI ratings and serious consequences suggesting higher frailty. Furthermore, it was shown that milder adverse outcomes could not be linked to a high NTFI score, since individuals with high NTFI scores were less likely to be released to a rehabilitation unit. This confirms the reliability of the NTFI's performance.

Many studies have used ROC curve analysis to determine the ideal threshold by combining a few unfavourable outcomes into a composite outcome, such as the TSFI (25), but this approach does not specify which outcome the threshold corresponds to, which may not accurately reflect the instrument's discriminating capacity. The varied outcomes utilised for NTFI could not be combined since each represents a different trauma-frailty outcome. Combining these outcomes may misrepresent. Other approaches, including the Youden index, were unsuitable for clinical use on NTFI because they ignore the clinical effects of false positives and negatives (320). Thus, there may exist alternative methodologies that are statistically relevant but were not taken into account for clinical purposes or have recently been

introduced and need additional validation in clinical settings. For this reason, further validation of the discovered optimum cut-off (NTFI≥4.345) was performed to verify the cut-off in adverse outcomes prediction, which resulted in NTFI≥4.345 being a significant independent predictor for adverse outcomes, supporting the threshold's risk stratification.

6.5 Implications for practice

In clinical practice, defining clinically relevant frailty measures that can be assessed rapidly and objectively is a challenge. The thesis identified several implications from the NTFI and systematic review that may be beneficial to researchers, clinicians, patients, trauma care, and systems. Taken as a whole, the systemic review, NTFI, and validation of NTFI against outcomes confirm that frailty is an important factor in trauma outcomes. The impact of frailty on survival, hospital length of stay, discharge destination, and the occurrence of complications is so great as to warrant routine frailty screening with a trauma-specific tool such as the NTFI. This information carries equal weight to age or injury severity in prognosis assessment and care planning for older individuals who have experienced major trauma. Frailty status should be considered when preparing prognosis-based care plans, communicating expectations to patients and their families, and directing intensive care efforts. When used in conjunction with other triage tools accessible for trauma care, NTFI allows clinicians to optimise the identification of critically injured patients by quantifying their risk of adverse outcomes when adjusting for frailty. The thesis has significant implications for patients, carers, health care professionals, and trauma systems.

We have produced a straightforward, easy-to-administer instrument that can be executed in a matter of minutes, requires no training, and can be used either at the bedside or with routinely collected data. As a result, the NTFI should be equally useful in a research setting for outcome adjustment or in a clinical setting to guide patient care. Although statistical prediction frequently surpasses clinical judgement (321), the practical implementation of this tool requires the integration of patient-specific factors and clinical expertise. As a result, clinicians' judgements remain critical in prognosis and diagnosis and should not be underestimated. The incorporation of a validated tool to assess the concept of frailty in the older patient with a traumatic injury can assist clinicians in understanding patients' data linked to observations following trauma, thereby facilitating the prediction of outcomes and the direction of patient care strategies.

Furthermore, the implications of these findings may extend to various systems and aspects of the trauma care chain. The utilisation of NTFI for early detection of frailty risk would facilitate prompt intervention as part of a comprehensive geriatric review. This is a critical aspect of trauma care that is well-established and known to improve outcomes. In other settings, trauma-frailty triage for those systems with specific care pathways for the frail can be more easily accessed by differentiating patients who need to be treated in specialist frailty pathways, wards, or settings. This would enhance the overall efficacy of trauma care systems through the prioritisation of resources in areas with the greatest need.

Combining the NTFI with other early diagnostic tools utilised in trauma (e.g., NHFS, fracture risk/assessment tools), patients at higher risk can be more comprehensively screened, resulting in more opportunity to intervene. Administrative time, specialised clinicians, and training are not prerequisites for NTFI, all of which are critical elements

contributing to its enhanced accessibility and utility in research and clinical practice. Further external validation in other populations, settings, and countries may further enhance the generalizability of NTFI by expanding its applicability across various trauma systems and presentations.

6.6 Recommendations for Future research

A number of future research directions are informed by limitations and implications developed within this thesis as a way to further enhance both the validity and generalisability of the NTFI. The first future research recommendation would be to expand the NTFI construct to populations suffering from different traumas. This would establish it as a more complete instrument capable of representing different patient demographics in trauma. Furthermore, it would be advantageous to conduct prospective validation in other centres, countries, and healthcare systems to guarantee that the NTFI possesses sufficient capabilities in diverse trauma clinical scenarios, thereby improving its generalisability. This approach would also facilitate the consideration of variations in healthcare delivery, patient treatment, and social/cultural circumstances, therefore assuring the worldwide applicability of the NTFI. Additional research could potentially investigate the application of automated frailty assessment (NTFI) in clinical practice and treatments for older trauma patients, and its impact on enhancing patient outcomes and alleviating the workload on healthcare professionals. Additionally, the optimisation of resource allocation and the reduction of the burden of the healthcare team could be investigated, as well as the impact of NTFI on the triage and management of older trauma patients. The NTFI's simplicity would facilitate its implementation in clinical practices or research, both of

which could contribute to a variety of additional research. In terms of clinical outcomes, a number of outcomes could be further tested against the NTFI in a follow-up study. The long-term outcomes would measure the consequences of frailty on quality of life among older trauma patients after discharge. This may involve PROMs or HRQLE outcomes relating to NTFI. Where relevant, identification and validation of the cut-off for adverse long-term outcomes could also be refined to ensure generalisability in future research.

6.7 conclusion

Frailty as a concept has become central to the early assessment of older people who are experiencing trauma. The link between age and frailty with regard to trauma is complex, since frailty is a distinct condition with a greater frequency among those aged 65 and older. Although age might be an indication of frailty, it is not the only factor determining the condition. Frailty in trauma, as established by the NTFI, is a composite measure of pre-admission mobility, age, AMT, Hb, and falls from standing height. NTFI has demonstrated significant results across various performance and clinical outcome stages. The NTFI's validity was consistent across all stages and outcomes. The implementation of NTFI could simplify a number of variables impacting older persons who have experienced trauma, including triage, early detection of frailty, and the prediction of unfavourable outcomes. The NTFI is the only validated instrument for use in clinical and research settings, created and tailored exclusively for older individuals who have experienced trauma.

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Appendices

Appendix 1: JBI critical appraisal checklist for cohort studies



JBI Critical Appraisal Checklist for Cohort Studies

Reviewer_____Date_____

Author _____Year_____Record Number_____.

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Appendix 2: Development of Groupings

Study	Frailty measured as (frail vs non frail)	Trauma measured for (frail vs. non frail)	In-hospital mortality	Mortality at discharge	30-days mortality	3-month mortality	6-month mortality	1-year mortality or 1-year survival	Institutionalisation		Delirium	In-hospital complications
									Length of stay (LOS)	Discharge disposition		
Joseph B, et al. 2016.	√√	√√	√√						√√	√√		√√
Cheung A, et al. 2017.	√√	√√	√√							√√		√√
Pecheva M, et al. 2020.	√√	√√		√√				√√m	√√	√√		√√
Joseph B, et al. 2017.	√√	√√	√√				√√		√√	√√		√√
Joseph B, et al. 2014.	√√	√√	√√						√√	√√		√√
Hamidi M, et al. 2019.	√√	√√	√√						√√	√√	√√	√√
Jarman H, et al. 2021.	√√	√√	√√						√√	√√		

Rickard F, et al. 2020.	√√	√√			√√				√√		√√	√√
Shah P, et al. 2019.	√√	√√	√√						√√	√√		
Thompson A, et al. 2021.	√√	√√	√√						√√	√√		√√
Herklots M, et al. 2022	√√	√√	√√						√√			√√
Guiab K, et al. 2022	√√	√√	√√						√√	√√		√√

*√√: studied and directly measured

Appendix 3: JBI Data extraction form for included studies

Reference (authors /year)	Frailty measurement	Groups	Trauma measurement	Clinical outcomes measured	Description of main results	Relationship impact
Joseph B, et al. 2016 (103)	Trauma Specific Frailty Index(TSFI)	**Non-frail** N=93; Age mean ± SD = 68.52 ± 9.55; male = 63% (58); TSFI, mean ± SD 0.063 ± 0.035; ISS, median (IQR) = 9 (9-14). **Pre-frail** N=139; Age mean ± SD = 74.71 ± 9.74; male = 65% (90); TSFI, mean ± SD 0.17 ± 0.03; ISS, median (IQR) = 11 (9-14). **Frail** N=136; Age mean ± SD = 78.83 ± 10.63; male = 57% (77); TSFI, mean ± SD 0.40 ± 0.14; ISS, median (IQR)= 13 (9-19)	ISS, median was 11 (IQR 9 - 17)	- In-hospital complications - Discharge disposition - In-hospital mortality - Length of stay (LOS) - failure to rescue (FTR)	- **Frail** group was associated with in-hospital complications=42% (57); home discharge= 29% (39); in-hospital mortality= 17%(23); LOS= 5(3-8) and FTR 12.5% (20). -**Pre-frail** group was associated with in-hospital complication=42% (33); home discharge= 59% (82); in-hospital mortality= 5 %(7); LOS= 4(2-7) and FTR 3.5% (5). -**Non-frail** group was associated with in-hospital complication=23% (21); home discharge= 72% (67); in-hospital mortality= 7%(6); LOS= 4(2-7) and FTR 4.6% (4).	FTR is associated with frail status, fall as mechanism and head-AIS. Frailty status associated with increases in ISS and an increase in age.
Cheung A, et al. 2017 (104)	Admission laboratory frailty index (FI-lab) and the 7-point clinical frailty scale (CFS)	**Non-frail**(1-3) N=95; Age mean ± SD = 73.9 ± 6.4; male = 65.3%; ISS, median (IQR)= 17(13-24). **Apparently vulnerable** (4) N=68; Age mean ± SD = 76.5 ± 7.5; male = 41.2%; ISS, median (IQR)= 19(14-25). **Mildly frail** (5) N=60; Age mean ± SD = 79.0 ± 8.4; male = 50%; ISS, median (IQR)= 17(11-22) **Frail** (6-7) N=37; Age mean ± SD = 80.5± 7.9; male = 46%; ISS, median (IQR)= 17(9-24)	ISS, median was 17 (IQR 13 - 24)	- Adverse discharge destination (mortality, long term care, chorionic care or home) -In-hospital complications	No correlation between Admission laboratory frailty index (FI-lab) and CFS, and was not found to predict adverse discharge destination in older trauma patients. **Frail** (6-7) were more likely to have adverse discharge destination compared with **non-frail** (1-3) (71.4% vs 28.4%, p<0.001), and the same with CFS (4) and (5) in comparison with non-frail (1-3) (30.8% vs 36.2 vs 28.4%, p<0.001)	No significant differences in number of comorbidities or ISS among frailty categories except age. CFS is independently associated with adverse discharge destination
Pecheva M, et al. 2020 (46)	modified Frailty Index (mFi)	**Low (mFI<0.18)** N=412; Age mean ± SD = 73.3 ± 9.12; male = 59.2% (244); ISS,(SD)= 25.2 (8.9). **Intermediate (mFI 0.18 - 0.35)** N=280; Age mean ± SD = 79.1 ± 8.62; male = 58.9% (165);	ISS >15	- Mortality at discharge and at one year - Length of stay (LOS) - Glasgow outcome score on discharge from acute care	- Mortality at discharge in Low mFi = 77 (18.7%) ,intermediate mFi= 41 (14.6%) and high mFi = 29 (26.4%) - Mortality at one year in Low mFi = 90 (26.2%) ,intermediate mFi= 80 (35.2%) and	No significant difference in number of complications and mFi. LOS is not associated with mFi level. Frailty is

