The effect of diabetes mellitus on outcomes following colorectal resections.

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Declaration

I hereby declare that this thesis is the result of original research work performed by myself. It has not been submitted for any degree or other qualification elsewhere. All research and publications to which reference has been made are fully acknowledged.

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Abstract

Introduction

Diabetes mellitus affects over 9% of the global population, with an increasing prevalence over the last 15 years. Haemoglobin A1c (HbA1c) is a known measure of long-term diabetic control and can be used as a treatment target and referral threshold for patients with diabetes receiving surgery.
Diabetes is known to predict poorer outcomes in general medical and surgical patients, however the impact of diabetes on outcomes after colorectal resections has yet to be fully quantified. This thesis aimed to investigate the effect of diabetes and insulin-use on outcomes following colorectal resections using a national cohort and explore the perioperative use of HbA1c in current practice.

Methods

All adult patients with a recorded colorectal resection in England between 2010 and 2020 were identified from Hospital Episode Statistics (HES) data linked to the Clinical Practice Research Database (CPRD).
The primary outcome was 90-day mortality. Secondary outcomes included hospital length of stay (LOS), unplanned hospital readmissions within 90 days of discharge and the proportion patients with diabetes with HbA1c measured within one year before surgery.
Adjusted hazard ratios (HR) were calculated using Cox proportional hazard models for 90-day mortality and 90-day readmission. Length of stay was analysed using a loglogistic accelerated failure time model, with results presented as adjusted time ratios (TR).

Results

106,139 (50% male) patients were included with a median age of 66 (Interquartile Range (IQR) 52 to 76). The prevalence of diabetes was 10% (n = 10,931), encompassing 653 (6%) patients with type 1 and 10,278 (94%) patients with type 2

diabetes. 20% of all patients with diabetes had a record of insulin-use and 70% had a recorded HbA1c measured within one year before surgery.
The overall unadjusted 90-day mortality risk was 5.7%, with an increased hazard rate for patients with diabetes (adjusted HR 1.28, 95% CI 1.19 to 1.37, $p < 0.001$) compared to patients without diabetes. This risk was higher in both patients with diabetes with insulin-use (adjusted HR 1.51, 95% CI 1.31 to 1.74, $p < 0.001$) and without insulin-use (adjusted HR 1.22, 95% CI 1.13 to 1.33, $p < 0.001$), compared to patients without diabetes.
90-day readmission occurred in 19.4% (n = 20,542) of all patients. Patients with diabetes were more likely to experience 90-day readmission (HR 1.23, 95% CI 1.18 to 1.29, $p < 0.001$) compared to patients without diabetes. Patients with diabetes and insulin-use had an increased hazard rate for 90-day readmission (adjusted HR 1.46, 95% CI 1.34 to 1.59, $p < 0.001$), over and above patients with diabetes without insulin-use (adjusted HR 1.17, 95% CI 1.12 to 1.23, $p < 0.001$), compared to patients without diabetes (reference group).
Median length of stay was 8 days (IQR 5 to 15). Length of stay was increased by 10% in patients with diabetes (adjusted TR 1.10, 95% CI 1.08 to 1.11, $p < 0.001$).

Conclusion

Patients with diabetes undergoing colorectal resections are at a higher risk of 90-day mortality, prolonged length of stay and 90-day readmission, with insulin-use conferring additional risk. HbA1c is underutilised as a measure of risk stratification in the perioperative optimisation window for patients with diabetes requiring colorectal surgery. Awareness of these increased risks for patients with diabetes should be considered during perioperative optimisation of the patient, as well as in consent discussions and patient selection processes.

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List of Abbreviations

aDCSI	Diabetes Complications Severity Index
AIC	Akaike Information Criterion
AFT	Accelerated Failure Time
ASGBI	Association of Surgeons of Great Britain and Ireland
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CORECT	COloRECTal cancer data Repository
CPOC	Centre for Perioperative Care
CPRD	Clinical Practice Research Datalink
DCCT	Diabetes Control and Complications Trial (DCCT)
DD	Diverticular Disease
DM	Diabetes Mellitus
ERAS	Enhanced Recovery After Surgery
GI	Gastrointestinal
HbA1c	Haemoglobin A1c
HES APC	Hospital Episode Statistics Admitted Patient Care
HPB	Hepatopancreaticobiliary
HR	Hazards Ratio
IBD	Inflammatory Bowel Disease
IFCC	International Federation of Clinical Chemistry
ICD-10	International Classification of Diseases and Related Health Problems 10th Revision
IQR	Interquartile Range
IMD	Index of Multiple Deprivation 2015
ISAC	Independent Scientific Advisory Committee
JDBS	Joint British Diabetes Societies for Inpatient Care
LOS	Hospital Length of Stay
MIS	Minimally-Invasive Surgery
NCEPOD	National Confidential Enquiry into Patient Care and Outcomes
NDA	National Diabetes Audit
NGSP	National Glycohemoglobin Standardization Program
NHS	National Health Service

NICE	National Institute for Care and Health Excellence
NIS	National Inpatient Sample
ONS	Office for National Statistics databases
OPCS-4	Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures Version 4
OR	Odds Ratio
Pyrs	Person-years
RDG	Research Data Governance
SD	Standard Deviation
SE	Standard Error
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T1DM	Type 1 Diabetes
T2DM	Type 2 Diabetes
TR	Time Ratio
UK	United Kingdom
UTS	Up-to-standard time

1 Chapter 1. Background

1.1 Diabetes Mellitus and Perioperative Outcomes

Diabetes mellitus (DM) affects over 9% of the global population, with an increasing prevalence recorded for the last 15 years.[1–3] This estimate is predicted to increase to 10.9% by 2045, reflecting a potential 700 million people living with diabetes worldwide.[1] In the United Kingdom, there are over 4.7 million people living with diabetes[4], of whom over 750,000 require the use of insulin[5]. The use of insulin is neccessitated in all patients with type 1 diabetes, who are unable to produce their own insulin for the metabolism of glucose, as well as patients with type 2 diabetes in whom glycaemic control is not sufficiently achieved using other antidiabetic medications. The proportion of patients with diabetes who are prescribed insulin for glycaemic control has increased significantly over the last 20 years, largely due to the rising number of patients with type 2 diabetes requiring insulin.[6]

Diabetes Mellitus results from the body´s inability to utilise glucose due to a lack of or inability to respond appropriately to insulin. This leads to increased blood glucose levels, which in turns leads to a range of longer-term complications, including most commonly; neuropathy (damage to the nervous system), nephropathy (damage to the kidneys), retinopathy (damage to the retina of the eyes), and damage to blood vessels leading to events such as stroke, myocardial infarction or ischaemia of the limbs.[7] The lifelong impact of diabetes, including the described subsequent microvascular and macrovascular complications, is significant - translating to an increased comorbidity burden and a reduced life expectancy, ranging from an average 7.6 lost life years in patients with type 1 diabetes to an average of 1.7 lost life years in patients with type 2 diabetes.[8]

People with diabetes are more likely to require surgery than those without diabetes, with around half of all people with diabetes expected to undergo surgery over the course of their lifetime.[9,10] Patients with diabetes make up 10-14% of all patients undergoing surgery[11], and 12- 14% of colorectal surgical patients.[12,13] Additionally,

there is a growing awareness of patients with undiagnosed diabetes undergoing surgery, with an estimated prevalence of 7.4%.[14]

There are several mechanisms through which patients with diabetes may experience delayed postoperative recovery and poorer outcomes, including an increased comorbidity burden resulting from diabetic complications, errors in insulin prescribing and perioperative diabetic medication management, episodes of hypo- and hyperglycaemia, dysregulated inflammatory response to surgery, and impaired healing.[15–18] Subsequently, patients with diabetes have been shown to experience poorer outcomes, including prolonged hospital stay, increased postoperative complications and mortality, as well as increased readmission rates across medical and several surgical hospital settings.[19–22]

Zhang et al.[20] conducted a recent meta-analysis of 125 studies, summarising the postoperative outcomes for patients with diabetes undergoing non-cardiac surgery. The authors found diabetes to be an independent risk factor for postoperative mortality (OR 1.61, 95% CI 1.18 to 2.19), hospital readmission (OR 1.40, 95% CI 1.27 to 1.55) and reoperation (OR 1.57, 95% CI 1.12 to 2.19). In a subgroup analysis of the ten general surgical cohorts, postoperative mortality was increased by 40% (OR 1.40, 95% CI 0.98 to 2.01), although this result was not statistically significant. Only three of the total 125 included studies specifically described a colorectal surgical population, and none of these three studies were included in the pooled analysis of postoperative mortality.

1.2 Relevant Guidelines

Diabetes is a significant modulator of postoperative outcomes and is considered an important risk factor in the patient selection process. Several guidelines have been published by anaesthetic, surgical and diabetic societies on the perioperative management of patients with diabetes undergoing surgery. These include, but are not limited to, guidelines issued by the Centre for Perioperative Care (CPOC), the Joint British Diabetes Societies for Inpatient Care (JBDS) and the Association of Surgeons of Great Britain and Ireland (ASGBI) [18,23,24]. These guidelines describe

recommendations on the careful preoperative planning and optimisation of glycaemic control (with referral to specialist diabetic teams if required), safe use of insulin and medication management throughout the hospital episode, involvement of critical care and diabetic specialist teams as needed and facilitation of prompt return to normal diet and usual diabetic treatment regimen postoperatively.

The mainstay of treatment, and the key modifiable factor advocated by these guidelines, as well as the current Enhanced Recovery After Surgery (ERAS) protocol for colorectal surgery[25], is vigilant short-term and long-term glycaemic control. Poor glycaemic control is associated with increased postoperative infections, major complications, mortality and length of stay in general surgical patients.[10,26,27] Conversely, moderate glycaemic control is associated with reduced postoperative mortality and complications in patients with diabetes compared to liberal glycaemic control.[28] Nevertheless, adherence to guidelines on the perioperative risk modification and optimisation of patients with diabetes undergoing surgery remains poor.[4,17]

1.3 Perioperative Use of HbA1c

Haemoglobin A1c (HbA1c) is a measure of glycaemic control over the preceding 3 months and is recommended for use in both the diagnosis and monitoring of diabetes mellitus. It is a reliable method of quantifying diabetic control, whilst offering a target for treatment and threshold for further intervention. In patients with diabetes, each point reduction in HbA1c levels may reduce the patient's risk of developing microvascular complications by up to 40%.[7] Meanwhile in surgical patients, elevated HbA1c has been shown to be independently associated with major postoperative complications, such as anastomotic leak and infections, in patients undergoing major abdominal and colorectal surgery.[26,29]

Annual HbA1c measurement is a central component of the nine National Institute for Care and Health Excellence (NICE) care processes for all patients over the age of 12 with diabetes, with compliance monitored through the National Diabetes Audit (NDA).[30] The recent "Highs and Lows" National Confidential Enquiry into Patient

Care and Outcomes (NCEPOD) report[17] on patients with diabetes over 16 undergoing surgery recommends that an HbA1c measured within the last 3 months should be provided with every surgical referral for patients with diabetes. This was reportedly achieved in 42% of all surgical referrals for the 509 patient cases examined.

The treatment target for patients with type 1 and type 2 diabetes is set at equal to or less than 58 mmol/mol[30], whilst the diagnostic cut-off for patients without diabetes is 48 mmol/mol[31]. There is no established HbA1c threshold at present that would prevent a patient from undergoing elective surgery, due to a lack of evidence on this topic.[18] The use of HbA1c has also been incorporated into the aforementioned guidelines for patients with diabetes undergoing surgery. Recommendations include; provision of most recent HbA1c value in referrals from primary to secondary care services, optimisation of HbA1c (<69 mmol/mol) before referral if feasible, and involvement of the diabetes specialist team if the HbA1c is greater than 69 mmol/mol for preoperative optimisation.[18,23,24,32]

Although the National Diabetes Audit publishes regular reports including the proportion of patients with diabetes receiving an HbA1c measurement within 12 months and the proportion of patients with diabetes reaching treatment targets, these do not provide a breakdown of results by division or specialty. There are also no national reports on the rate of HbA1c measurement in patients with diabetes undergoing surgery beyond the NCEPOD report published in 2018, and none describing this important outcome and targetable risk factor in a national colorectal surgical cohort.

1.4 Current Evidence in Colorectal Surgery

The literature describing the impact of diabetes in patients undergoing colorectal resections is largely limited to a recent meta-analysis.[12] This study showed significantly increased risk of anastomotic leakage, surgical site infection, urinary and cardiac complications, ileus and readmission for patients with diabetes, compared to patients without diabetes. However, the authors found no statistically significant

difference in 30-day mortality (OR 2.65, 95% CI 0.80 to 8.70, p = 0.109) after colorectal surgery for patients with diabetes, compared to patients without diabetes. Due to limited outcome reporting, their results for 30-day mortality were based on a pooled analysis of three studies, encompassing only 3,526 patients with diabetes, warranting further investigation using a large-scale cohort.