		ISS,(SD)= 23.2 (7.26). **High (mFI>0.36)** N=110; Age mean ± SD = 80.8 ± 9.11; male = 64% (70); ISS,(SD)= 24.1 (5.77)		- Serious medical complications	high mFi = 49(51%) - No significant difference between LOS and frailty groups (18.0, 19.2 and 18.8 days for low, medium and high frailty groups) - Common medical complication in all frailty groups was pneumonia (17.5%, 23.2% and 25.5% for low, intermediate and high frailty). - High frailty group was associated with complications including unplanned intubation, treatment for infection with antibiotics and progressive renal failure. - High frailty was associated with the highest surgical treatment (67.3% vs 41.2% vs 48.1%, for high, intermediate and low). - Moderate disability in GOS on discharge was the most frequently functional outcome with no difference in all groups ((40.8% vs 46.4 vs 36.4%, for low, intermediate and high) - High and medium mFi had the lower proportions of discharge to home compared with low (high=29.1% vs medium= 37.1% and low= 40.5%)	associated with the risk of mortality at discharge and one year. High mFi is associated with serious complications and discharge at other than patients' home
Joseph B, et al. 2017 (105)	Trauma Specific Frailty Index(TSFI)	**Non-frail** N=126; Age mean ± SD = 76.5 ± 5.1; male = 63 (50%); TSFI, mean ± SD 0.088 ± 0.024; ISS, median (IQR) = 10 (9-15).**Pre-frail** N=91; Age mean ± SD = 76.9 ± 7.9; male = 62 (68%); TSFI, mean ± SD 0.19 ± 0.03; ISS, median (IQR) = 10 (9-14).**Frail** N=133; Age mean ± SD = 77.5 ± 8.4; male = 71 (53%); TSFI, mean ± SD 0.36 ± 0.09; ISS, median (IQR) = 12 (9-19).	ISS, median was 11 (IQR 9 - 17)	Outcomes were measured at discharge as follows: - In-hospital complications - Discharge disposition - In-hospital mortality - Length of stay (LOS) - Mortality Outcomes at 6-months as follows: -Mortality - Trauma readmission - Recurrent falls - Trauma Specific Frailty Index (TSFI)	At discharge: - Frail group was associated with high in-hospital complications compared with others (nonfrail, 12%; prefrail, 17.4% and frail, 33.4%) and the highest complications were UTI and pneumonia in frail group (9.7% and 9%). - Discharge to SNF was more in frail group (nonfrail,8%; prefrail, 18% and frail, 47%) - Discharge to home was the lowest in frail group (nonfrail,55%; prefrail, 55.4% and frail, 34%) - LOS median (IQR) was (nonfrail, 3(1-6); prefrail, 4(2-6)and frail, 5(2-7)) - No significant difference between groups at in-hospital mortality (nonfrail,2.4%; prefrail, 3.3% and	-TSFI is associated with poorer outcomes at long term outcomes. – Higher trauma readmissions were associated with frail group. – Recurrent falls after discharge are high in frail group (65%). - No significant relationship between TSFI and ISS and mortality.

					frail, 4.6%) After 6 months: - TSFI was (nonfrail,99 (35.3%); prefrail, 84 (30%) and frail, 97 (34.6%)) - Trauma readmission (nonfrail,1 (4%); prefrail, 12(14%) and frail, 39(40%)) - Recurrent falls (nonfrail,2(5%); prefrail, 11(13%) and frail, 63(65%)) - Mortality (nonfrail,1(1%); prefrail, 3(3.5%) and frail, 8(8.2%))	
Joseph B, et al. 2014 (106)	Frailty Index (FI)	**Non-frail** N=140; male= 70%; FI, mean ± SD 0.20 ± 0.05; ISS, median (IQR)=15 (9-17). **Frail** N=110; male= 68.2%; FI, mean ± SD 0.31± 0.09; ISS, median (IQR)= 16(9-16)	ISS, median was 15 (IQR 9 - 18)	- In-hospital complications - Discharge disposition (home, rehab or SNF) - In-hospital mortality - Length of stay (LOS)	Patients with frailty had a higher hospital complications compared with non-frail (37.3% vs 21.4%), where UTI and pneumonia were the highest. In univariate analysis, FI= 0.25 and more were associated with in-hospital complications and ISS. Patients with frailty had longer hospital stays compared with non-frail. Discharge disposition (frail vs non-frail): - Home (40.9% vs 53.6%) - Rehabilitation (21.8% vs 33.6%) - Skilled nursing facility (32.7% vs 13.9%) - in-hospital mortality (4.5% vs 0%)	No correlation between frailty and age. Frail patients group had higher ISS (16, frail vs 15, non-frail). Poor outcomes are associated with frailty status.
Hamidi M, et al. 2019 (107)	Trauma Specific Frailty Index (TSFI), The modified Frailty Index (mFI), Rockwood Clinical Frailty Scale (RFS) and 5-item Fried's phenotypic model (FS)	**[TSFI] Non-frail** N=239; Age mean ± SD = 75±7; male = 67%; TSFI <0.25; ISS, median (IQR)= 12(10-17). **[TSFI] Frail** N=102; Age mean ± SD =77±8; male = 69%; TSFI ≥0.25; ISS, median (IQR)= 12(9-18). **[mFI] Non-frail** N=247; Age mean ± SD = 75±8; male = 69%; mFI <0.25; ISS, median (IQR)= 13(9-17). **[mFI] Frail** N=94; Age mean ± SD = 78±9; male = 64%; mFI ≥0.25; ISS, median (IQR) = 13(8-18). **[FS]Non-frail** N=252; Age mean ± SD = 74±7; male = 68%; FS ⩽2; ISS, median (IQR)= 12(8-17). **[FS] Frail** N=89; Age mean ± SD = 77±7; male = 68%; FS >2; ISS, median (IQR)= 13(9-18).	ISS, median was 13 (IQR 9 - 18)	- In-hospital complications - SNF disposition - Mortality - 30-day readmission	Outcomes (frail vs non-frail): In-hospital complications; - [TSFI] (33% vs 17%) - [mFI] (30% vs 19%) - [FS] (32% vs 19%) - [RFS] (34% vs 16%) SNF disposition; - [TSFI] (42% vs 27%) - [mFI] (41% vs 28%) - [FS] (40% vs 29%) - [RFS] (43% vs 27%) Mortality; - [TSFI] (19% vs 6%) - [mFI] (16% vs 7%) - [FS] (13% vs 9%, p=0.21) - [RFS] (18% vs 6%) 30-day readmission; - [TSFI] (32% vs 18%) - [mFI] (30% vs 19%) - [FS] (30% vs 19%) - [RFS] (32% vs 17%)	Large numbers were categorised as frail when using RFS (32%) and TSFI (30%) in comparison to mFI (28%) and FS (26%). Classified frail patients were more likely to be older, higher comorbidities and more likely to sustain falls leading to high ISS. RFS and TSFI were more sensitive in detecting frailty compared with FS and mFI, as the large number of those tools (RFS

		[RFS]Non-frail N=231; Age mean ± SD = 75±6; male = 68%; FS <5; ISS, median (IQR)= 13(8-17). **[RFS] Frail** N=110; Age mean ± SD = 76±8; male = 66%; FS ≥5; ISS, median (IQR)= 14(9-18).				and TSFI) produced a significant results in the 4 outcomes and the same with low numbers which resulted no outcomes. TSFI is strongly correlated with RFS (rs>0.9) across all four outcomes. No significant difference were found between frail and non-frail in all frailty tools in terms of gender, race, systolic blood pressure, heart rate and GCS.
Jarman H, et al. 2021 (108)	Clinical Frailty Scale (CFS), Program of Research to Integrate services for the Maintenance of Anatomy 7 (PRISMA7) and Trauma Specific Frailty Index (TSFI)	**[TSFI]** Non-frail N=6(4.2%); Age Median(IQR) = 69 (67-71); male = 83.3%; TSFI <0.27; ISS, median (IQR)= 23(20-29). [**TSFI**] frail N=113(95%); Age Median(IQR) = 81 (74-86); male = 46.9%; TSFI >0.27; ISS, median (IQR)= 17(9-26). **[PRISMA7]** Non-frail N=147(42.4%); Age Median(IQR) = 75 (70-80); male = 48.3%; PRISMA7 < 3 points; ISS, median (IQR)= 16(9-20). **[PRISMA7]** frail N=199(57.1%); Age Median(IQR) = 84 (77-89); male = 46.2%; PRISMA7 ≥ 3 points; ISS, median (IQR)= 13(9-20). **[CFS]** Non-frail N=251(68.2%); Age Median(IQR) = 78 (71-82); male = 53.4%; CFS < 5 points; ISS, median (IQR)= 16(9-22). **[CFS]** frail N=117(31.8%); Age Median(IQR) = 87 (81-91); male = 32.5%; CFS ≥ 5 points; ISS, median (IQR)= 13(9-20).	ISS, median (IQR) was 16 (9-21)	- Identification of frailty - In-hospital mortality - Critical care and hospital length of stay - Discharge to the usual place of residence	The study was aimed to evaluate the performance of frailty assessment tools between emergency department (ED) and geriatrician (GA) and examine frailty outcomes. Completion rates of assessment was variable (CFS= 98.9%, PRISMA7= 98.9% and TSFI= 31.9%) and TSFI was the highest in identifying frail patients 95%. inter-rater agreement between ED and GA was at the highest in using CFS (kappa 0.637, p<0.001), moderate in PRISMA7 (kappa 0.458, p<0.001) and slight in TSFI (kappa 0.103, p=0.017). In-hospital mortality was high in all frail patients across all tools (TSFI= 10.6%, CFS= 17.1% and PRISMA7= 13.6%). No significant difference between tools and frail status in terms of critical care stays, MTC length of stay and discharge.	Frailty was significantly associated with the increase in age (p=0.0012). ISS was not associated with frailty status in all tools. Frail patients had higher mortality rates compared with non-frail in all tools. CFS is suitable to identify frailty in trauma patients.
Rickard F, et al. 2020 (59)	Frailty Score (9-points)	**Non-frail**, CFS(1-4) N=154; Age median (IQR)= 76(71-83); male = 81 (52.6%); Ageless Charlson	ISS, median (IQR) was 14 (9-24)	- 30-d mortality - Number of major complications	Twenty-six of patients (8.7%) died at 30-days. Mortality increasing with frailty as (non-frail 5%,	Fall less than 2m was 100% in severe frail, 90.7% in

		Comorbidity index, median (IQR)= 1(0-2); ISS, median (IQR)= 16 (9-25) **Mild to moderate-frail**, CFS(5-6) N=118; Age median (IQR)= 86(80-89); male = 38(32.2%); Ageless Charlson Comorbidity index, median (IQR)= 2(1-3); ISS, median (IQR)= 9(8-17) **Severe-frail**, CFS(7-9) N=28; Age median (IQR)= 88(81-91); male = 8(28.6%); Ageless Charlson Comorbidity index, median (IQR)= 2(1-3); ISS, median (IQR)= 10(4-16)		- Length of stay (LOS) - Increased care requirement at discharge	moderate 12.7% and severe 14%), p=0.03. LOS and number of complications were not different between frailty groups. Moderate and severe frail groups were more likely to required additional care at discharge (non-frail 27.3%, moderate 43.2% and severe 42.9%), p<0.01. In univariate analysis for associations; age, gender, aCCI, number of complications and delirium were not associated with 30-day mortality (p>0.05) but was significant in CFS (5-6) and ISS (p<0.05). Increased care level at discharge was associated with CFS (5-6) based on univariate analysis (OR= 2.38, p<0.01) and multivariate analysis (OR= 2.32, p<0.01). Added to this, there was a univariate association between increased care at discharge and aCCI (OR=1.21, p=0.02) and major complications (OR= 2.21, p<0.01).	moderate and 71.4% in non-frail. CFS (5-6) group was associated with frailty in binary and multiple regression as (OR=3.06, p=0.02, multivariate OR= 5.08, p<0.01. However, CFS (7-9) group was not associated with mortality as univariate analysis (OR= 3.50, p=0.06) but was associated in multivariate analysis (OR=10.38, p<0.01). ISS was associated with 30-d mortality at univariate analysis (OR=1.05, p=0.01) but was not significant in multivariate analysis (OR= 1.00, p=0.93). This shows the nonlinearity of CFS in prediction outcomes. There was a univariate association between the increase in complications and comorbidities will lead to increased care requirement at discharge.
Shah SP, et al. 2019 (109)	Simple FRAIL scale items (FRAIL-5) which are Fatigue, Resistance, Ambulation, Illness and Loss of weight. And Clinical Frailty Scale (9-points), mid upper-arm	**[Simple FRAIL score]** frail ≥3, N=15; Age mean ± SD = 79.5 ± 7.36; male 53%; ISS, mean ± SD 15.9 ± 18.2 **[Simple FRAIL score]** non-frail<3, N=50; Age mean ± SD = 76.8± 8.38; male 50%; ISS, mean ± SD 12.3 ± 6.7	Injury severity score (ISS) >9	- In-hospital mortality - Length of stay (LOS) - Hospital disposition: -- Home health -- Home -- MORGUE	Only n=-46 had CFS-physician results. However, those forty-six were involved in all other test, missed patients were attended CFS-self reported and FRAIL score and other tests were conducted to all 65 patients. Mortality outcomes	Age was higher in frail groups compared with non-frail across all tools. ISS was not associated with frailty status based

	circumference(MUAC) and ultrasound screening measures	**[CFS-self reported]** frail ≥4, N=21; Age mean ± SD = 82.4± 7.64; male 43%; ISS, mean ± SD 15± 15.5 **[CFS-self reported**] non-frail <4, N=44; Age mean ± SD = 75± 7.38; male 55%; ISS, mean ± SD 12.2± 6.6 **[CFS-physician]** frail ≥4, N=23; Age mean ± SD = 81.2± 8.69; male 57%; ISS, mean ± SD 15± 15.5 **[CFS- physician]** non-frail <4, N=23; Age mean ± SD = 72.2± 6.47; male 61%; ISS, mean ± SD 12.5± 5.97		-- Transferred to another acute care facility -- Skilled Nursing facility (SNF)	were not significant and p value were higher than 5% in all tests and groups. LOS was higher in all (frail vs non-frail) groups across all tools, mean (SD) (FRIAIL score= 8.3(6.65) vs 4.7(3.56), CFS-self= 7.76(6.36) vs 4.17(3.17) and CFS-physician= 6.83(6.3) vs 3.4(2.44), p<0.05. Discharge top home was significantly high in non-frail compared to frail in all frailty tools (frail vs non-frail (%) ;(FRAIL score= 2(13%) vs 31(62%) , CFS-self= 4(19%) vs 29(66%) and CFS-physician= 8(35%) vs 18 (78%), p<0.05. Discharge to SNF was significantly high in frail group compared with non-frail in all tools (frail vs non-frail (%) ;(FRIAIL score= 10(67%) vs 13(26%) , CFS-self= 12 (57%) vs 11(25%) and CFS-physician= 12(52%) vs 3(13%), p<0.05. In ROC analysis curve, sensitivity of CFS was at the highest when performed by surrogate /participants and CFS ≥4 compared with physician ; ((CFS-self, AUROC=0.909, 95%CI:0.843-0.975, sensitivity=0.905, specificity= 0.569) vs. (CFS-physician AUROC=0.771, 95%CI:0.634-0.908, sensitivity=0.74, specificity= 0.46). As well as, CFS<4 by physician was sensitivity=0.90 and by patients/surrogates sensitivity= 0.95. Grip strength and MUAC were not a predictors for frailty and not correlated with the reference FRAIL scale. Ultrasound measures of thickness has shown a significant AUROC= 0.75, sensitivity=0.67, specificity= 0.80.	on group means in all tools. CFS tool was sensitive when matched with FRAIl scale as a reference if both surrogate/pt and physician preformed CFS. MUAC was not a significant predictor of frailty based on t-test and man-Whitney tests performed for two samples. Ultrasound thickness of biceps and quadriceps (with/without subcutaneous fat) has shown 0.75 on ROC analysis.
Thompson A, et al. 2021 (110)	Clinical Frailty Scale CFS (9-points)	**Non-frail**, CFS (1-4) N=285; Age median (IQR) = 81(77-86); male = 122(42.8%); Charleson	ISS, median (IQR) was 10 (9-20)	- Mortality during admission	Mortality in comparison between (frail vs non-frail) was [57(12.8%) vs 15(5.3%)], LOS; median (IQR)	Fall less than 2 m was the highest mechanism of injury

		Comorbidity index CCI, median (IQR) = 4(3-5); ISS, median (IQR) = 16(9-21). **Frail**, CFS(5-9) N=444; Age median(IQR) = 86(81-90); male = 153(34.5%); Charleson Comorbidity index CCI, median(IQR)= 5(4-6); ISS, median (IQR)= 16(9-17)		- Length of Stay (LOS - Trauma call activation received - discharge to unusual residence	[12(7-20) vs 11(7-17)], trauma call received [58(13.1%) vs 72(25.3%)] and discharge to unusual residence [192(49.6%) vs 293(71.5%)]. In univariate analysis, unadjusted CFS (5-9); OR= 2.65 for mortality, OR=2.17 for LOS, OR= 0.44 for received trauma call and OR= 0.39 for discharge to unusual residence ($p<0.05$). Adjusted for age was an independent predictor with significant p vale for all outcomes except received trauma call where p= 0.20. Adjusted for ISS and sex were an independent predicators for all outcomes with $p<0.02$. Adjusted for CCI was an independent predictor except for LOS. A comparison between (survival vs dead) groups were performed and were; ISS, median (IQR) = [(10(9-18) vs 16(9-25)], CFS5-9= [387(58.9%) vs 57(79.2%)] and CCI, median (IQR) = [4(4-5) vs 5(4-6)], ($p<0.001$).	by 84.2%. ISS was significantly lower in frail group ($p<0.05$). Univariate analysis was performed for all variables (adjusted and unadjusted). After adjustment for Sex and ISS were independent predictors for mortality , length of stay, received trauma call and discharge to unusual residence ,$p<0.01$. After adjustment CFS (5-9); ORs were significant in mortality, LOS and discharge to unusual residence ($p<0.05$) except, received trauma call. The mortality group had higher CFS5-9, higher ISS and higher CCI compared with survival group.
Herklots M, et al. 2022 (111)	Clinical Frailty Scale (CFS, 9 items)	**Low frailty**, CFS (1-2) N=59; Age median (IQR) = 68 (64-72); male = 32(54%); ISS, mean (SD) = 30 (11.6). **High frailty**, CFS(3-9) N=58; Age median(IQR) = 72.5 (64-79); male = 43 (74%); ISS, mean (SD) = 25 (6.4).	ISS, mean (SD)= 27 (7)	- Mortality within 24 hours - In- hospital mortality - Glasgow Outcome Scale (GOS) at discharge and after 6 months - In- hospital complications - Length of stay (LOS) -Daus in ICU - therapy intensity level score (TIL)	High frailty was associated with shorter LOS median ((range)= 16.7(0-77) vs 8.4(0-52) compared with low frailty group.ISS was higher in low frailty compared with high frailty ISS, mean (SD) = 30 (11.6) vs 25 (6.4). Complication was haigher in low frailty compared with high frailty = 40 (67%) vs. (31(53%)	It might be the survival rate has impact LOS in this study as patients were those with Traumatic brain injury TBI. High frailty was associated with higher mortality rate, low ISS and older age, and less complications.

Guiab K, et al. 2022 (112)	The 5 items modified frailty index (mFI-5, 5 items)	**0 No frailty**= 6872 (25%); Age, median (IQR)= 74 (69,84); Male= 4357 (63.4%); ISS median (IQR) = 21 (14.26). **0.2 Moderate frailty**= 10234 (38%); Age, median (IQR)= 76 (70,82); Male= 6259(61.2%); median (IQR)= 18(12,26). **≥0.4 Severe frailty**= 9857 (36.6%); Age, median (IQR)= 76 (70,81); Male= 5972 (60.6%); median (IQR) = 17(10,25).	ISS, median (IQR) was 17 (10,26)	- Mortality - In-hospital complications - Length of stay (LOS) -discharge to home - non- home discharge (SNF, rehab, hospice, long term acute care) - ICU days -ventilator days	Severe frailty patients had longer LOS comparted with no frailty group LOS, median (IQR)= 13(7,21) vs 12 (6,21). Complications were higher in severe frailty group= 5512 compared with no frailty group= 3623. Mortality was higher in severe frailty in comparison with no frailty= 3166(32%) vs. 2101 (30.6%). Discharge to home was more in no frailty group compared with severe frailty group= 774(11.3%) vs. 752 (7.6%). While non discharge to home (SNF, rehab, hospice, and long term acute care) was higher in sever frailty compared with no frailty= 5478 (55.6%) vs. 3662 (53.3%).	Older people with frailty are less likely to discharge to home and more likely to discharge to rehab, long term acute care, SNF or hospice. Frailty is associated with mortality, complications and longer LOS.