There are two large studies focussed specifically on the effect of diabetes on postoperative outcomes in patients undergoing surgery for colorectal cancer. Anande et al.[33] based their study on a cohort extracted from the National Inpatient Sample (NIS) between 1998 and 2005, which represents a 20% stratified sample of non-governmental acute-care hospitals in the United States (US). Their study, including over 33,000 patients with diabetes, found a reduced in-hospital mortality risk for patients with diabetes compared to patients without diabetes (adjusted OR 0.77, 95% CI 0.71 to 0.84). The main limitation of this paper lies in the time-frame (1998 to 2005), which does not include the introduction of diabetes-specific guidelines for patients undergoing surgery, nor reflect current surgical and perioperative care practices. Their cohort was also identified as having a prevalence of complicated diabetes of 1%, which does not align with the contemporary burden of complicated diabetic disease.[3] In addition to this, the defined study setting (non-governmental acute-care hospitals), location (US) and 20% stratified sampling strategy may limit the generalisability of these results, which are unlikely to be representative of our contemporary population of interest.
A more recent study, limited to patients with colorectal malignancy and conducted by Birch et al.[13] (study period 2005 to 2016) describes an increased 90-day mortality risk for patients with diabetes and vascular complications receiving surgery for colorectal cancer in England, compared to patients without diabetes (6.6% vs 3.2%). This study used the COloRECTal cancer data Repository (CORECT) to identify patients for inclusion in their study cohort, and adapted Diabetes Complications Severity Index (aDCSI) to stratify patients with vascular complications. They did not find any statistically significant difference in 90-day mortality with patients with uncomplicated diabetes compared to those without diabetes, although exact rates are not reported. These findings represent crude proportion calculations and do not include any adjusted analysis for this outcome.

In summary, there is no reliable, contemporary estimate in current literature that accurately reflects the impact of diabetes on 90-day mortality in patients undergoing colorectal resections. Furthermore, there is no specific information available on whether insulin-use infers any additional risk of poorer postoperative outcomes in patients with diabetes who present for colorectal resection, in comparison to patients with diabetes without insulin-use and patients without diabetes.

2 Chapter 2. Aims and Objectives

The overall aim of the study was to investigate and quantify the effect of diabetes and insulin-use on outcomes following colorectal resections using a national cohort, as well as delineate the use of perioperative Hba1c in current practice as captured by a local audit.

The specific objectives are:

1. To provide population-based estimates of mortality and readmission rates following colorectal surgery in patients with diabetes, as well as delineate the role of insulin-use in determining postoperative mortality and readmission risk.
2. To assess the impact of diabetes on hospital length of stay in patients undergoing colorectal resections.
3. To describe the contemporary, perioperative use of HbA1c in colorectal surgery in a local audit against national perioperative guidelines.

3 Chapter 3. Methods

3.1 Ethical Approval

This study applied for ethical approval through the CPRD Research Data Governance (RDG) Process, which was formally approved on 10/05/2021 by the Independent Scientific Advisory Committee (ISAC) approval board (protocol number 21_00040). It adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[34] guidelines.

3.2 Study Outcomes

The primary outcome was 90-day mortality, which was defined as all-cause mortality occurring within 90 days of the index operation. There has been some debate regarding the use of 30-day versus 90-day mortality after surgery as an outcome measure. Compared to 30-day mortality, 90-day mortality is up to twice as more common an outcome.[35–39] The main argument for the use of 90-day mortality is that this timeframe better reflects the sequelae and true impact of surgery in the postoperative period, as it allows later events that may still be related to the surgery to be captured. Although 90-day mortality is limited to short-term postoperative events, it has been shown to correlate with longer-term (180-day and 365-day) postoperative mortality, whilst still reflecting outcomes related to the surgical intervention.[35] Based on this rationale, 90-day mortality was chosen as the primary outcome for this study.

Secondary outcomes included 90-day readmission; defined as any emergency readmission within 90 days of discharge after the index operation, hospital length of stay; defined as days in hospital from admission date to discharge date, and HbA1c measurement rate; defined as the proportion of patients with diabetes with a recorded HbA1c measured up to one year before surgery.

3.3 Data Acquisition and Management

3.3.1 Data Sources

Linked patient data for all adult patients undergoing a first colorectal resection in England between 01.01.2000 and 01.01.2020 were extracted from the Clinical Practice Research Datalink (CPRD) Aurum, Hospital Episode Statistics Admitted Patient Care (HES APC) and Office for National Statistics (ONS) databases. This represents data recorded by the government research service for primary care data (CPRD) and a national secondary care (HES) database. Patients are linked across these databases by a trusted third party (NHS Digital), using established processes involving multiple patient-identification criteria (NHS number, date of birth, postcode and sex).[40]

The HES APC database routinely collects data on every hospital admission into secondary care within the NHS, which represents approximately 98-99% of all hospital activity in England.[41] The HES database uses the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) to assign a primary diagnosis and record patient comorbidities for each hospital spell. Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures Version 4 (OPCS-4) codes are employed to record information regarding any procedures undertaken during hospitalisation.[41]

The CPRD encompasses over 60 million patients, with 18 million patients actively registered across over 2000 primary care practices and currently contributing data.[42] It contains information on patient demographic characteristics, clinical encounters and investigations, administered treatments, referrals and primary care registration details. The majority of this information is encoded using CPRD Read Codes. The CPRD supplies two metrics of data quality to inform patient selection for use in research, including the acceptability of patients and up-to-standard time (UTS) for general practices. The former deems data reliable and suitable for use in research based on validity of age and sex records, as well as recorded patient events and registration within the database. The latter measures the continuity of data recording and adherence of primary care practices to the minimum quality criteria determined by the CPRD.[43]

These datasets undergo extensive internal validation, as well as external validation through linkage of datasets, and have been shown to be representative of the general United Kingdom (UK) population.[40,41,44,45]

3.3.2 Data Extraction

OPCS-4 codes were used to identify patients who had undergone surgery for colorectal disease within the HES database (Appendix Table 1). Patients who had undergone colorectal surgery for a malignant indication were differentiated from those with a benign indication using ICD-10 codes, including C18, C19, and C20 (excluding C18.1) for colorectal malignancy. Patients were additionally classified as having an operation for a malignancy if a diagnosis of colorectal cancer was recorded in the CPRD database within 6 months of the index surgery. Benign indications for colorectal resection included inflammatory bowel disease (IBD) and diverticular disease (DD), as identified by ICD-10 discharge codes. Additional operative details regarding surgical approach and operation urgency were obtained from the HES database. Patient details, including sex and ethnicity, were also extracted from HES data. All included codes are listed in Appendix Table 1.

Data on patient diabetes status, diabetes type, and records of insulin-use, were extracted from the CPRD database using CPRD Read codes (Appendix Tables 2-4). Gestational diabetes, type 3c diabetes subtypes (diabetes secondary to pancreatic disease, cystic fibrosis, or monogenic diabetes) and diabetes caused by rare syndromes, and any ambiguous diabetes terms were excluded (Appendix Table 5). HbA1c measurement dates and values recorded within one year before the date of surgery were extracted from the CPRD database (Appendix Table 3). Data regarding patient comorbidity burden (Charlson Comorbidity Index score[46]) and deprivation (Index of Multiple Deprivation 2015 score[47]) were obtained from both CPRD and HES data.

Data pertaining to the defined study outcomes were obtained from ONS death certificate records (non-hospital deaths), the HES database (in-hospital deaths,

hospital length of stay, emergency 90-day readmissions), and further validated using the CPRD database (mortality status).

3.3.3 Data Cleaning and Exclusion Criteria

After acquisition, the database was independently screened for inconsistencies in patient information, as well as dyssynchronous data recording across linked databases. Any data that did not meet the CPRD quality assurance ("acceptability") criteria were excluded, to allow for meaningful interpretation of the data, and ensure the synchrony of data collection periods for each patient across primary and secondary databases.

This analysis was restricted to patients undergoing colorectal surgery from the beginning of the year 2010, and therefore all patients with hospital episodes beginning prior to 01.01.2010 were excluded. Similarly, patients whose hospital episode did not overlap with a primary care registration period were excluded, to ensure validation across datasets as well as allow for analysis of linked patient data. Patients for whom the outcome of death had occurred before their index colorectal surgery were excluded. Further exclusion criteria were defined as; patient age less than 18 years or over 113 years, and misclassified admission pathways (coded as "other"). Records of diabetes status and type were correlated with insulin prescription records and validated accordingly. Patients with inconsistent or implausible data, namely a record of insulin-use in patients without diabetes, patients with type 1 diabetes without a record of insulin-use, or an HbA1c value of < 4% or < 20mmol/mol, were excluded.

Following the Diabetes Control and Complications Trial (DCCT) and related National Glycohemoglobin Standardization Program (NGSP), which used percentage (%) as the unit for HbA1c values, the International Federation of Clinical Chemistry (IFCC) Working Group was established in an effort to provide an internationally standardised, replicable and accurate measure of HbA1c.[48] The IFCC reference method results in HbA1c values with the unit of mmol/mol, known as IFCC units, which have been internationally adapted as the standardised unit of choice.

All HbA1c values in this study that were recorded using the older NGSP unit format (%) were converted to the new, standardised IFCC unit (mmol/mol) using the master equation provided by the IFCC (IFCC = (10.93*NGSP) - 23.50).[49]

3.3.4 Substudy: Local Audit of HbA1c Measurement Rates

The primary analysis in this study includes an evaluation of contemporary preoperative HbA1c measurement rates in a national colorectal surgical cohort. The HbA1c records used in this primary analysis were obtained from the CPRD database, and do not necessarily represent HbA1c data recorded by secondary health care systems at the time of surgical delivery.

Therefore, a local audit of the HbA1c measurement rates within one year before surgery was conducted at our single tertiary hospital (Nottingham University Hospitals NHS Trust) to provide information on compliance with ASGBI, CPOC and JDBS guideline recommendations on HbA1c measurement rates in patients undergoing surgery[18,23,24], as recorded by a secondary care-based data collection system using electronic health records. The audit was registered at the Nottingham University Hospitals NHS Trust (registration number 22-426C) on 31/08/2022. Patients undergoing general surgical procedures between 01/07/2022 and 11/08/2022 were identified from a local database, and their most recent HbA1c measurement dates and values obtained from linked electronic health records. Further details pertaining to operative urgency and surgical specialty were also extracted. The proportion of patients with a documented HbA1c within one year before surgery was compared to results from the National Diabetes Audit and the primary analysis of the described national cohort of patients undergoing colorectal surgery in England between 2010 and 2020.

3.4 Covariates and Exposures of Interest

Patient sex (binary variable), age (factor variable), deprivation (factor variable), comorbidity burden (factor variable), operation urgency (binary variable), operative indication (binary variable), and surgical access (binary variable) were all evaluated

as covariates for the exposure of interest; diabetes status (binary variable) or insulin-use (factor variable).

Patient sex was categorised into either male or female. Age was categorised into groups of ages 18 to 50, 51 to 60, 61 to 70, 71 to 80 and more than 80 years old. Deprivation was defined according to the Index of Multiple Deprivation (IMD) 2015[47], which is a measure of relative deprivation across the UK. This measure can be divided into five quintiles based on relative disadvantage, ranging from most deprived (1st quintile) to least deprived (5th quintile). The Charlson Comorbidity Index (CCI)[46] provides a measure of comorbidity for each patient as quantified before the index hospital admission. Patients were grouped according to a CCI score of zero (CCI 0), one (CCI 1) or two or more (CCI 2), with a higher score indicating increased comorbidity burden. Diabetes was excluded as a contributor to the CCI score, to prevent co-linearity and allow for an independent analysis of this variable.

The surgical factors considered in the regression analysis included operation urgency (emergency vs elective), which describes whether the operation was performed as an emergency or as a planned procedure. The operative indication defines the underlying reason for which the patient received colorectal surgery and was classified as benign (non-cancerous) or malignant (cancerous). Lastly, surgical access refers to the surgical approach used to perform a colorectal resection and was categorised into either open (laparotomy) or minimally-invasive (including laparoscopic and robotic procedures) surgery (MIS).

Two distinct exposure variables of interest were investigated in this study, including diabetes status (patients with diabetes vs patients without diabetes) and insulin-use (patients with diabetes with Insulin-use, patients with diabetes without Insulin-use or patients without diabetes). The group of patients without diabetes was used as the baseline reference group throughout all regression models.