Appendix 4: Frailty and mortality outcomes

Study	Mortality within 24 hours	In-hospital mortality	30-day mortality	6-month mortality	One-year mortality
Joseph B, et al. 2016.	N/A	NF,n(%)=6(7) PF,n(%)=7(5) F,n(%)=23(17) P=0.001	N/A	N/A	N/A
Cheung A, et al. 2017.	N/A	NF,n(%)=4(4.2) PF,n(%)=2(3.1) MF,n(%)=4(6.8) F,n(%)=1(2.8) P<0.05	N/A	N/A	N/A
Pecheva M, et al. 2020.	N/A	PF,n(%)=77(18.7) MF,n(%)=41(14.6) F,n(%)=29(26.4) P<0.006	N/A	N/A	PF,n(%)=90(26.2) MF,n(%)=80(35.2) F,n(%)=49(51) P<0.001
Hamidi M, et al. 2019.	N/A	NF,(%)=9.7 F,(%)=18.1 P<0.001	N/A	N/A	N/A
Joseph B, et al. 2017.	N/A	NF,n(%)=3(2.4) PF,n(%)=3(3.3) F,n(%)=5(4.6) P=0.61	N/A	NF,n(%)=1(1) PF,n(%)=3(3.5) F,n(%)=8(8.2) P=0.04	N/A
Joseph B, et al. 2014.	N/A	NF,n(%)=0 F,n(%)=5(4.5) P=0.01	N/A	N/A	N/A
Hamidi M, et al. 2019.	N/A	[TSFI]NF,n(%)=15(6) [TSFI]F,n(%)=19(9) [mFI]NF,n(%)=19(7) [mFI]F,n(%)=15(6) [FS]NF,n(%)=22(9) [FS]F,n(%)=12(13) [RFS],n(%)NF=13(6) [RFS]F,n(%)=20(18) P<0.001	N/A	N/A	N/A
Jarman H, et al. 2021.	N/A	[TSFI]NF,n(%)=0 [TSFI]F,n(%)=12(10.6) [PRISMA7]NF,n(%)=5(3.4) [PRISMA7]F,n(%)=27(13.6 [CFS]NF,n(%)=15(6) [CFS]F,n(%)=20(17.1) P<0.05	N/A	N/A	N/A
Rickard F, et al. 2020.	N/A	N/A	NF,n(%)=7(4.5) MF,n(%)=15(12.7) F,n(%)=4(14.3) P=0.03	N/A	N/A
Shah S P, et al. 2019.	N/A	[FRAIL-5]NF,n(%)=0 [FRAIL-5]F,n(%)=1(7) P=0.023 [CFS-self]NF,n(%)=0 [CFS-self]F,n(%)=1(5) P=0.323 [CFS-physician]NF,n(%)=0 [CFS-physician]F,n(%)=1(4) P=0.50	N/A	N/A	N/A
Thompson A, et al. 2021.	N/A	NF,n(%)=15(5.3) F,n(%)=57(12.8) P=0.001	N/A	N/A	N/A
Herklots M, et al. 2022	- CFS (1-2) ,n(%)= 9 (15.3) - CFS(3-9) ,n(%)=13 (22.4)	- CFS (1-2) ,n(%)= 38(64.4) - CFS(3-9) ,n(%)=44 (76%)			
Guiab K, et al. 2022	N/A	- 0 mFI-5,n(%)= 2101(30.6) - 0.2 mFI-5,n(%)= 2979 (29.1) - ≥0.4 mFI-5,n(%)=3166 (32.1)	N/A	N/A	N/A

P: p value, F: Frail or high frail, NF: Non-frail, PF: Pre/low/apparently frail, MF: moderate/intermediate/mildly frail, TSFI: Trauma Specific Frailty Index, mFI: The modified Frailty Index, RFS,CFS: Rockwood Clinical Frailty Scale, FS: 5-item Fried's phenotypic model, FRAIL-5: Simple FRAIL scale items

Appendix 5: Frailty and length of stay outcomes

Study	In-hospital/total hospital LOS(days)	Total major trauma centre LOS (days)	Critical care/Intensive care unit (ICU) LOS	Ventilator days
Joseph B, et al. 2016.	NF,median[IQR]=4[2-7] PF, median[IQR]=4[2-7] F, median[IQR]=5[3-8] P=0.48	N/A	NF,median[IQR]=0[0-1] PF,median[IQR]=1[0-3] F, median[IQR]=1[0-4] P=0.23	NF,median[IQR]=2[0-3] PF,median[IQR]=1[0-6] F,median[IQR]=0[0-5] P=0.46
Cheung A, et al. 2017.	N/A	N/A	N/A	N/A
Pecheva M, et al. 2020.	PF,mean(days)=18(1-114) MF,mean(days)=19.2(1-161) F,mean(days)=18.8(1-157) P<0.05	N/A	PF,mean(days)=7.8(1-37) MF,mean(days)=8.9(1-47) F,mean(days)=6.3(1-35) P<0.05	N/A
Hamidi M, et al. 2019.	N/A	N/A	NF,median[IQR]=6[3-11] F,median[IQR]=6[3-12] P=0.21	N/A
Joseph B, et al. 2017.	NF,median[IQR]=3[1-6] PF,median[IQR]=4[2-6] F,median[IQR]=5[2-7] P=0.08	N/A	NF,median[IQR]=2[1-4] PF,median[IQR]=1[1-3] F,median[IQR]=2[1-5] P=0.10	N/A
Joseph B, et al. 2014.	NF,mean(SD)=5.4(4.8) F,mean(SD)=7.3(6.2) P=0.01	N/A	NF,mean(SD)=3(2.1) F,mean(SD)=4.6(3.2) P=0.01	NF,mean(SD)=1.4(0.7) F,mean(SD)=1.6(0.9) P=0.35
Hamidi M, et al. 2019.	[TSFI]NF,mean(SD)=4(±2) [TSFI]F,mean(SD)=6(±4) [mFI]NF,mean(SD)=3(±1) [mFI]F,mean(SD)=5(±4) [FS]NF,mean(SD)=3(±2) [FS]F,mean(SD)=5(±3) [RFS]NF,mean(SD)=4(±1) [RFS]F,mean(SD)=6(±3) P<0.05	N/A	[TSFI]NF,mean(SD)=2(±1) [TSFI]F,mean(SD)=3(±2) [mFI]NF,mean(SD)=1(±1) [mFI]F,mean(SD)=3(±2) [FS]NF,mean(SD)=1(±1) [FS]F,mean(SD)=3(±1) [RFS]NF,mean(SD)=2(±2) [RFS]F,mean(SD)=2(±1) P<0.05	N/A
Jarman H, et al. 2021.	N/A	[TSFI]NF,median[IQR]=24(8-28) [TSFI]F,median[IQR]=9(3-19) [PRISMA7]NF,median[IQR]=12(4-21) [PRISMA7]F,median[IQR]=12(5-19) [CFS]NF,median[IQR]=12(4-20) [CFS]F,median[IQR]=13(6-21) P<0.05	[TSFI]NF,mean(SD)=10.5(17.9) [TSFI]F, mean(SD)=0.64(4.22) [PRISMA7]NF, mean(SD)=1.8(6.2) [PRISMA7]F, mean(SD)=0.55(4.6) [CFS]NF,mean(SD)=1.5(6.3) [CFS]F,mean(SD)=0.03 (0.29) P<0.05	N/A
Rickard F, et al. 2020.	NF,median[IQR]=11[6-21] MF,median[IQR]=14[6-21]	NF,median[IQR]=9[5.75-16] MF,median[IQR]=10[6-16]	N/A	N/A

	F,median[IQR]=12[6-28] P=0.64	F,median[IQR]=12[6-23] P=0.44		
Shah S P, et al. 2019.	[FRAIL-5]NF,mean(SD)=4.7(3.56) [FRAIL-5]F,mean(SD)=8.33(6.65) P=0.0072 [CFS-self]NF,mean(SD)=4.47(3.17) [CFS-self]F,mean(SD)=7.76(6.36) P=0.0069 [CFS-physician]NF,mean(SD)=3.4(2.44) [CFS-physician]F,mean(SD)=6.83(6.3) P=0.019	N/A	**(Hours)** [FRAIL-5]NF,mean(SD)=52.46(36) [FRAIL-5]F,mean(SD)=112.1(103) P=0.0009 [CFS-self]NF,mean(SD)=61.5(45.2) [CFS-self]F,mean(SD)=75(81.7) P=0.3938 [CFS-physician]NF,mean(SD)=53.1(47.2) [CFS-physician]F,mean(SD)=80.1(79.8) P=0.1695	N/A
Thompson A, et al. 2021.	NF,median[IQR]=11[7-17] F,median[IQR]=12[7-20] P=0.1498	N/A	N/A	N/A
Herklots M, et al. 2022	Days hospitalised : - CFS (1-2) , median(range)= 16.7 (0-77) - CFS(3-9) , median(range)=8.4 (0-52)	N/A	- CFS (1-2) , median(range)= 11 (0-68) - CFS(3-9) , median(range)=6.8 (0-52)	N/A
Guiab K, et al. 2022	- 0 mFI-5, median[IQR]= 12 (6,21) - 0.2 mFI-5, median[IQR]= 13(7,21) - ≥0.4 mFI-5, median[IQR]=13(7,21)	N/A	- 0 mFI-5, median[IQR]= 8 (3,14) - 0.2 mFI-5, median[IQR]= 8 (4,15) - ≥0.4 mFI-5, median[IQR]=8 (4,14)	- 0 mFI-5, median[IQR]= 4 (2,10) - 0.2 mFI-5, median[IQR]= 4 (2,10) - ≥0.4 mFI-5, median[IQR]= 4 (2,10)

SD: Standard deviation, P: p value, IQR: Interquartile range, F: Frail or high frail, NF: Non-frail, PF: Pre/low/apparently frail, MF: moderate/intermediate/mildly frail, TSFI: Trauma Specific Frailty Index, mFI: The modified Frailty Index, RFS,CFS: Rockwood Clinical Frailty Scale, FS: 5-item Fried's phenotypic model, FRAIL-5: Simple FRAIL scale items

Appendix 6: Frailty and discharge destinations

Study	Home	Rehabilitation	Skilled Nursing facility (SNiF)	Others
Joseph B, et al. 2016.	NF,n(%)=67(72) PF,n(%)=82(59) F,n(%)=39(29) P=0.001	NF,n(%)=7(8) PF,n(%)=19(14) F,n(%)=51(38) P=0.001	NF,n(%)=12(13) PF,n(%)=30(22) F,n(%)=22(16) P=0.13	N/A
Cheung A, et al. 2017.	With/without support NF,n(%)=20(21) PF,n(%)=12(18.5) MF,n(%)=6(10.3) F,n(%)=1(2.8) P<0.05	Regular or specialised NF,n(%)=4(4.2) PF,n(%)=2(3.1) MF,n(%)=4(6.8) F,n(%)=1(2.8) P<0.05	N/A	Transfer to acute hospital NF,n(%)=21(22.1) PF,n(%)=16(24.6) MF,n(%)=16(27.6) F,n(%)=18(51.4) P<0.05 Chronic or long-term care NF,n(%)=2(2.1) PF,n(%)=2(3.1) MF,n(%)=1(1.7) F,n(%)=6(17.1) P<0.05
Pecheva M, et al. 2020.	PF,n(%)=167(40.5) MF,n(%)=104(37.1) F,n(%)=32(29.1) P<0.05	PF,n(%)=17(4.1) MF,n(%)=5(1.8) F,n(%)=0 P<0.05	PF,n(%)=6(1.5) MF,n(%)=19(6.8) F,n(%)=11(10) P<0.05	Local hospital PF,n(%)=135(32.8) MF,n(%)=95(33.9) F,n(%)=30(27.3) P<0.05 Long-term residential care PF,n(%)=7(1.7) MF,n(%)=13(4.6) F,n(%)=5(4.6) P<0.05
Joseph B, et al. 2017.	NF,n(%)=69(55) PF,n(%)=50(55.4) F,n(%)=45(34) P=0.01	NF,n(%)=43(34) PF,n(%)=21(23.4) F,n(%)=19(14.7) P=0.01	NF,n(%)=10(8) PF,n(%)=16(18.2) F,n(%)=62(46.8) P=0.001	N/A
Joseph B, et al. 2014.	NF,n(%)=75(53.6) F,n(%)=45(40.9) P=0.04	NF,n(%)= 47(33.6) F,n(%)=24(21.8) P=0.04	NF,n(%)=18(12.9) F,n(%)=36(32.7) P=0.01	N/A
Hamidi M, et al. 2019.	N/A	N/A	[TSFI]NF,n(%)=66(27) [TSFI]F,n(%)=43(42) [mFI]NF,n(%)=70(28) [mFI]F,n(%)=39(41) [FS]NF,n(%)=73(29) [FS]F,n(%)=36(40) [RFS]NF, n(%)=62(27) [RFS]F,n(%)=47(43) P<0.04	30-d readmission [TSFI]NF,n(%)=42(18) [TSFI]F,n(%)=33(32) [mFI]NF,n(%)=47(19) [mFI]F,n(%)=28(30) [FS]NF,n(%)=48(19) [FS]F,n(%)=20(30) [RFS]NF, n(%)=40(17) [RFS]F,n(%)=35(32) P<0.04
Jarman H, et al. 2021.	N/A	N/A	N/A	Discharge to usual place of residence [TSFI]NF,n(%)=2(33.3) [TSFI]F,n(%)=62(62.8) [PRISMA7]NF,n(%)=106(75.6) [PRISMA7]F,n(%)=119(69.1) [CFS]NF,n(%)=169(71.6) [CFS]F,n(%)=66(68) P<0.05
Rickard F, et al. 2020.	N/A	N/A	N/A	Increased care requirement at discharge NF,n(%)=42(27.3) MF,n(%)=51(43.2) F,n(%)=12(42.9) P<0.01
Shah SP, et al. 2019.	[FRAIL-5]NF,n(%)=31(62) [FRAIL-5]F,n(%)=2(13) P=0.0009 [CFS-self]NF,n(%)=29(66) [CFS-self]F,n(%)=4(19) P=0.0004 [CFS-physician] NF,n(%)=18(78)	N/A	[FRAIL-5]NF,n(%)=13(26) [FRAIL-5]F,n(%)=10(67) P=0.0047 [CFS-self]NF,n(%)=11(25) [CFS-self]F,n(%)=12(57) P=0.0099 [CFS-physician] NF,n(%)=3(13)	MORGUE, Home health, transfer to acute hospital and died on ED were not significant outcomes and less than one patient in each category.

	[CFS-physician] F,n(%)=8(35) P=0.0029		[CFS-physician] F,n(%)=12(52) P=0.0047	
Thompson A, et al. 2021.	N/A	N/A	N/A	Discharge to usual residence NF,n(%)=193(71.5) F,n(%)=192(49.6) P<0.001
Herklots M, et al. 2022	N/A	N/A	N/A	N/A
Guiab K, et al. 2022	- 0 mFI-5,n(%)= 774 (11.3) - 0.2 mFI-5,n(%)= 956 (9.3) - ≥0.4 mFI-5,n(%)=752 (7.6)	N/A	N/A	Non-home discharge (SNF, rehab, hospice, long term acute care): - 0 mFI-5,n(%)= 3662 (53.3) - 0.2 mFI-5,n(%)= 5800 (56.7) - ≥0.4 mFI-5,n(%)= 5478 (55.6)

P: p value, F: Frail or high frail, NF: Non-frail, PF: Pre/low/apparently frail, MF: moderate/intermediate/mildly frail, TSFI: Trauma Specific Frailty Index, mFI: The modified Frailty Index, RFS,CFS: Rockwood Clinical Frailty Scale, FS: 5-item Fried's phenotypic model, FRAIL-5: Simple FRAIL scale items

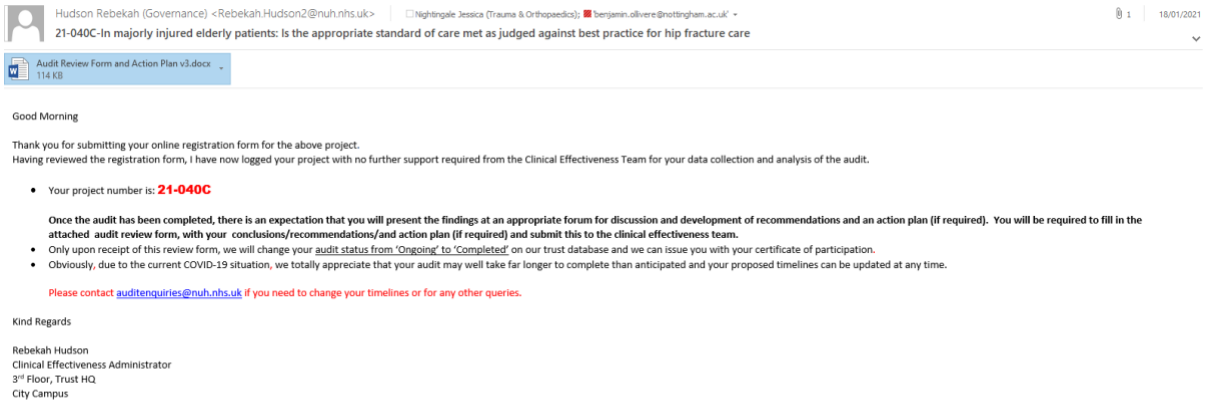
Appendix 7: Frailty and complications

Study	Number of complications	Urinary tract infection (UTI)	Pneumonia	Deep vein thrombosis/ pulmonary embolism (DVT/PE)	Infection/sepsis	Acute kidney injury (AKI)	Cardiac arrest/ Myocardial infraction (MI)	Others
Joseph B, et al. 2016.	In-hospital Complications NF,n(%)=21(23) PF,n(%)=33(24) F,n(%)=57(42) P=0.002	NF,n(%)=1(1.1) PF,n(%)=2(1.4) F,n(%)=7(5.1) P=0.09	NF,n(%)=3(3.5) PF,n(%)=4(2.8) F,n(%)=9(6.5) P=0.28	DVT NF,n(%)=1(1.1) PF,n(%)=1(0.7) F,n(%)=1(0.7) P=0.92	N/A	NF,n(%)=0 PF,n(%)=3(2.1) F,n(%)=8(5.8) P=0.03	N/A	Anaemia NF,n(%)=0 PF,n(%)=5(3.6) F,n(%)=7(5) P=0.04
Cheung A, et al. 2017.	Complication N=0 NF,n(%)=64(67.3),PF,n(%)=39(57.3) MF,n(%)=31(51.7), F,n(%)=21(56.7) Complication N=1 NF,n(%)=14(14.7),PF,n(%)=14(20.6) MF,n(%)=16(26.7), F,n(%)=9(24.3) Complication N=2 NF,n(%)=7(7.4),PF,n(%)=11(16.2) MF,n(%)=9(15), F,n(%)=6(16.2) Complication N= 3 NF,n(%)=3(3.1), PF,n(%)=3(4.4) MF,n(%)=3(5), F,n(%)=1(2.7) Complication N= +4 NF,n(%)=7(7.4), PF,n(%)=1(1.5) MF,n(%)=1(1.7), F,n(%)=0 ;P<0.05	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pecheva M, et al. 2020.	Complication N=0 PF,n(%)=87(21.1),MF,n(%)=44(15.7) F,n(%)=23(20.9) Complication N=1 PF,n(%)=126(30.6),MF,n(%)=83(29.6),F,n(%)=40(36.4) Complication N>1 PF,n(%)=199(48.3),MF,n(%)=153(54.6),F,n(%)=47(42.7), P<0.05	N/A	PF,n(%)=72(17.5) MF,n(%)=65(23.2) F,n(%)=23(25.5) P<0.05	N/A	PF,n(%)=61(14.8) MF,n(%)=45(16.1) F,n(%)=33(30) P<0.05	Acute renal failure PF,n(%)=23(5.6) MF,n(%)=22(7.9) F,n(%)=6(5.5) P<0.05	PF,n(%)=4(1) MF,n(%)=5(1.8) F,n(%)=2(1.8) P<0.05	Unplanned intubation PF,n(%)=15(3.6) MF,n(%)=16(5.7) F,n(%)=17(15.5) P<0.05
Hamidi M, et al. 2019.	In-hospital Complications NF,(%)=18.1 F,(%)=34.2 P<0.001	NF,(%)=3.2 F,(%)=7 P<0.001	NF,(%)=4 F,(%)=8.5 P<0.001	DVT NF,(%)=3.3 F,(%)=8.1 P<0.001 PE NF,(%)=1.2 F,(%)=1.1	Infectious NF,(%)=7.3 F,(%)=16.2 P<0.001 Severe sepsis NF,(%)=1.5 F,(%)=2.7	NF,(%)=3 F,(%)=5.9 P<0.001	Cardiac arrest NF,(%)=1.2 F,(%)=3.9 P<0.001 MI NF,(%)=3 F,(%)=7.7	Unplanned intubation NF,(%)=2.1 F,(%)=3.4 P<0.001

				P=0.39	P<0.001		P<0.001	
Joseph B, et al. 2017.	<u>In-hospital Complications</u> NF,n(%)=15(12) PF,n(%)=19(17.4) F,n(%)=44(33.4) P=0.02	NF,n(%)=4(3.3) PF,n(%)=5(5.5) F,n(%)=13(9.7) P=0.01	NF,n(%)=3(2.3) PF,n(%)=4(4.4) F,n(%)=12(9) P=0.01	NF,n(%)=2(1.6) PF,n(%)=3(4) F,n(%)=7(5.3) P=0.21	<u>Sepsis</u> NF,n(%)=2(1.6) PF,n(%)=4(4.4) F,n(%)=5(3.3) P=0.41	N/A	N/A	<u>Reoperation</u> NF,n(%)=3(2.3) PF,n(%)=2(2.1) F,n(%)=5(3.3) P=0.11
Joseph B, et al. 2014.	N/A	NF,n(%)=9(6.4) F,n(%)=12(10.9) P=0.04	NF,n(%)=6(4.3) F,n(%)=10(9.1) P=0.01	<u>DVT</u> NF,n(%)=5(3.6) F,n(%)=7(6.4) P=0.01 <u>PE</u> NF,n(%)=3(2.1) F,n(%)=2(1.8) P=0.11	<u>Sepsis</u> NF,n(%)=2(1.4) F,n(%)=4(3.6) P=0.01	N/A	N/A	<u>Reoperation</u> NF,n(%)=3(2.1) F,n(%)=4(3.6) P=0.54
Hamidi M, et al. 2019.	<u>In-hospital complications</u> [TSFI]NF,n(%)=41(17) [TSFI]F,n(%)=34(33) [mFI]NF,n(%)=47(19) [mFI]F,n(%)=28(30) [FS]NF,n(%)=47(19) [FS]F,n(%)=28(32) [RFS],n(%)NF=38(16) [RFS]F,n(%)=37(34) P<0.05	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Jarman H, et al. 2021.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rickard F, et al. 2020.	<u>In-MTC with major complications</u> NF,n(%)=64(41.9) MF,n(%)=58(49.2) F,n(%)=14(50) P=0.40	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Shah SP, et al. 2019.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Thompson A, et al. 2021.	<u>Charleson Comorbidity Index</u> NF,median(IQR)=4(3-5) F,median(IQR)=5(4-6) P<0.001	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Herklots M, et al. 2022	- CFS (1-2) ,n(%)= 40(67.8) - CFS(3-9) ,n(%)=31 (53)	N/A	N/A	N/A	N/A	N/A	N/A	Intubation - CFS (1-2) ,n(%)= 58 (98.3) - CFS(3-9) ,n(%)=56(97)