Missing values were presented as separate categories where applicable, but were not considered as an individual covariate in our regression analysis. The statistical approach used for regression modelling was based on an available case analysis.

3.5 Statistical Analysis

3.5.1 Descriptive statistics

Continuous variables were summarised using mean and standard deviation (SD) or median and interquartile range (IQR), according to parametric or non-parametric distribution. Mean differences were calculated to compare continuous variables between groups using unpaired t-tests for parametric data, and Wilcoxon Rank Sum tests for used to compare groups with non-parametric continuous data. The distribution of continuous data was visually assessed in the form of histograms. Categorical variables were presented as frequency and percentage, and compared using Chi-squared tests, with results presented as odds ratios (OR).
95% confidence intervals (95% CI) were presented where applicable. A p value of < 0.05 was considered statistically significant. All data was analysed in STATA® v17 (StataCorp, College Station, TX, USA).

3.5.2 Unadjusted Time-to-Event Analysis

Person-time at risk of mortality was calculated from start of follow-up (defined as date of surgery) to the censoring date (death or loss-to-follow-up). Crude 90-day mortality rates were calculated per 1000 person-years for all included patients and were presented across all included exposure variables.
Person-time at risk of hospital readmission was calculated from start of follow-up (defined as date of discharge) to the censoring date (readmission, death or loss-to-follow-up). Unadjusted 90-day readmission rates per 1000 person-years were similarly determined for patients with and without diabetes, as well as across all other previously listed covariates.

Kaplan Meier survival estimates were calculated and presented graphically as survival functions, with stratification by diabetes status, insulin-use and diabetes type. Kaplan Meier failure estimates were calculated and plotted for 90-day readmission, with stratification by diabetes status and insulin-use. Risk tables, denoting the number of patients at risk at 30, 60 and 90 days, were included in the

resulting figures. Log rank tests were used to compare the survival and failure functions (limited to a 90-day postoperative period) between groups. A smoothed hazard function was plotted to assess the hazard distribution for length of stay.

3.5.3 Semi-parametric Time-to-Event Modelling

Adjusted hazard rates were modelled using Cox proportional hazard regression, accounting for patient age, sex, deprivation, comorbidity burden, operation urgency, operative indication and surgical access and including diabetes status as the exposure variable of interest. Each exposure variable was initially investigated using univariate analysis, to determine inclusion within the final model. Likelihood ratio tests were used to determine the overall significance of individual factor variables for inclusion in the final model, by comparing a model with the factor variable to the null model. A subsequent multivariate Cox regression model was formed including any variables that had reached statistical significance ($p < 0.05$) on univariate analysis. Any covariates which no longer reached statistical significance in the multivariate model were excluded one-by-one. Results from the final model were presented as adjusted hazard ratios.

An additional Cox regression model was built to assess the impact of insulin-use on 90-day mortality. This encompassed a comparison between patients with diabetes with insulin-use, patients with diabetes without insulin-use, and patients without diabetes as a reference group. A similar process of backwards stepwise regression, starting with univariate analysis and followed by multivariate, adjusted modelling was performed to obtain adjusted hazard ratios. The same covariates (age, sex, deprivation, comorbidity burden, operation urgency, operation indication and surgical access) were considered in this model.

Lastly, 90-day readmission hazard rates were also modelled using Cox proportional hazards regression. The same stepwise selection approach was used to identify covariates of statistical significance to be included in the final multivariate models. Age, sex, deprivation, comorbidity burden, operation urgency, operative indication

and surgical access were each considered as covariates in this process, with either diabetes status or insulin-use as the exposure of interest.

For each of these four multivariate Cox regression models, interactions between the exposure of interest (either diabetes status or insulin-use, respectively) were assessed using interaction terms. The significance of these interactions was determined in a stepwise fashion, using likelihood ratio tests to compare models with and without each interaction term. Interactions reaching statistical significance were included in the final model and reflected in the reported coefficients.
The proportional hazards assumption was assessed visually for the exposure of interest using log-log plots for survival. If the proportional hazards assumption was deemed to have been met for a given exposure of interest and a given outcome based on visual assessment of the relevant log-log functions, further assessment was undertaken using Schoenfeld residuals, which were plotted over time. The proportional hazard assumption for the overall model and individual covariates (including each level of categorical variables) was assessed by testing the zero slope of the Schoenfeld residuals graph. A p value of <0.05 was considered statistically significant and would indicate breach of the proportional hazards assumption for either the model overall (global test) or individual covariates.

3.5.4 Parametric Time-To-Event Modelling

Based on preliminary analysis of this outcome, an explorative analysis of length of stay was performed using several accelerated-failure time (AFT) survival models, to account for the parametric distribution of the data. The distributions considered for these AFT models included exponential, Weibull, lognormal, loglogistic and generalised gamma. Age, sex, deprivation, comorbidity burden, operation urgency, operation indication and surgical access were considered in the model building process, with diabetes status defined as the exposure of interest. The suitability and fit of each model were subsequently compared using Log likelihood values and the Akaike information criterion (AIC). The model with the lowest AIC was chosen as the final model for the outcome of length of stay. Results were presented in the form of adjusted time ratios (TR).

4 Chapter 4. Results

4.1 Population

A total of 106,139 (50% male) patients met the inclusion criteria for final analysis (Figure 1), with a median age of 66 years (Interquartile Range (IQR) 52 to 76 years). In this cohort, 67.8% of patients were admitted to hospital electively, with the remaining 32.2% admitted through emergency pathways. Benign indications for surgery included diverticular disease in 14,555 (30.6%) patients and inflammatory bowel disease in 11,057 (23.2%) patients. The full list of patient demographics is summarised in Table 1.

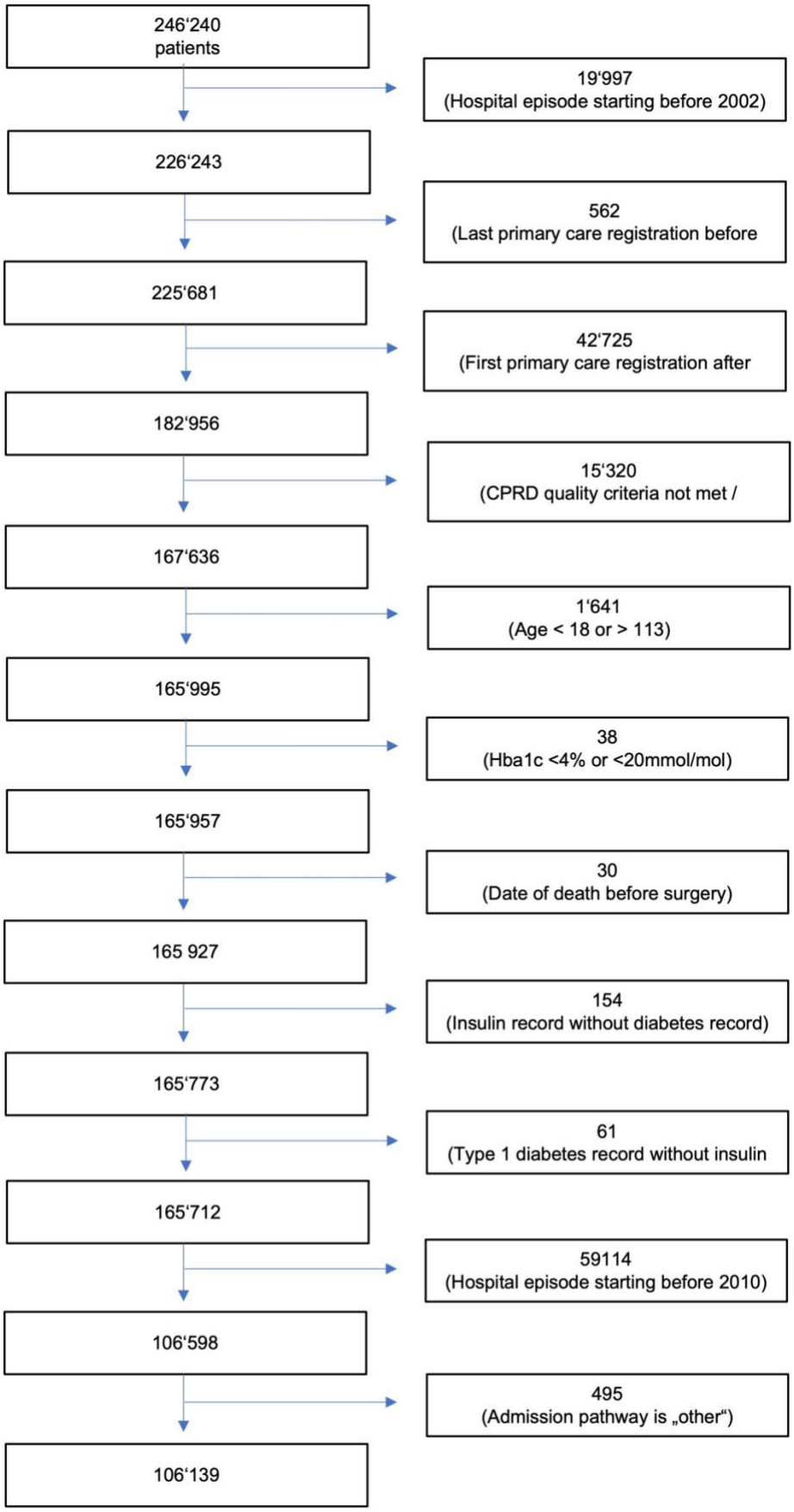


Figure 1: Flow chart describing the patient selection process for inclusion in the primary analysis.

Table 1: Population Demographics for Patients by Diabetes Status

	Without DM	**With DM**	**p value**	**Total**
Total n (%)	95208 (89.7)	10931 (10.3)	-	106931
Sex				
Female n (%)	48865 (51.3)	4399 (40.2)	p < 0.001	53264 (50.2)
Male n (%)	46343 (48.7)	6532 (59.8)		52875 (49.8)
Age				
Median (IQR)	64.7 (50.1 to 74.9)	72.8 (65.0 to 79.2)	p < 0.001	65.8 (51.8 to 75.6)
Deprivation Quintile				
1 n (%)	21444 (22.5)	2156 (19.7)	p < 0.001	23600 (22.2)
2 n (%)	20335 (21.4)	2146 (19.6)		22481 (21.2)
3 n (%)	19264 (20.2)	2214 (20.3)		21478 (20.2)
4 n (%)	18034 (18.9)	2244 (20.5)		20278 (19.1)
5 n (%)	16004 (16.8)	2166 (19.8)		18170 (17.1)
Missing n (%)	127 (0.13)	5 (0.1)		132 (0.12)
CCI				
0 n (%)	26179 (27.5)	1071 (9.8)	p < 0.001	27250 (25.7)
1 n (%)	7947 (8.4)	754 (6.9)		8701 (8.2)
2 n (%)	61082 (64.2)	9106 (83.3)		70188 (66.1)
Ethnicity				
White n (%)	87262 (91.7)	9640 (88.2)	p < 0.001	96902 (91.3)
Black n (%)	1900 (2.0)	379 (3.5)		2279 (2.2)
Asian n (%)	2505 (2.6)	560 (5.1)		3065 (2.9)
Mixed n (%)	469 (0.5)	60 (0.6)		529 (0.5)
Unknown n (%)	3072 (3.2)	292 (2.7)		3364 (3.2)

Diabetes Type				
T1DM	-	653 (6.0)	-	-
T2DM	-	10278 (94.0)	-	-
T2DM – No Insulin-use	-	8786 (85.5)	-	-
T2DM – Insulin-use	-	1492 (14.5)	-	-
Urgency				
Elective	64589 (67.8)	7888 (72.2)	p < 0.001	72477 (68.3)
Emergency	30619 (32.2)	3043 (27.8)		33662 (31.7)
Operative Indication				
Benign n (%)	44191 (46.4)	3432 (31.4)	p < 0.001	47623 (44.9)
Malignant n (%)	51017 (53.6)	7499 (68.6)		58516 (55.1)
Access				
Open n (%)	57834 (60.7)	6943 (63.5)	p < 0.001	64777 (61.0)
MIS n (%)	37374 (39.3)	3988 (36.5)		41362 (39.0)

DM = Diabetes Mellitus, IQR = Interquartile Range, CCI = Charlson Comorbidity Index, T1DM = Type 1 Diabetes Mellitus, T2DM = Type 2 Diabetes Mellitus, MIS = Minimally-invasive surgery.

4.2 Use of HbA1c in Contemporary Clinical Practice

Amongst patients with diabetes, 69.9% (n = 7,635) of patients had had an HbA1c measured up to 12 months before surgery. This represents a 59.3% of patients with type 1 diabetes, compared to 70.5% of patients with type 2 diabetes. An additional 12.0% (n = 11,388) of patients without a record of diabetes had a documented HbA1c. The proportion of patients with diabetes and a record of HbA1c measurement within one year of surgery remained relatively stable between 2010 and 2020 (Figure 2).

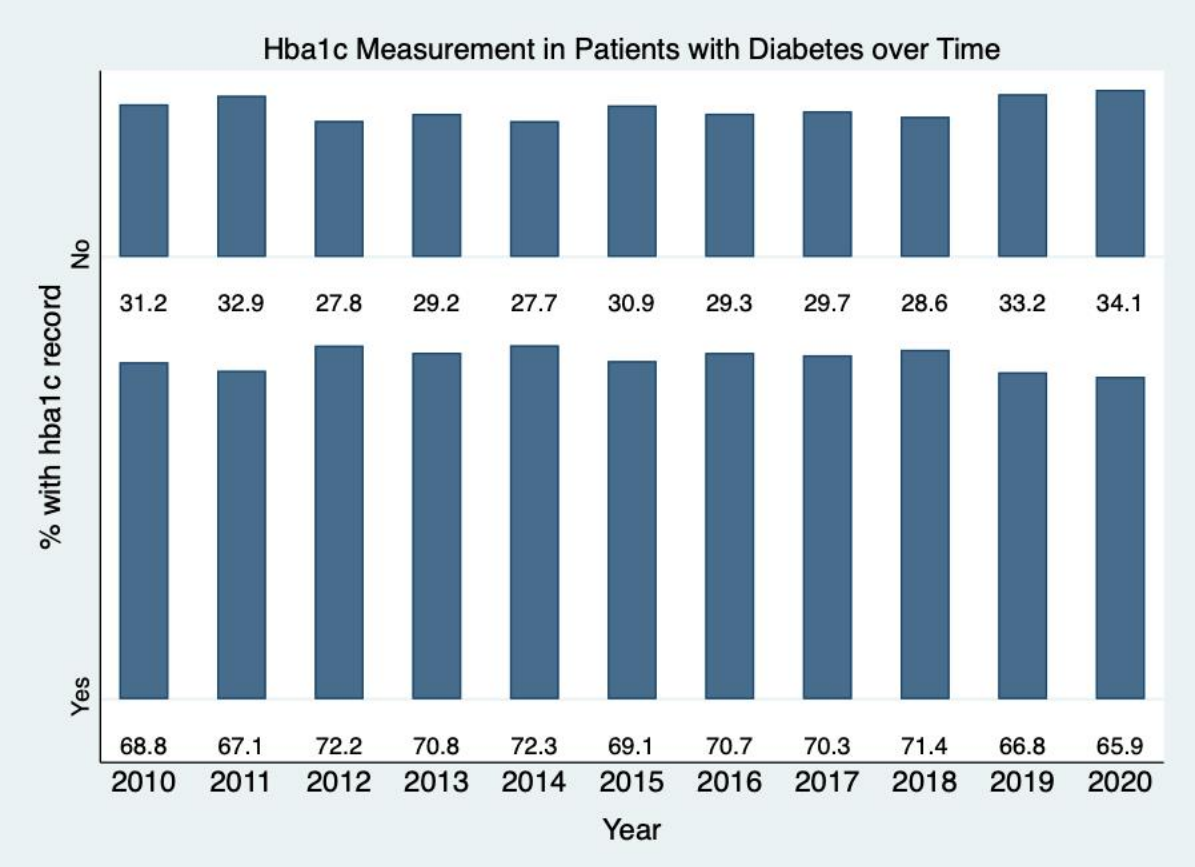


Figure 2: Proportion of patients with diabetes who had a measurement of HbA1c within one year before undergoing colorectal surgery between 2010 and 2020

Patients with type 1 diabetes were significantly less likely to have an HbA1c measured within one year before surgery compared to patients with type 2 diabetes. (OR 0.61, 95% CI 0.52 to 0.72, $p < 0.001$). Patients with diabetes undergoing elective surgery were more likely to have a HbA1c measured within the preceding 12 months than those undergoing emergency surgery (OR 1.19, 95% CI 1.09 to 1.31, $p < 0.001$). The characteristics of patients with diabetes, stratified by whether they had a record of timely preoperative HbA1c measurement or not, are displayed in Table 2.

Table 2: Population Demographics for Patients with Diabetes by HbA1c Record

	Without HbA1c	**With HbA1c**	**p value**	**Total**
Total n (%)	3296 (30.2)	7635 (69.9)	-	10931

Sex				
Female n (%)	1330 (40.3)	3069 (40.2)	0.879	4399
Male n (%)	1966 (59.7)	4566 (59.8)		6532
Age				
Median (IQR)	71.7 (63.5 to 78.5)	73.2 (65.6 to 79.5)	<0.001	72.8 (65.0 to 79.2)
Deprivation Quintile				
1 n (%)	591 (17.9)	1565 (20.5)	<0.001	2156
2 n (%)	632 (19.2)	1514 (19.8)		2146
3 n (%)	627 (19.0)	1587 (20.8)		2214
4 n (%)	737 (22.4)	1507 (19.7)		2244
5 n (%)	707 (21.5)	1459 (19.1)		2166
Missing n (%)	2 (0.06)	3 (0.04)		5
CCI				
0 n (%)	433 (13.1)	638 (8.4)	<0.001	1071
1 n (%)	206 (6.3)	548 (7.2)		754
2 n (%)	2657 (80.6)	6449 (84.5)		9106
Ethnicity				
White n (%)	2817 (85.5)	6823 (89.4)	<0.001	9640
Black n (%)	146 (4.4)	233 (3.1)		379
Asian n (%)	220 (6.7)	340 (4.5)		560
Mixed n (%)	25 (0.8)	35 (0.5		60
Unknown n (%)	88 (2.7)	204 (2.7)		292
Diabetes Type				
T1DM	266 (8.1)	387 (5.1)	<0.001	653
T2DM	3030 (91.9)	7248 (94.9)		10278

Urgency				
Elective	2295 (69.6)	5593 (73.2)	<0.001	7888
Emergency	1001 (30.4)	2042 (26.8)		3043
Operative Indication				
Benign n (%)	1130 (34.3)	2302 (30.2)	<0.001	3432
Malignant n (%)	2166 (65.7)	5333 (69.9)		7499
Access				
Open n (%)	2126 (64.5)	4817 (63.1)	<0.001	6943
MIS n (%)	1170 (35.5)	2818 (36.9)		3988

"Without HbA1c" refers to patients with diabetes who did not have an HbA1c measured within one year before their index surgery, "with HbA1c" refers to patients with diabetes who did have an HbA1c measured within one year before their index surgery. IQR = Interquartile Range, CCI = Charlson Comorbidity Index, T1DM = Type 1 Diabetes Mellitus, T2DM = Type 2 Diabetes Mellitus, MIS = Minimally-invasive surgery.

4.2.1 Timing and Value of HbA1c Measurements

The median time from most recent HbA1c measurement to surgery in patients with was 255 days (IQR 179 to 314). 1.6% of patients with diabetes had had an HbA1c measured within the 3 months preceding surgery, which increased to 3.6% within 6 months before surgery. The average HbA1c in patients with diabetes was 56.5 mmol/mol (SD 15.8) (Appendix Figure 1). In patients with type 1 diabetes, the average HbA1c was significantly higher (mean 66.9, SD 16.3) compared to those with type 2 diabetes (mean 56.0, SD 15.6) (MD 10.9, 95% CI 9.3 to 12.5, $p < 0.001$) (Figure 3). In patients with diabetes with a recorded HbA1c value within one year before surgery, 259 (66.9%) patients with type 1 diabetes and 2265 (31.3%) patients with type 2 diabetes did not reach the treatment target of less than 58 mmol/mol.

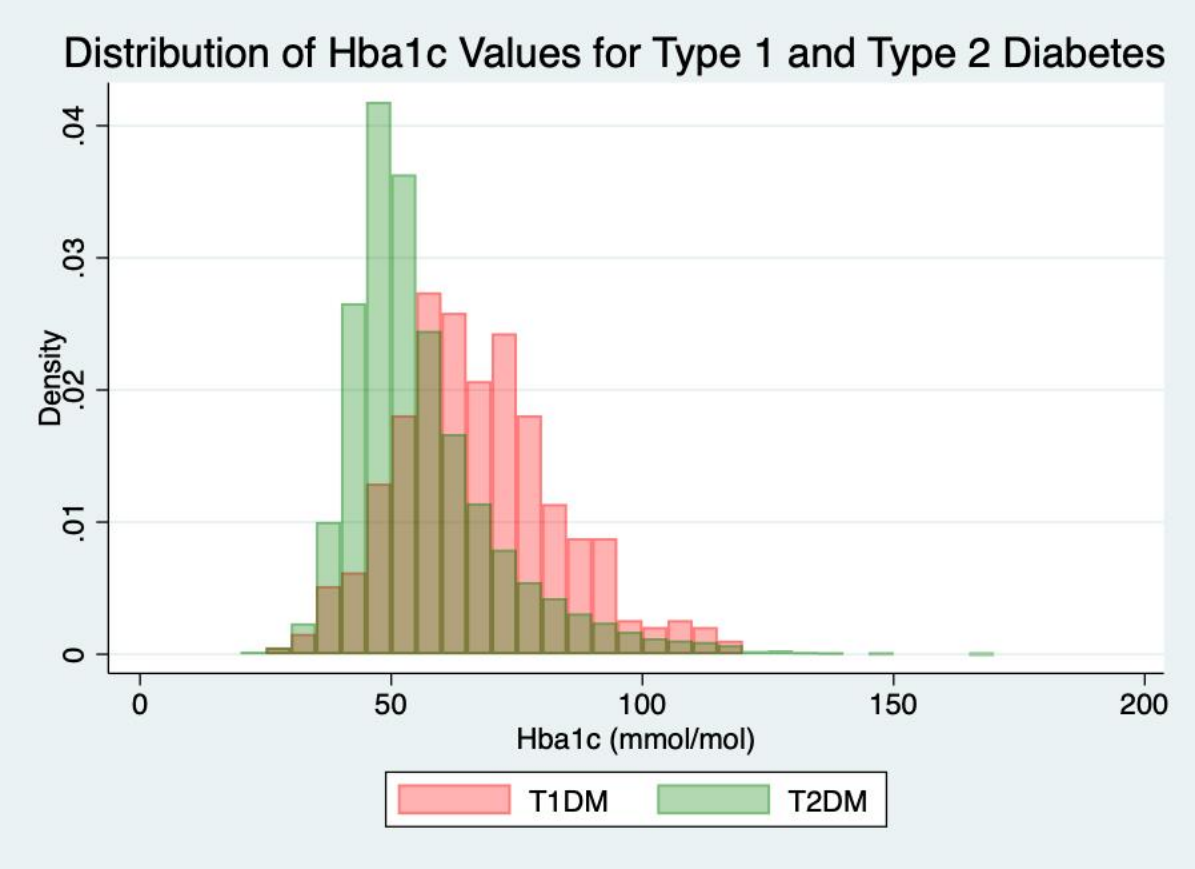


Figure 3: Distribution of preoperative HbA1c values in patients with type 1 versus type 2 diabetes

The average HbA1c in patients without diabetes was 39.1 (SD 5.5). There were 315 (2.8%) patients without a diagnosis of diabetes who had a recorded HbA1c value above the diagnostic limit of 48 mmol/mol. 39 (0.3%) patients without a record of diabetes had HbA1c value greater than 58mmol/mol.

4.2.2 Local Audit

97 patients with diabetes undergoing general surgical procedures over a 6-week period at the University Hospitals of Nottingham were identified for analysis. The median age of all patients was 65 years (IQR 56 to 74 year). The majority of patients underwent surgery for an emergency indication (73.2%) under the care of the trauma (34.0%) or colorectal teams (24.7%) (Table 3).

Table 3: Patient Characteristics in Local Audit at Nottingham University Hospitals

	Without HbA1c n (%)	With HbA1c n (%)	Total
All patients	31 (32%)	66 (68%)	97
Urgency			
Elective	5 (19%)	21 (81%)	26
Emergency	26 (37%)	45 (63%)	71
Discharging Specialty			
Colorectal	8 (33%)	16 (67%)	24
Endocrinology	1 (33%)	2 (67%)	3
General Surgery	1 (12.5%)	7 (87.5%)	8
HPB	3 (25%)	9 (75%)	12
Upper GI	6 (55%)	5 (45%)	11
Vascular	1 (17%)	5 (83%)	6
Trauma	11 (33%)	22 (67%)	33

"Without HbA1c" refers to patients with diabetes who did not have an HbA1c measured within one year before their index surgery, "with HbA1c" refers to patients with diabetes who did have an HbA1c measured within one year before their index surgery. HPB = Hepatopancreaticobiliary Surgery, Upper GI = Upper Gastrointestinal Surgery.