Guiab K, et al. 2022	- 0 mFI-5,n(%)= 3623 (33.4) - 0.2 mFI-5,n(%)= 5409 (39.2) - ≥0.4 mFI-5,n(%)=5512 (43.3)	N/A	Pulmonary: - 0 mFI-5,n(%)= 1428(20.8) - 0.2 mFI-5,n(%)= 2472(24.2) - ≥0.4 mFI-5,n(%)=2430 (24.7)	N/A	Infectious : - 0 mFI-5,n(%)= 779 (11.3) - 0.2 mFI-5,n(%)= 1416 (13.8) - ≥0.4 mFI-5,n(%)=1493(15.1)	- 0 mFI-5,n(%)= 304 (4.4) - 0.2 mFI-5,n(%)= 519 (5.1) - ≥0.4 mFI-5,n(%)=681 (6.9)	Cardiovascular: - 0 mFI-5,n(%)=632 (9.2) - 0.2 mFI-5,n(%)= 1130 (11) - ≥0.4 mFI-5,n(%)=1354 (13.7)	N/A

Appendix 8: Audit approval



Hudson Rebekah (Governance) <Rebekah.Hudson2@nuh.nhs.uk> | Nightingale Jessica (Trauma & Orthopaedics); benjamin.ollivere@nottingham.ac.uk | 1 | 18/01/2021

21-040C-In majorly injured elderly patients: Is the appropriate standard of care met as judged against best practice for hip fracture care

Audit Review Form and Action Plan v3.docx
114 KB

Good Morning

Thank you for submitting your online registration form for the above project.
Having reviewed the registration form, I have now logged your project with no further support required from the Clinical Effectiveness Team for your data collection and analysis of the audit.

- Your project number is: **21-040C**

Once the audit has been completed, there is an expectation that you will present the findings at an appropriate forum for discussion and development of recommendations and an action plan (if required). You will be required to fill in the attached audit review form, with your conclusions/recommendations/and action plan (if required) and submit this to the clinical effectiveness team.

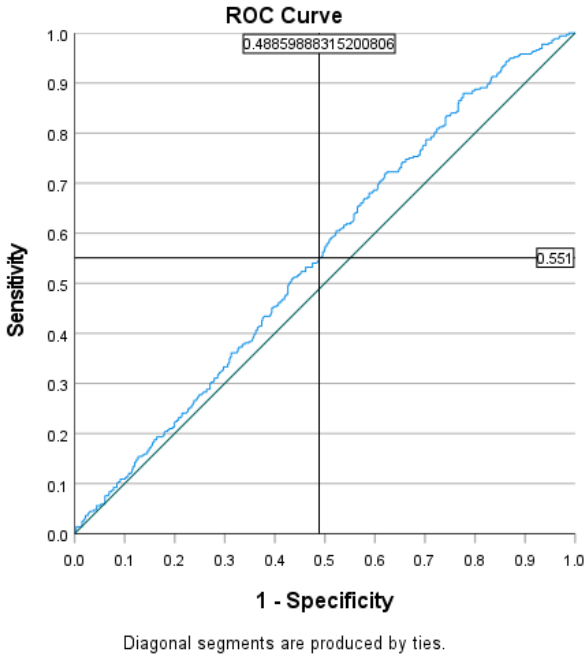
- Only upon receipt of this review form, we will change your audit status from 'Ongoing' to 'Completed' on our trust database and we can issue you with your certificate of participation.
- Obviously, due to the current COVID-19 situation, we totally appreciate that your audit may well take far longer to complete than anticipated and your proposed timelines can be updated at any time.

Please contact auditenquiries@nuh.nhs.uk if you need to change your timelines or for any other queries.

Kind Regards

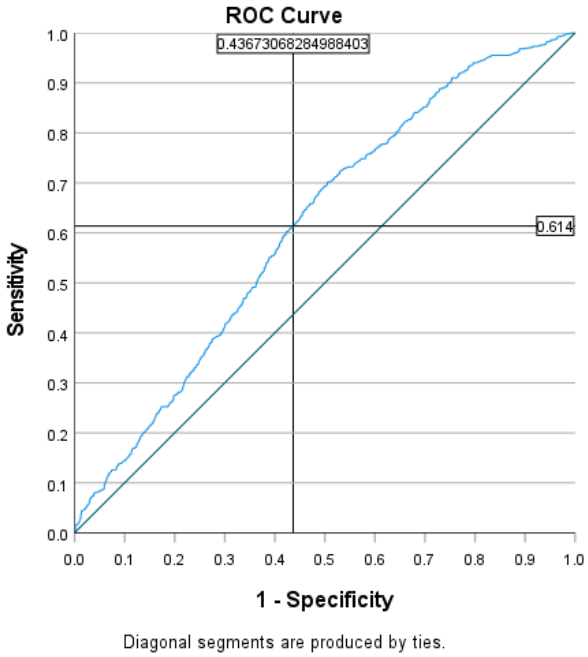
Rebekah Hudson
Clinical Effectiveness Administrator
3rd Floor, Trust HQ
City Campus

Appendix 9: ROC curve for at least one and more complications in the internal cohort



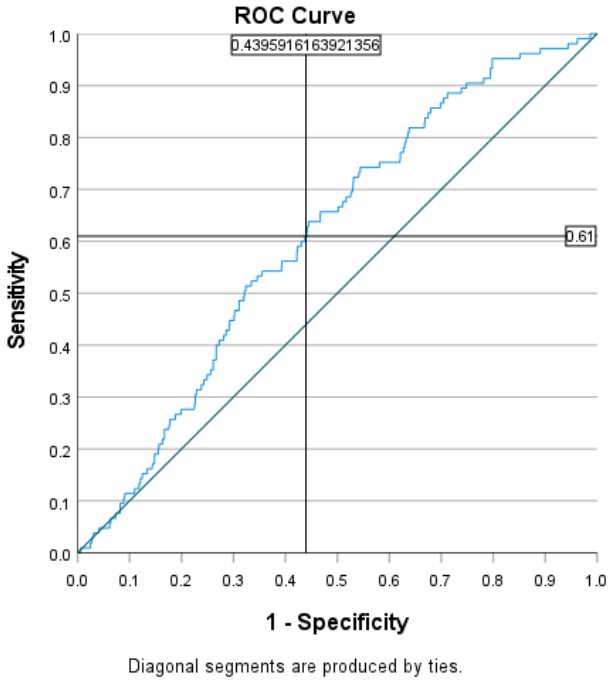
NTFI= 4.4905 [0.546 – 0.489]

Appendix 10: ROC curve for at least one and more complications in the external cohort



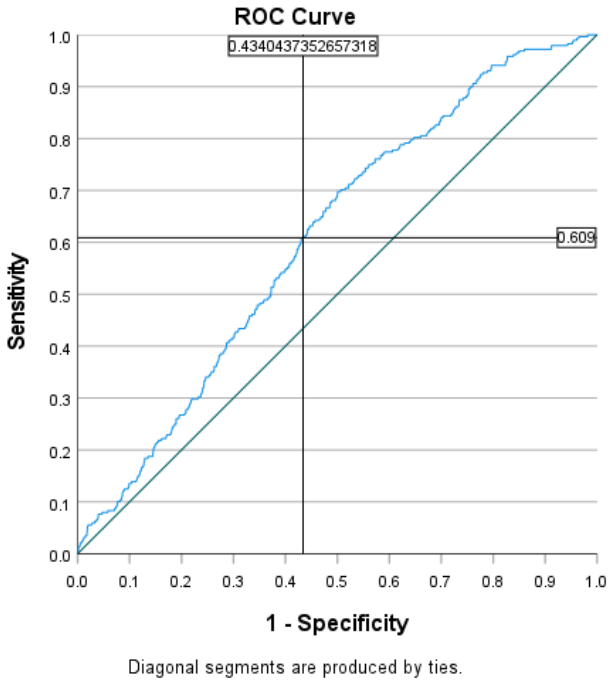
NTFI= 4.4320 [0.613- 0.436]

Appendix 11: ROC curve for at least two and more complications in the internal cohort



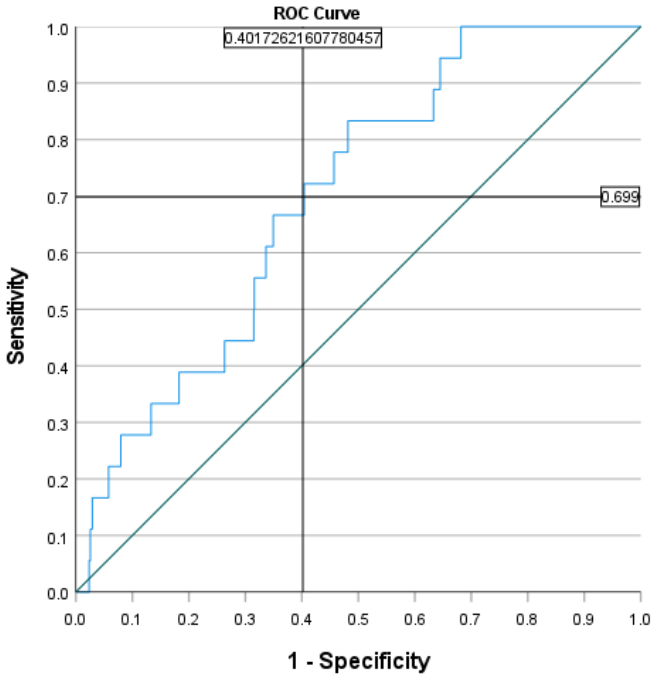
NTFI= 4.6200 [0.610 – 0.439]

Appendix 12: ROC curve for at least two and more complications in the external cohort