The HbA1c measurement rate within one year before surgery was 68% (n = 66) in all patients with diabetes, and 67% (n= 16) in colorectal patients only. This is consistent with HbA1c measurement rates resulting from the analysis of our main study, where HbA1c records were obtained from the primary health care database described in section 4.2 (CPRD), and similarly falls below national average rates of annual hb1ac measurement in patients with diabetes. A larger proportion of patients had had an HbA1c measured within 3 months (n = 43 (44.3%)) or 6 months (n = 60 (61.9%)) before surgery when using this audit data obtained from a local secondary care database, compared to HbA1c data obtained through CPRD alone (1.5% and 3.6%). The median time difference from most recent HbA1c measurement to surgery was 48 days (IQR 13 to 105). The average HbA1c was 66.36 mmol/mol (SD 23.22).

4.3 Diabetes

The prevalence of diabetes in our main study was 10% (n = 10,931), including 653 (6%) patients with Type 1 and 10,278 (94%) patients with Type 2 diabetes. 19.6% of all patients with diabetes had a record of insulin-use, encompassing both all patients with Type 1 diabetes and 14.5% of patients with Type 2 diabetes. (Table 1)

4.3.1 Crude 90-day Mortality

The overall unadjusted 90-day mortality risk was 5.7% for the entire cohort, and 8.7% for patients with diabetes. Patients with diabetes were more likely to experience 90-day mortality compared to patients without diabetes (unadjusted HR 1.72, 95% CI 1.60 to 1.84). There was no significant difference in 90-day mortality risk between type 1 and type 2 diabetes (OR 0.98, 95% CI 0.72 to 1.34, p = 0.916).

The overall unadjusted 90-day mortality rate was 226.4 per 1000 person-years (95% CI 220.6 to 232.4). Patients with diabetes had a higher 90-day mortality rate (367.84 per 1000 person-years, 95% CI 344.91 to 392.30) than those without diabetes (212.27 per 1000 person-years, 95% CI 206.34 to 218.36). The 90-day mortality rates per 1000 person-years are presented for age, sex, deprivation, comorbidity, diabetes status, operation urgency, operative indication and surgical access in Table 4.

Table 4: Cox Regression Model for 90-day Mortality with Diabetes as the Exposure of Interest

Covariate	Pyrs at risk	N Dead at 90 days	90-day Mortality Rate per 1000-pyrs	95% CI	Unadjus-ted HR	95% CI	p value	Adjusted HR	95% CI	p value
Sex										
Male	1.3E+04	2891	231.36	222.98 to 239.84	1	-		-	-	-
Female	1.3E+04	2834	224.52	216.40 to 232.94	0.98	0.93 to 1.03	0.491	-	-	-
Age										
0-50	6.2E+03	370	59.35	53.60 to 65.71	1	-	<0.001	1	-	
51-60	4.0E+03	539	133.94	123.09 to 145.73	2.25	1.97 to 2.58	<0.001	2.36	2.06 to 2.70	<0.001
61-70	5.9E+03	1182	200.70	189.57 to 212.47	3.36	2.99 to 3.78	<0.001	3.66	3.25 to 4.14	<0.001
71-80	6.0E+03	1825	304.08	290.45 to 318.36	5.08	4.54 to 5.69	<0.001	5.25	4.67 to 5.90	<0.001

>80	3.0E+03	1809	608.33	580.93 to 637.02	9.99	8.93 to 11.12	<0.001	8.82	7.84 to 9.93	<0.001
Deprivation										
1	5.6E+03	1186	211.36	199.66 to 223.73	1	-	<0.001	1		
2	5.3E+03	1100	206.21	194.38 to 218.77	0.97	0.89 to 1.05	0.446	0.99	0.91 to 1.07	0.764
3	5.1E+03	1170	230.25	217.43 to 243.83	1.09	1.00 to 1.18	0.038	1.08	1.00 to 1.17	0.064
4	4.8E+03	1149	240.03	226.55 to 254.32	1.14	1.05 to 1.23	0.002	1.18	1.09 to 1.28	<0.001
5	4.3E+03	1108	258.95	244.14 to 274.66	1.22	1.13 to 1.34	<0.001	1.23	1.14 to 1.34	<0.001
CCI										
0	6.6E+03	938	143.03	134.16 to 152.48	1	-	<0.001	1	-	
1	2.1E+03	382	183.84	166.30 to 203.23	1.28	1.13 to 1.44	<0.001	1.17	1.04 to 1.32	0.011
2	1.6E+04	4405	267.17	259.39 to 275.17	1.84	1.72 to 1.98	<0.001	1.79	1.66 to 1.93	<0.001
Diabetes										

No	2.3E+04	4798	212.27	206.34 to 218.36	1	-		1	-	
Yes	2.5E+03	927	367.84	344.91 to 392.30	1.72	1.60 to 1.84	<0.001	1.28	1.19 to 1.37	<0.001
Urgency										
Elective	1.8E+04	1519	86.43	82.19 to 90.89	1	-	<0.001	1	-	
Emergency	7.4E+03	4147	556.88	540.19 to 574.09	6.25	5.89 to 6.63	<0.001	4.83	4.52 to 5.17	<0.001
Indication										
Benign	1.1E+04	3235	292.95	283.03 to 303.22	1	-		1	-	
Malignant	1.4E+04	2438	174.13	167.36 to 181.18	0.60	0.57 to 0.63	<0.001	0.77	0.73 to 0.82	<0.001
Access										
Open	1.5E+04	5149	342.48	333.25 to 351.96	1	-		1	-	
Minimally Invasive	1.0E+04	576	57.09	52.61 to 61.95	0.17	0.16 to 0.19	<0.001	0.4	0.35 to 0.42	<0.001

HR = Hazard Ratio, CI = Confidence Interval, Pyrs = person-years, CCI = Charlson Comorbidity Index. Deprivation was included in the final model based on likelihood ratio test results ($p < 0.001$).

Analysis of Kaplan Meier estimates of survival revealed a significant difference in the survival functions of patients with diabetes compared to patients without diabetes ($p < 0.001$) (Figure 4). The type of diabetes (type 1 vs type 2 diabetes) did not appear to have a significant impact on the survival function ($p = 0.799$) (Figure 5).

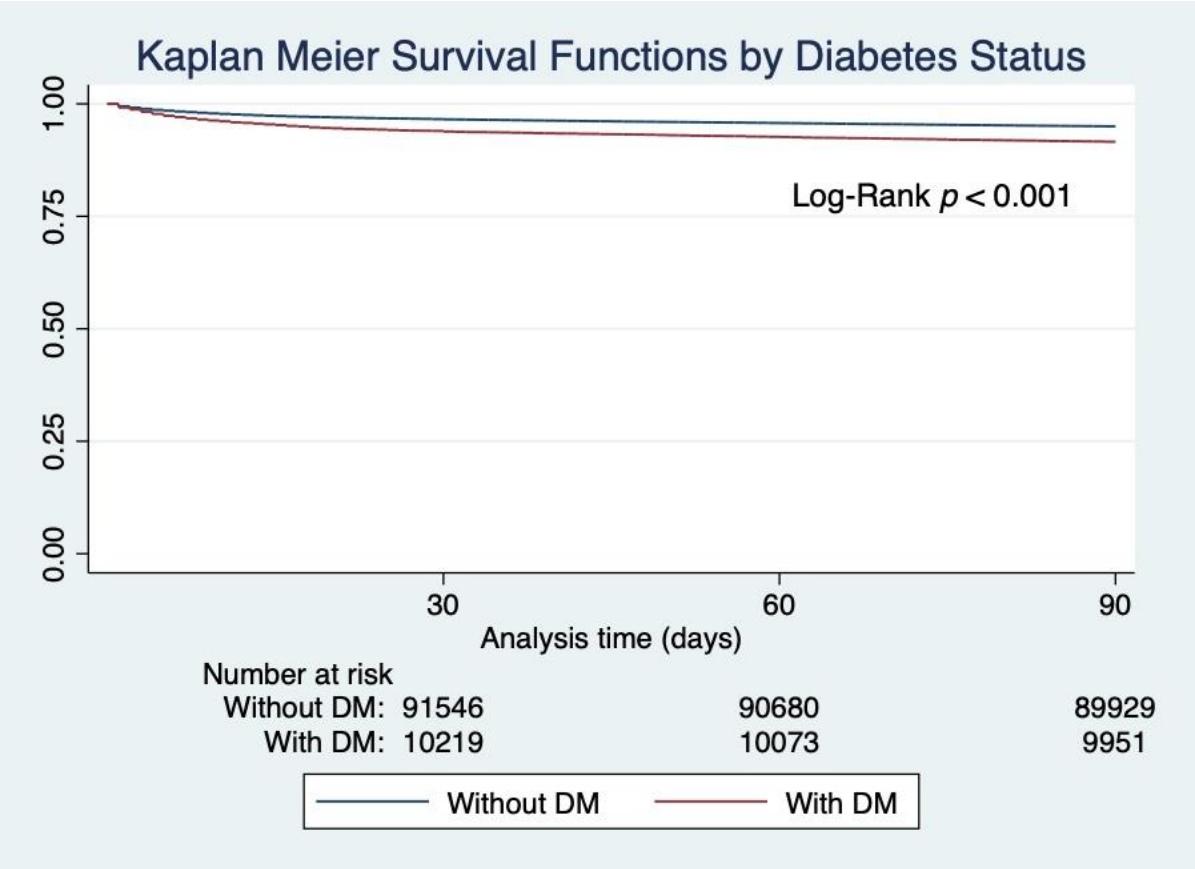


Figure 4: Kaplan Meier survival functions for patients with and without diabetes. DM = Diabetes Mellitus.

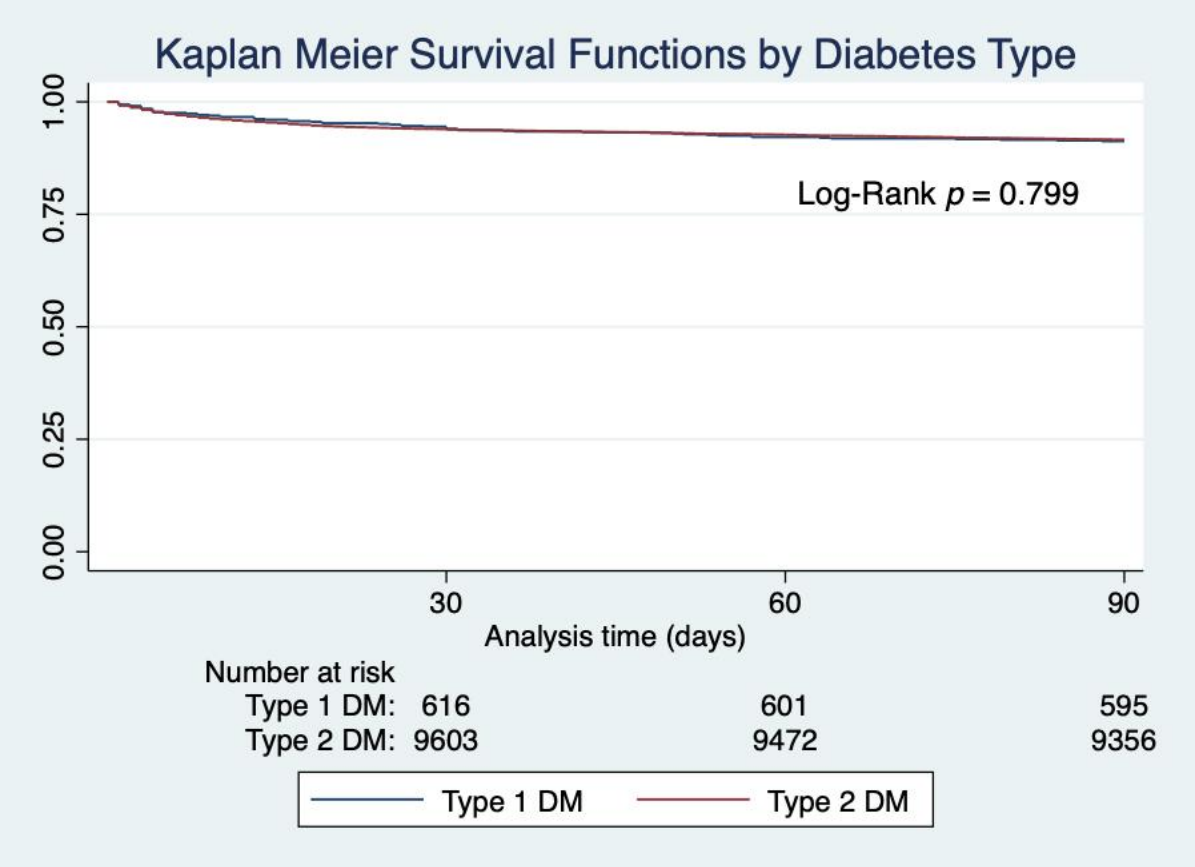


Figure 5: Kaplan Meier survival functions for patients with type 1 and type 2 Diabetes. Type 1 DM = Type 1 Diabetes Mellitus, Type 2 DM = Type 2 Diabetes Mellitus.

4.3.2 Adjusted 90-day Mortality

The results of the univariate and multivariate Cox regression analysis of 90-day mortality, with diabetes status considered the primary exposure of interest, are presented in Table 4. On univariate analysis, each of the considered exposure variables were statistically significant except for sex (unadjusted HR 0.98, 95% CI 0.93 to 1.03, p = 0.491), which was therefore not included in the multivariate model. The difference between individual levels of deprivation and the reference level of deprivation were not all statistically significant, however deprivation overall was deemed to be a statistically significant covariate based on a likelihood ratio test results ($p < 0.001$) and therefore included in the final multivariate model.

Patients with diabetes had an increased, unadjusted hazard rate for 90-day mortality (unadjusted HR 1.72, 95% CI 1.60 to 1.84) compared to patients with diabetes.

In the adjusted, multivariate model, patients with diabetes continued to demonstrate a significantly increased risk of 90-day mortality (adjusted HR 1.28, 95% CI 1.19 to 1.37, $p < 0.001$) compared to patients without diabetes. Other factors associated with an increased 90-day mortality after adjusted analysis were increasing age, deprivation, increasing comorbidity, emergency surgery, surgery for benign disease and open laparotomy.

Interactions were tested for using interaction terms between diabetes and each of the covariates included in the multivariate model. None of these interactions were statistically significant after likelihood ratio tests were performed (age; $p = 0.336$, comorbidity; $p = 0.197$, deprivation; $p = 0.930$, operation urgency; $p = 0.915$, operative indication; $p = 0.156$ and surgical access; $p = 0.426$), and were therefore not included in the final model.

Based on visual assessment of the log-log plots for survival, stratified by diabetes status, the proportional hazards assumption was deemed to have been met (Figure 6). Testing of the correlation between Schoenfeld residuals and time demonstrated a breach in the proportional hazards assumption for the overall model, and more specifically for the covariates age (third to fifth levels), deprivation (fifth quintile), comorbidity (category 1), urgency and operative indication (Appendix Table 6).

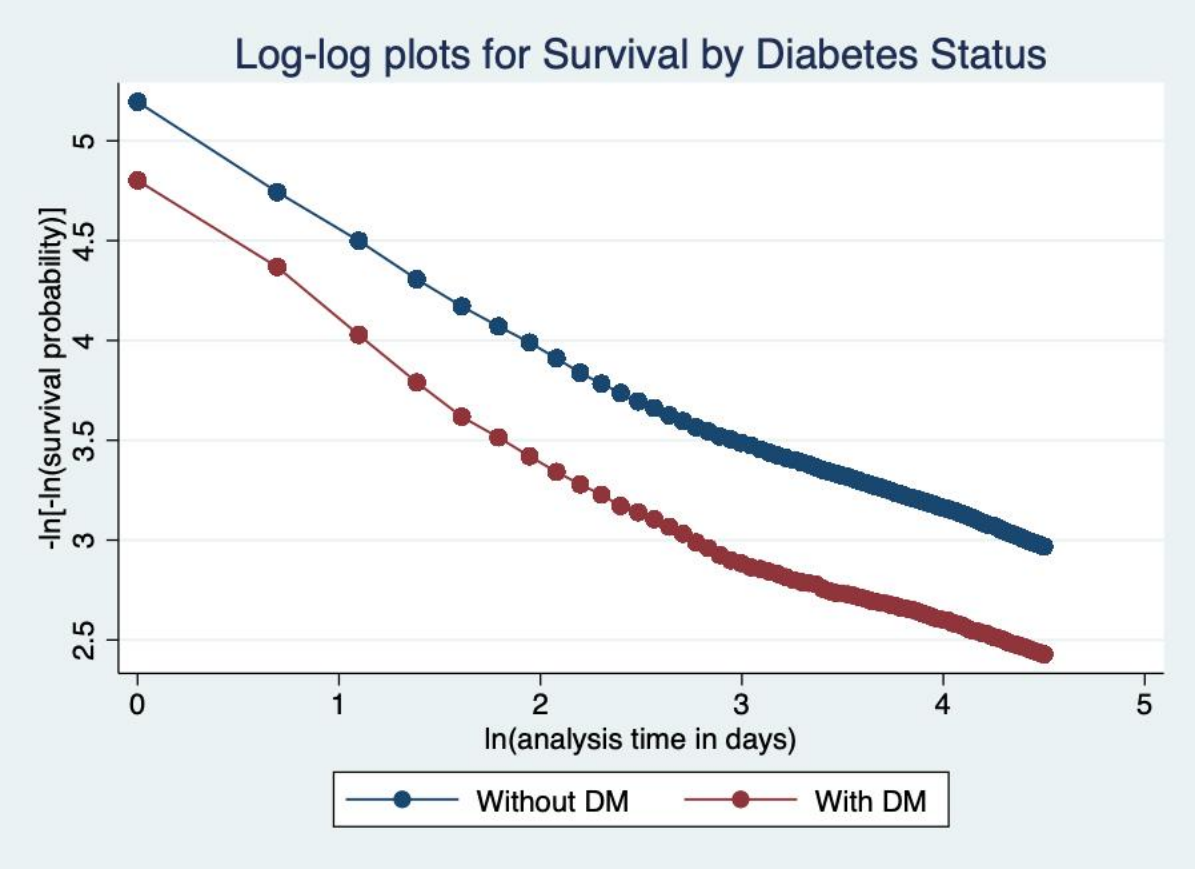


Figure 6: Log-log functions for patients with and without diabetes. DM = Diabetes Mellitus.

The smoothed hazard functions for mortality for each of these covariates are presented in Appendix Figures 2 – 5. There is no overlap between the smoothed hazard functions between the age categories or between the comorbidity groups. The smoothed hazard functions for the different levels of deprivation do show overlap, but with no clear point at which the hazards diverge and become separate. In contrast, the smoothed hazard functions for groups stratified by operative indication cross around the 55-day mark, with the subsequent hazards remaining distinct.

4.3.3 90-day Readmission

Emergency readmission within 90-days of discharge occurred in 19.4% (n = 20,542) of all patients and was more common in patients with diabetes compared to patients without diabetes (21.7% vs 19.1%, $p < 0.001$). Patients with type 1 diabetes

experienced significantly higher 90-day readmission rates than those with type 2 diabetes (26.3% vs 21.4%, p = 0.003).

After accounting for time-at-risk and censoring, the overall unadjusted 90-day readmission rate was 974.2 per 1000 person-years (95% CI 960.90 to 987.57). The rate of 90-day readmission was more common in patients with diabetes (1152.1 per 1000 person-years, 95% CI 1106.6 to 1199.5) compared to patients without diabetes (954.9 per 1000 person-years, 95% CI 941.1 to 968.9)

Cumulative risk of readmission up to 90 days postoperatively in patients with or without diabetes, as calculated using Kaplan Meier failure estimates, are depicted in Figure 7. This figure shows separation of the functions for patients with and without diabetes, with an increased risk of readmission for patients with diabetes at 30, 60 and 90 days postoperatively.

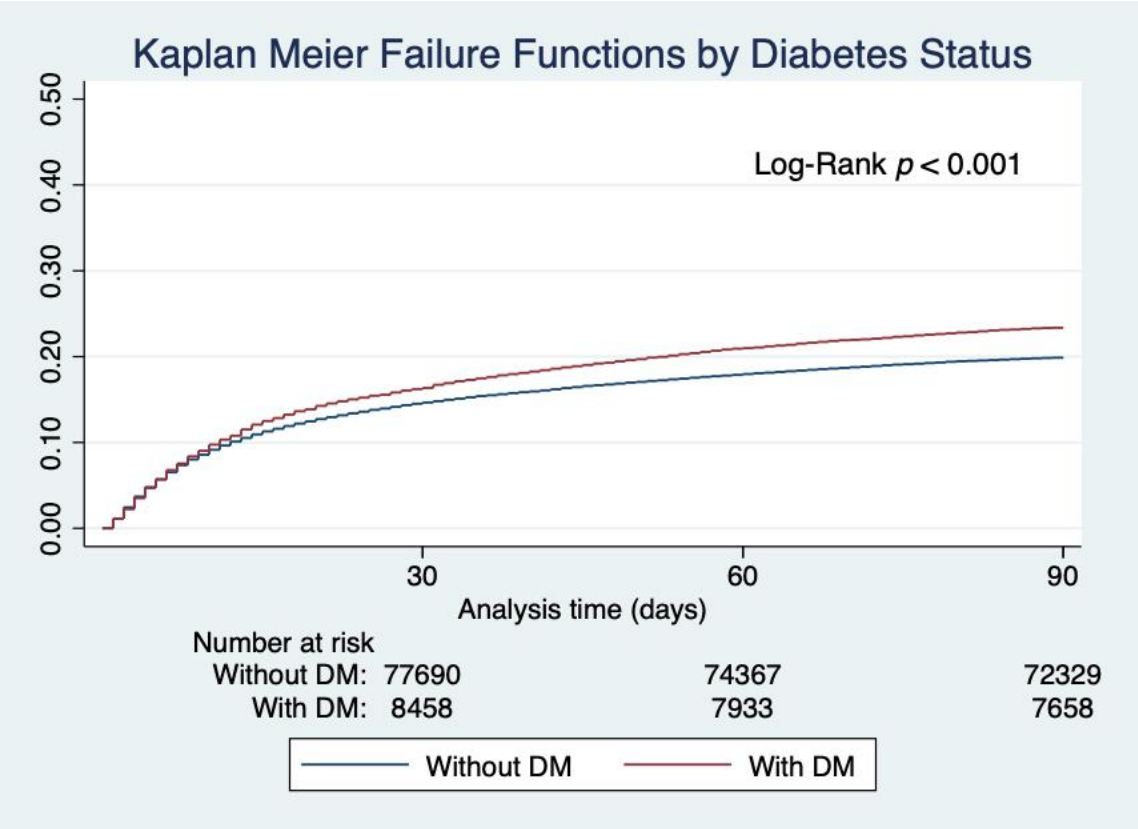


Figure 7: Kaplan Meier failure functions for readmission, stratified by patients with and without diabetes. DM = Diabetes Mellitus.

Results from the univariate and multivariate analysis of 90-day readmission, with diabetes as the exposure of interest, are presented in Table 5. All covariates were significantly associated with the outcome on univariate analysis, and therefore included in the multivariate model. Patients with diabetes demonstrated increased 90-day readmission rates in both the unadjusted (HR 1.19, 95% CI 1.14 to 1.24, $p < 0.001$) and adjusted (HR 1.23, 95% CI 1.18 to 1.29, $p < 0.001$) Cox proportional hazards regression model.

Table 5: Cox Regression Model for 90-day Readmission with Diabetes as the Exposure of Interest

Covariate	**Unadjus-ted HR**	**95% CI**	**p value**	**Adjusted HR**	**95% CI**	**p value**
Sex						
Male	1	-		1	-	
Female	0.96	0.94 to 0.99	0.009	0.95	0.92 to 0.98	<0.001
Age						
0-50	1	-	<0.001	1	-	
51-60	0.92	0.88 to 0.96	<0.001	0.92	0.88 to 0.97	<0.001
61-70	0.82	0.79 to 0.86	<0.001	0.83	0.80 to 0.87	<0.001
71-80	0.83	0.80 to 0.86	<0.001	0.83	0.79 to 0.86	<0.001
>80	0.84	0.80 to 0.88	<0.001	0.83	0.78 to 0.87	<0.001
Deprivation						
1	1	-	<0.001	1	-	<0.001
2	1.04	1.00 to 1.08	0.08	1.03	0.98 to 1.07	0.214
3	1.05	1.01 to 1.10	0.027	1.02	0.98 to 1.06	0.3999

4	1.15	1.10 to 1.20	<0.001	1.10	1.05 to 1.15	<0.001
5	1.28	1.23 to 1.34	<0.001	1.19	1.14 to 1.25	<0.001
CCI						
0	1	-	0.001	1	-	
1	0.98	0.92 to 1.03	0.419	1.12	1.06 to 1.19	0.049
2	1.05	1.02 to 1.08	0.003	1.28	1.23 to 1.32	<0.001
Diabetes						
No	1	-		1	-	
Yes	1.19	1.14 to 1.24	<0.001	1.23	1.18 to 1.29	<0.001
Urgency						
Elective	1	-		1	-	
Emergency	1.39	1.35 to 1.43	<0.001	1.27	1.23 to 1.31	<0.001
Indication						
Benign	1	-		1	-	
Malignant	0.74	0.71 to 0.76	<0.001	0.84	0.781to 0.86	<0.001
Access						
Open	1	-		1	-	
Minimally Invasive	0.77	0.75 to 0.80	<0.001	0.87	0.84 to 0.89	<0.001

HR = Hazard Ratio, CI = Confidence Interval, Pyrs = person-years, CCI = Charlson Comorbidity Index. Deprivation was included in the final model based on likelihood ratio test results ($p < 0.001$).