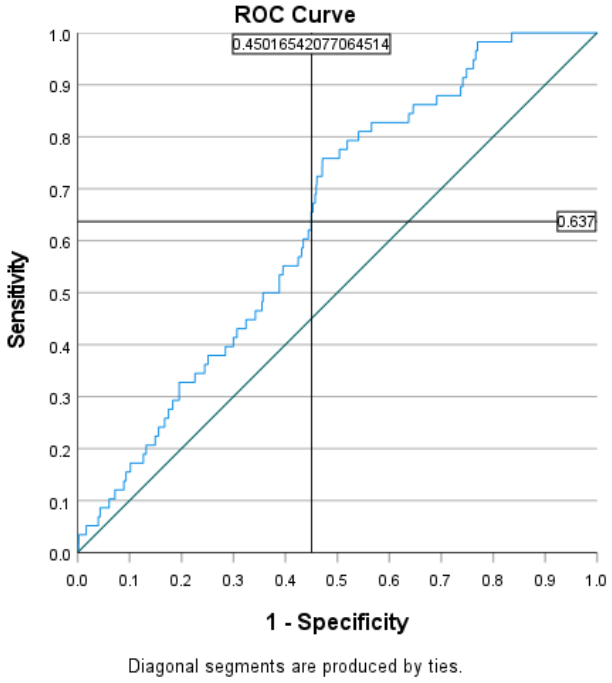
NTFI= 4.5515 [0.608- 0.434]

Appendix 13: ROC curve for at least three and more complications in the internal cohort



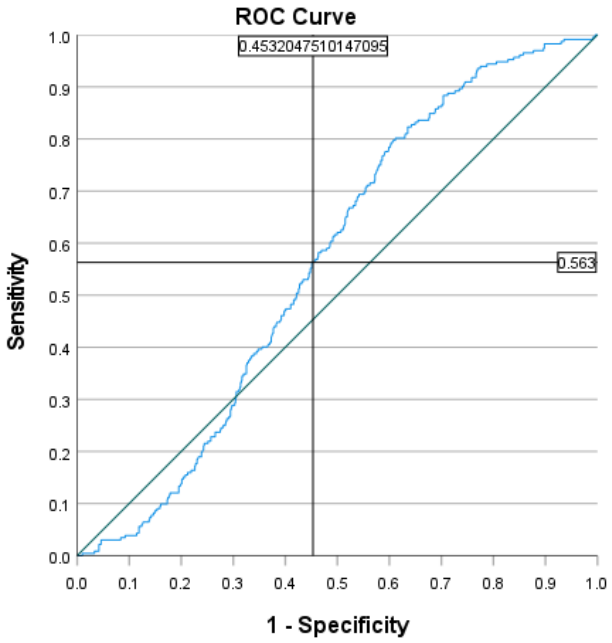
NTFI= 4.7580 [0.667 – 0.401]

Appendix 14: ROC curve for at least three and more complications in the external cohort



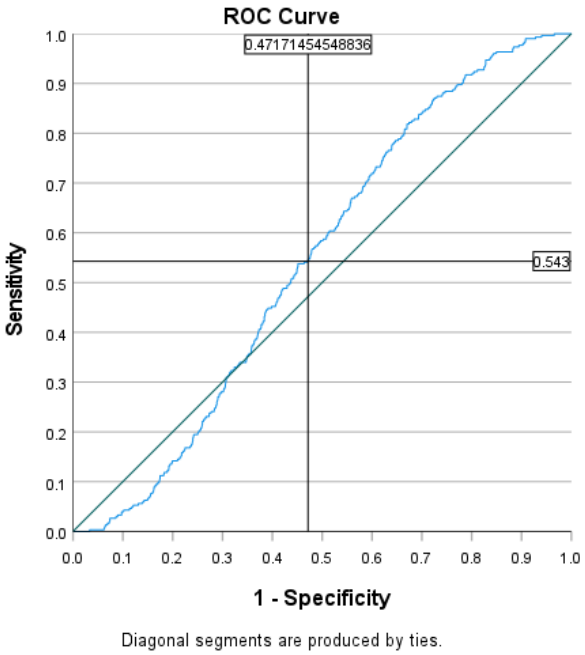
NTFI= 4.5625 [0.638- 0.450]

Appendix 15: ROC curve for discharge to rehabilitation unit in the internal cohort



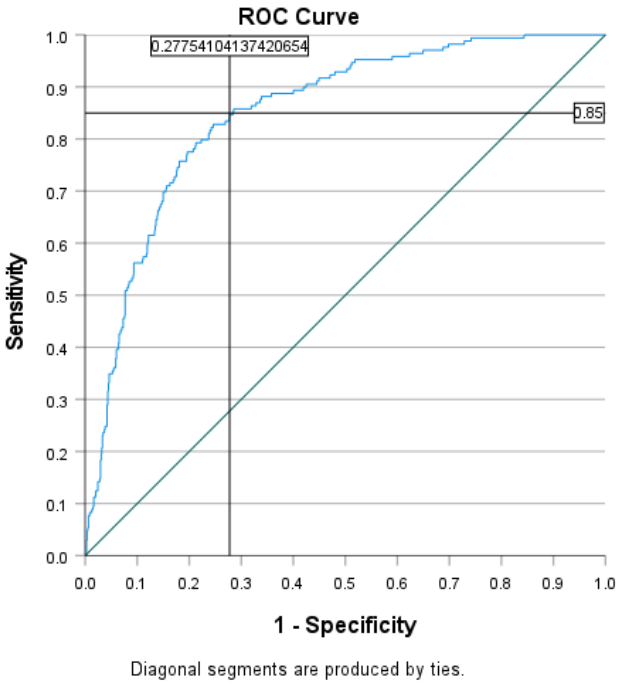
NTFI= 4.5605 [0.560 – 0.451]

Appendix 16: ROC curve for discharge to rehabilitation unit in the external cohort



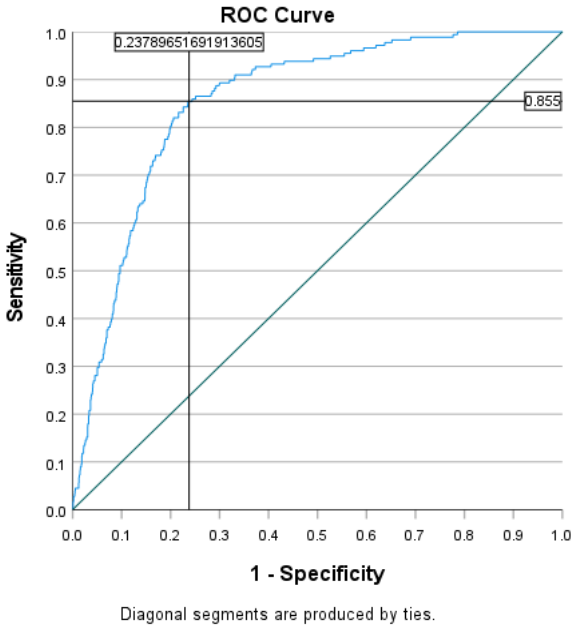
NTFI= 4.4960 [0.541- 0.471]

Appendix 17: ROC curve for discharge to nursing home care in the internal cohort



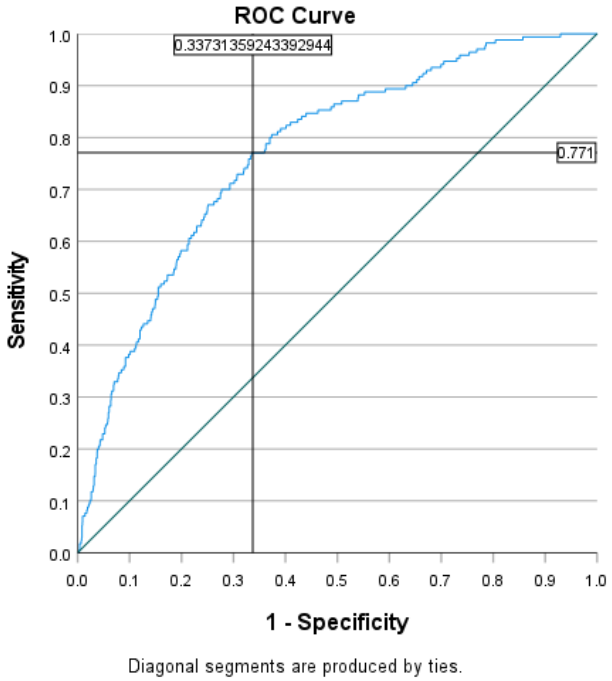
NTFI= 4.8490 [0.846 – 0.277]

Appendix 18: ROC curve for discharge to nursing home care in the external cohort



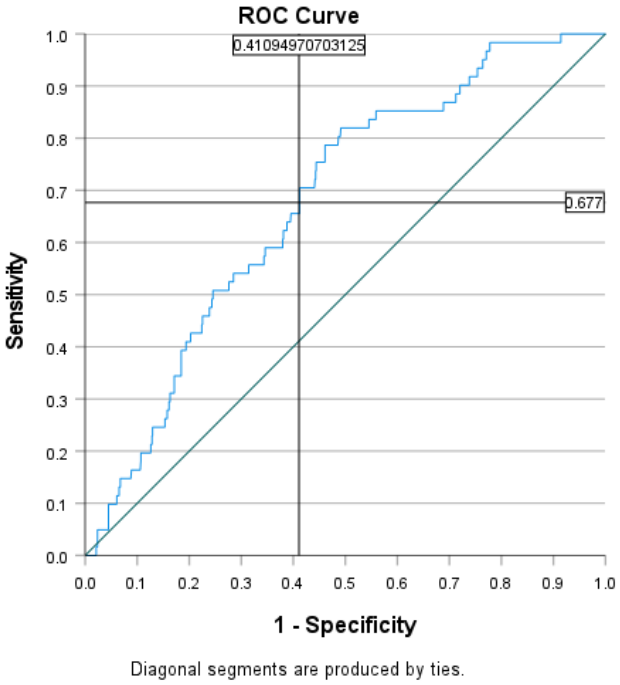
NTFI= 5.0225 [0.854- 0.237]

Appendix 19: ROC curve for discharge to residential care home in the external cohort



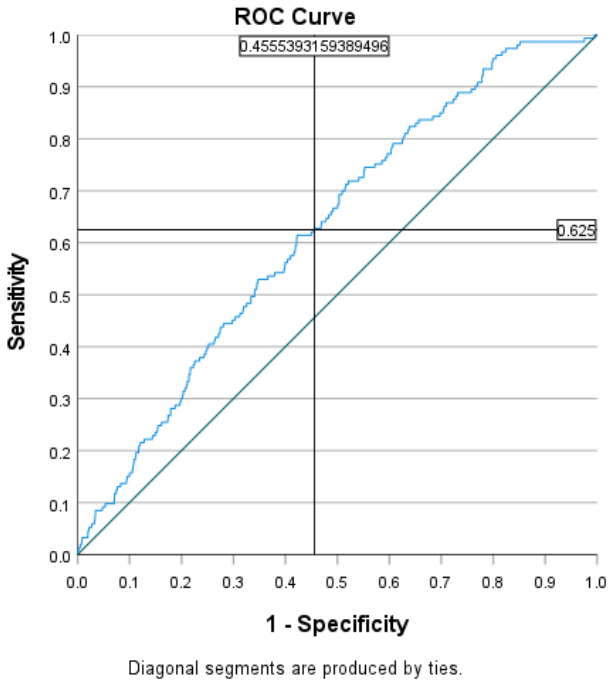
NTFI= 4.7655 [0.771- 0.337]