The log-log plots for readmission by diabetes status are presented in Figure 8. These show crossover between the groups of patients with and without diabetes between the first (ln(2.72 days) = 1) and second (ln(7.39 days) = 2) mark on the x-

axis, suggesting that the increased readmission hazard rate for patient with diabetes may not be consistently proportional to the baseline hazard rate of readmission for patients without diabetes across the first 90-days post-discharge. However, both the Kaplan Meier failure functions and the log-log plots begin to separate after equivalent of the first week of discharge and show marked divergence (with a trend towards increased separation of the log-log functions) between groups at 90-days post-discharge - our outcome of interest.

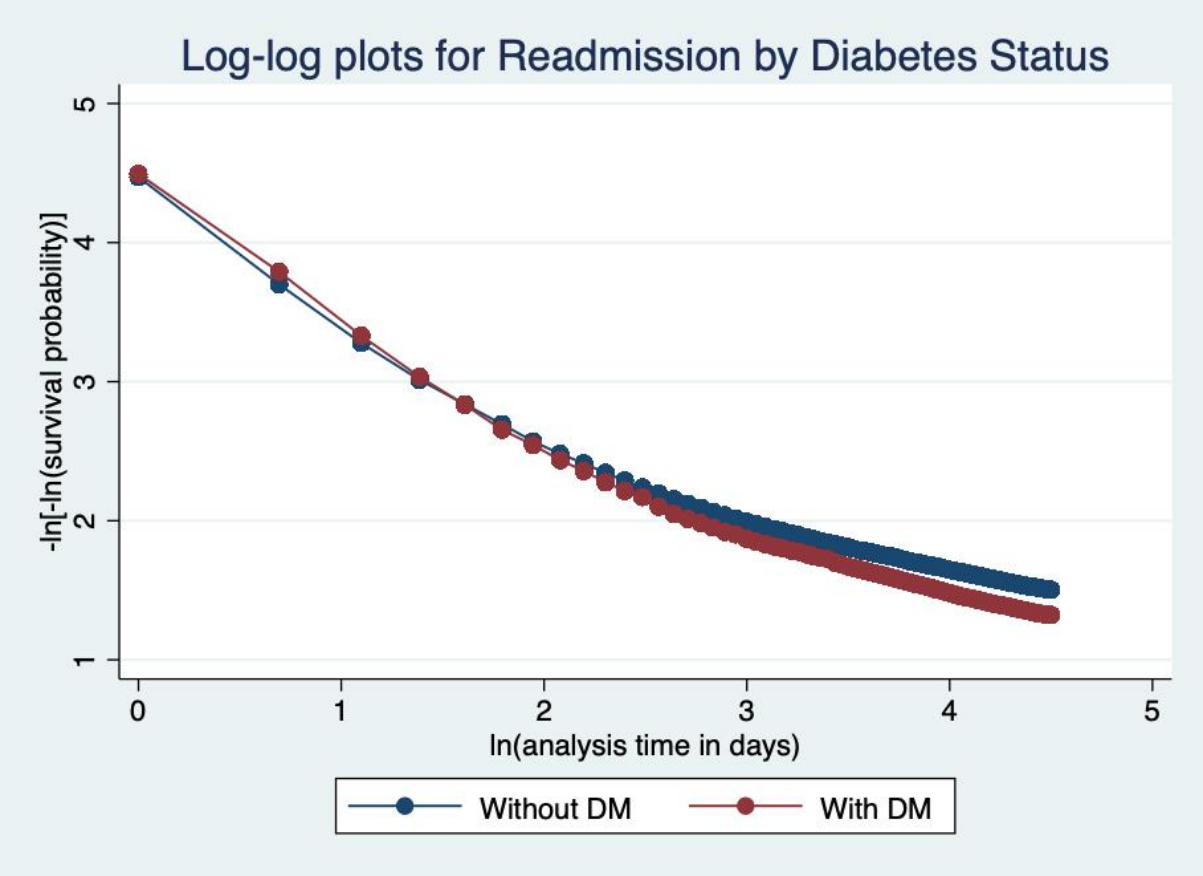


Figure 8: Log-log plots for patients with and without diabetes. DM = Diabetes Mellitus.

4.3.4 Hospital Length of Stay

The median hospital length of stay for the entire cohort was 8 days (IQR 5 to 15). In patients with diabetes, the median length of stay was 9 days (IQR 6 to 17). The median length of stay increased to 10 days (IQR 6 to 20) in patients with type 1

diabetes, compared to a median length of stay of 9 (IQR 6 to 17) in patients with type 2 diabetes.

A histogram of the hospital length of stay in days for the entire cohort revealed the non-parametric distribution of this outcome. (Figure 9)

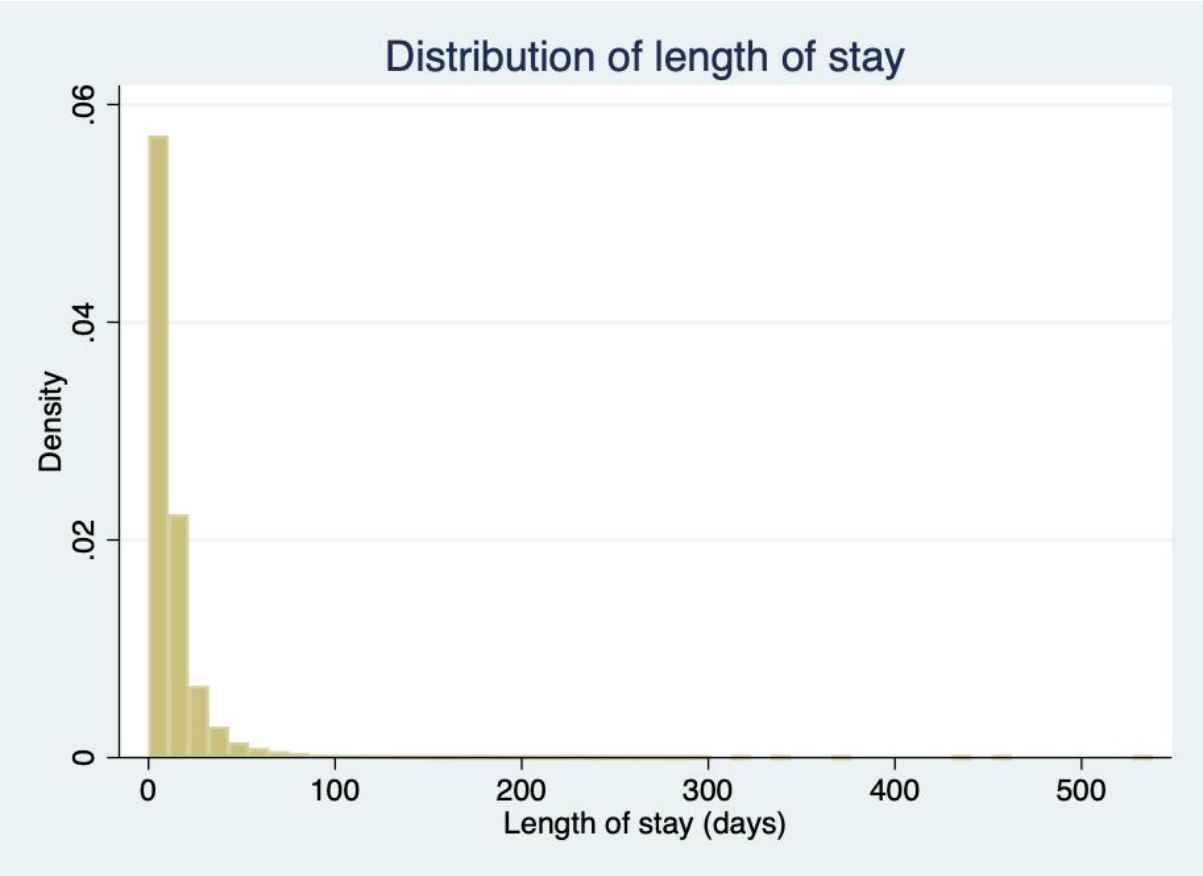


Figure 9: Histogram showing the distribution of hospital length of stay for all patients.

The smoothed hazard function for length of stay across the entire cohort was plotted and is presented in Figure 10. This revealed a non-monotonic hazard function, with an initial increase followed by a subsequent decrease in the hazard function.

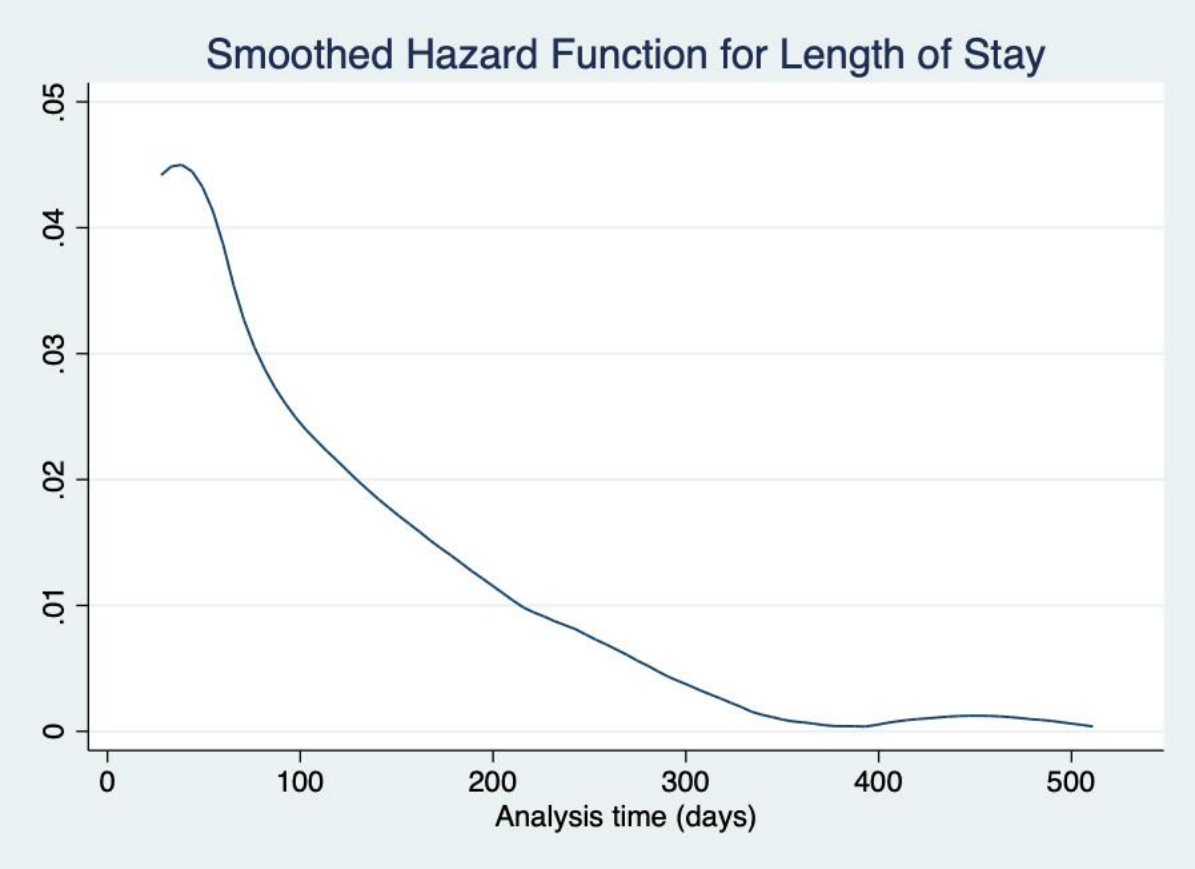


Figure 10: Graph of the smoothed hazard function for hospital length of stay for all patients.