Appendix 20: ROC curve for mortality at discharge in the internal cohort



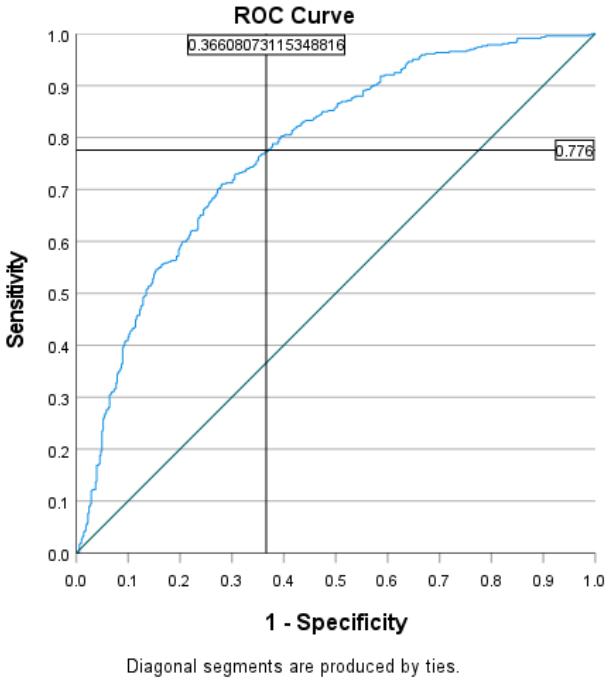
NTFI= 4.6865 [0.656 – 0.413]

Appendix 21: ROC curve for mortality at discharge in the external cohort



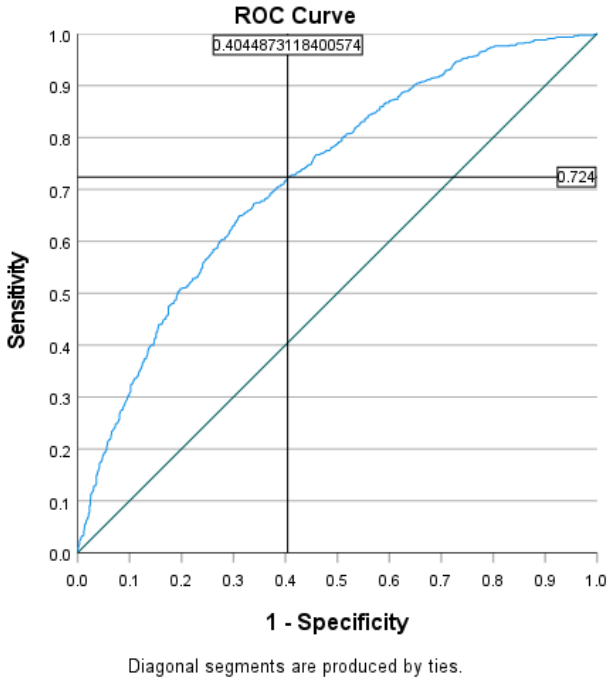
NTFI= 4.5280 [0.621- 0.455]

Appendix 22: ROC curve for at least one and more increase in dependency level in the internal cohort



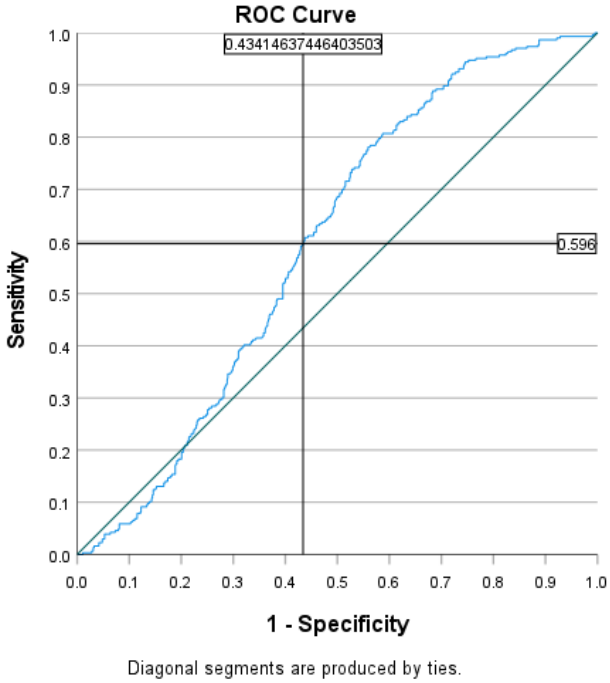
NTFI= 4.3455 [0.775 – 0.370]

Appendix 23: ROC curve for at least one and more increase in dependency level in the external cohort



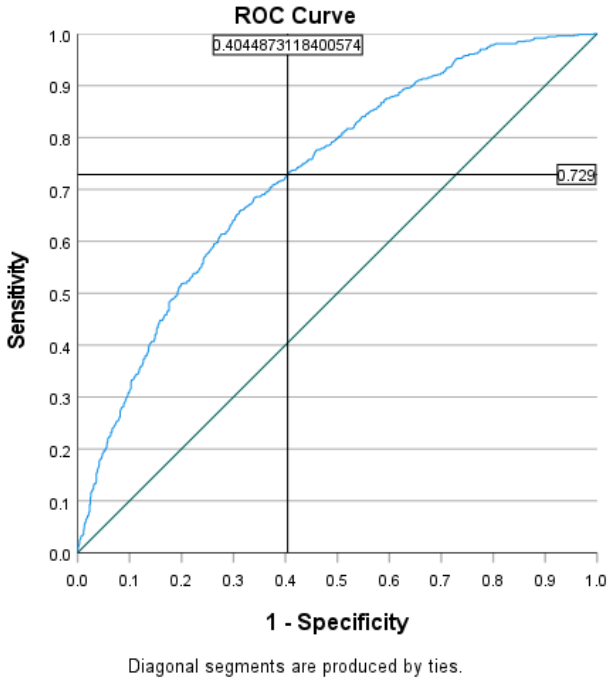
NTFI= 4.3990 [0.724- 0.404]

Appendix 24: ROC curve for at least two and more increase in dependency level in the internal cohort



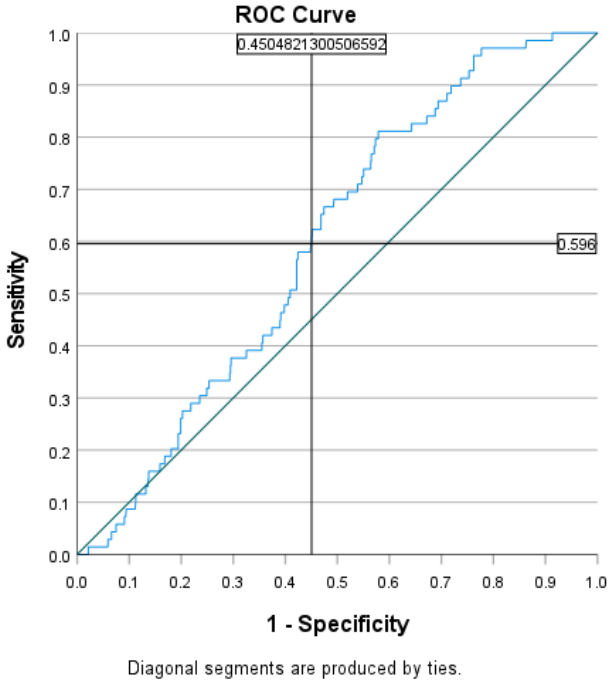
NTFI= 4.5475 [0.595 – 0.433]

Appendix 25: ROC curve for at least two and more increase in dependency level in the external cohort



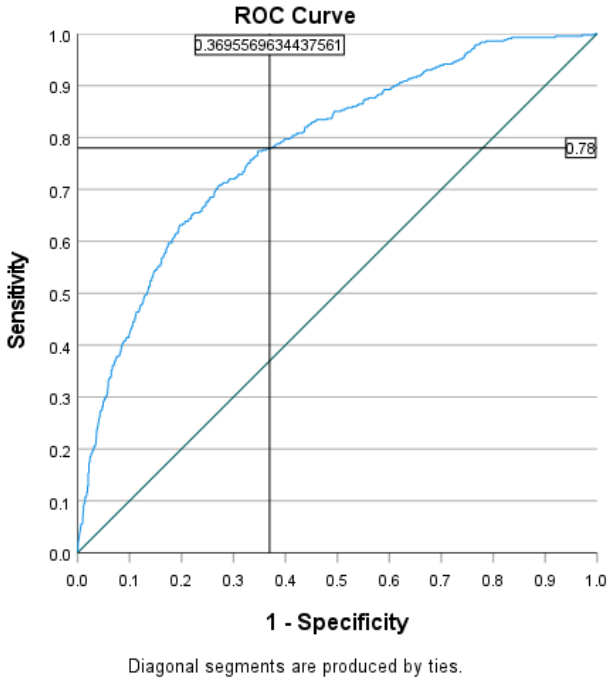
NTFI= 4.4045 [0.729 - 0.406]

Appendix 26: ROC curve for at least three and more increase in dependency level in the internal cohort



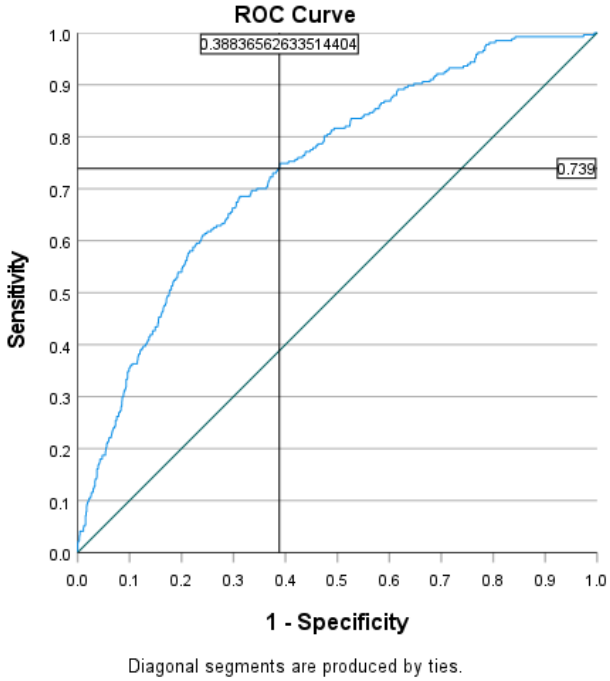
NTFI= 4.6065 [0.594 – 0.451]

Appendix 27: ROC curve for at least three and more increase in dependency level in the external cohort



NTFI= 4.5585 [0.779 - 0.369]

Appendix 28: ROC curve for at least four and more increase in dependency level in the external cohort



NTFI= 4.6015 [0.738 - 0.388]