Based on the preliminary evaluation of the smoothed hazard function for length of stay for the cohort as a whole, several AFT models were evaluated for the estimation of length of stay. In a comparison between AFT models based on varying distributions (exponential, Weibull, lognormal, loglogistic and generalised gamma), the AFT model based on a loglogistic distribution produced the lowest AIC (Table 6), and was therefore most suitably fit to model the outcome of hospital length of stay.

Table 6: Results of the Evaluation of AFT Models for Hospital Length of Stay

	Distribution				
Parameter	Exponential (AFT)	Weibull (AFT)	Lognormal	Loglogistic	Generalised gamma
Log likelihood	-107714.93	-106791.46	-83561.984	-81516.452	NA
AIC	215463.9	213618.9	167160	163068.9	NA
AFT = Accelerated Failure Time Model, AIC = Akaike Information Criterion.					

All covariates listed previously were considered in this model, and where each shown to be statistically significant. The results of the loglogistic AFT model for length of stay are presented as adjusted time ratios and summarised in Table 7.

Table 7: Loglogistic AFT Regression Model for Hospital Length of Stay

Covariate	**Adjusted TR**	**SE**	**95% CI**	**p value**
Sex				
Male	1	-	-	-
Female	0.96	0.00	0.95 to 0.97	<0.001
Age				
0-50	1	-	-	-
51-60	1.04	0.01	1.03 to 1.06	<0.001
61-70	1.09	0.01	1.08 to 1.10	<0.001
71-80	1.21	0.01	1.20 to 1.23	<0.001
>80	1.44	0.01	1.41 to 1.46	<0.001
Deprivation Quintiles				
1	1	-	-	-
2	1.01	0.01	1.00 to 1.02	0.029
3	1.05	0.01	1.03 to 1.06	<0.001
4	1.08	0.01	1.07 to 1.10	<0.001
5	1.13	0.01	1.12 to 1.15	<0.001
CCI				
0	1	-	-	-
1	1.05	0.01	1.03 to 1.06	<0.001
2	1.13	0.01	1.12 to 1.15	<0.001
Diabetes				
No	1	-	-	-
Yes	1.10	0.01	1.08 to 1.11	<0.001
Urgency				

Elective	1	-	-	-
Emergency	1.88	0.01	1.86 to 1.90	<0.001
Indication				
Benign	1	-	-	-
Malignant	0.84	0.00	0.83 to 0.85	<0.001
Access				
Open	1	-	-	-
MIS	0.7	0.00	0.70 to 0.71	<0.001
TR = Time Ratio, SE = Standard Error, 95% CI = 95% Confidence Interval, CCI = Charlson Comorbidity Index, MIS = Minimally Invasive Surgery.				

Patients with diabetes experienced a 10% longer period of hospital stay, compared to patients without diabetes (adjusted TR 1.10, 95% CI 1.08 to 1.11, p < 0.001). The largest proportional increase in hospital length of stay was seen in patients undergoing emergency surgery (80% increased length of stay) compared to patients undergoing elective surgery. There was in increase in length of stay across increasing patient age and comorbidity categories, as well as across deprivation quintiles. (Table 7)

4.4 Insulin-use

4.4.1 Crude 90-day Mortality

The crude 90-day mortality risk was 9.9% in patients with diabetes and insulin-use, compared to 8.5% in patients with diabetes without insulin-use and 5.3% in patients without diabetes. The odds of 90-day mortality were increased in both patients with diabetes and insulin-use (OR 1.18, 95% CI 1.01 to 1.39, p = 0.036) and patients with diabetes without insulin-use (OR 1.12, 95% CI 1.03 to 1.22, p = 0.011), compared to patients without diabetes.

Insulin-use in patients with diabetes was associated with the highest 90-day mortality rates (423.76 per 1000 person-years, 95% CI 370.03 to 485.29), over and above patients with diabetes without insulin-use (354.24 per 1000 person-years, 95% CI

329.25 to 381.12) and patients without diabetes (212.27 per 1000 person-years, 95% CI 206.34 to 218.36). 90-day mortality rates across all covariates are presented in Table 8.

Table 8: Cox Regression Model for 90-day Mortality with Insulin-use as the Exposure of Interest

Covariate	**Person-Years at risk**	**N Dead at 90 days**	**90-day Mortality Rate per 1000-pyrs**	**95% CI**	**Unadjus-ted HR**	**95% CI**	**p value**	**Adjusted HR**	**95% CI**	**p value**
Sex										
Male	1.3E+04	2891	231.36	222.98 to 239.84	1	-		-	-	-
Female	1.3E+04	2834	224.52	216.40 to 232.94	0.98	0.93 to 1.03	0.483	-	-	-
Age										
0-50	6.2E+03	370	59.35	53.60 to 65.71	1	-	<0.001	1	-	
51-60	4.0E+03	539	133.94	123.09 to 145.73	2.25	1.97 to 2.58	<0.001	2.36	2.06 to 2.70	<0.001
61-70	5.9E+03	1182	200.70	189.57 to 212.47	3.36	2.99 to 3.78	<0.001	3.66	3.25 to 4.14	<0.001
71-80	6.0E+03	1825	304.08	290.45 to 318.36	5.08	4.54 to 5.69	<0.001	5.25	4.67 to 5.90	<0.001

>80	3.0E+03	1809	608.33	580.93 to 637.02	9.99	8.93 to 11.12	<0.001	8.82	7.84 to 9.93	<0.001
Deprivation Quintiles										
1	5.6E+03	1186	211.36	199.66 to 223.73	1	-	<0.001	1		
2	5.3E+03	1100	206.21	194.38 to 218.77	0.97	0.89 to 1.05	0.446	0.99	0.91 to 1.07	0.764
3	5.1E+03	1170	230.25	217.43 to 243.83	1.09	1.00 to 1.18	0.038	1.08	1.00 to 1.17	0.064
4	4.8E+03	1149	240.03	226.55 to 254.32	1.14	1.05 to 1.23	0.002	1.18	1.09 to 1.28	<0.001
5	4.3E+03	1108	258.95	244.14 to 274.66	1.22	1.13 to 1.34	<0.001	1.23	1.14 to 1.34	<0.001
CCI										
0	6.6E+03	938	143.03	134.16 to 152.48	1	-	<0.001	1	-	
1	2.1E+03	382	183.84	166.30 to 203.23	1.28	1.13 to 1.44	<0.001	1.17	1.04 to 1.32	0.011
2	1.6E+04	4405	267.17	259.39 to 275.17	1.84	1.72 to 1.98	<0.001	1.79	1.66 to 1.93	<0.001
Diabetes										

No	2.3E+04	4798	212.27	206.34 to 218.36	1	-	<0.001	1		
DM without Insulin-use	2.0E+03	718	354.24	329.25 to 381.12	1.66	1.53 to 1.79	<0.001	1.22	1.13 to 1.33	<0.001
DM with Insulin-use	4.9E+02	209	423.76	370.03 to 485.29	1.95	1.70 to 2.25	<0.001	1.51	1.31 to 1.74	<0.001
Urgency										
Elective	1.8E+04	1519	86.43	82.19 to 90.89	1	-	<0.001	1	-	
Emergency	7.4E+03	4147	556.88	540.19 to 574.09	6.25	5.89 to 6.63	<0.001	4.83	4.52 to 5.16	<0.001
Indication										
Benign	1.1E+04	3235	292.95	283.03 to 303.22	1	-		1	-	
Malignant	1.4E+04	2438	174.13	167.36 to 181.18	0.60	0.57 to 0.63	<0.001	0.78	0.73 to 0.82	<0.001
Access										
Open	1.5E+04	5149	342.48	333.25 to 351.96	1	-		1	-	
MIS	1.0E+04	576	57.09	52.61 to 61.95	0.17	0.16 to 0.19	<0.001	0.40	0.36 to 0.45	<0.001

HR = Hazard Ratio, CI = Confidence Interval, Pyrs = person-years, CCI = Charlson Comorbidity Index, DM = Diabetes Mellitus, MIS = Minimally Invasive Surgery. Deprivation was included in the final model based on likelihood ratio test results ($p < 0.001$).

The difference in survival functions between patients with diabetes and insulin-use, patients with diabetes without insulin-use and patients without diabetes as a reference group, was similarly statistically significant (p < 0.001) (Figure 11).

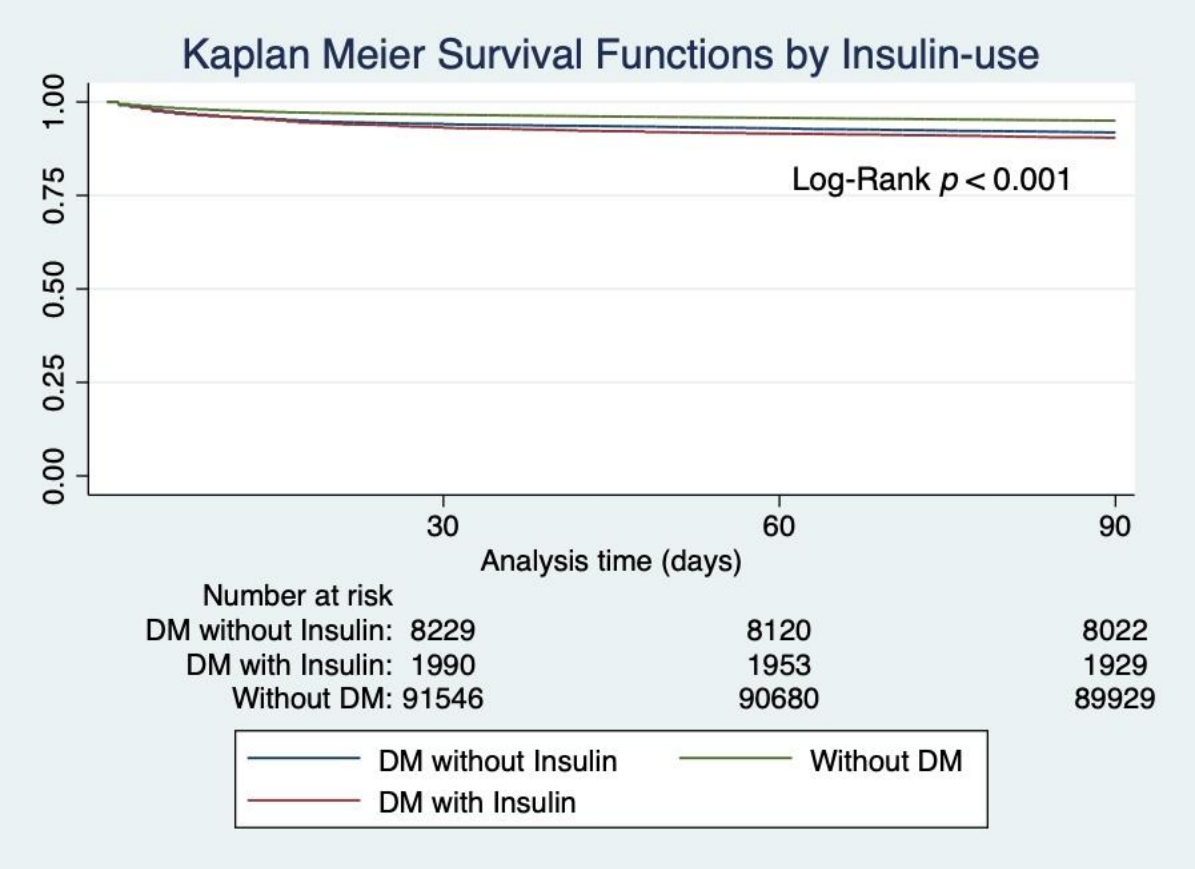


Figure 11: Kaplan Meier survival functions for patients with diabetes with insulin-use, patients with diabetes without insulin-use and patients without diabetes. DM = Diabetes Mellitus.

4.4.2 Adjusted 90-day Mortality

The results of the univariate and multivariate Cox regression analysis of 90-day mortality, with insulin-use considered the primary exposure of interest, are presented in Table 8. The only exposure variable which was not significantly associated with 90-day mortality on univariate analysis was sex (unadjusted HR 0.98, 95% CI 0.93 to 1.03, p = 0.483), which was subsequently not included in further multivariate analysis.

In both the univariate and multivariate Cox regression model, Insulin-use in patients with diabetes was significantly associated with increased 90-day mortality risk

(adjusted HR 1.51, 95% CI 1.31 to 1.74, p < 0.001) over and above the increased risk experienced by patients with diabetes (adjusted HR 1.22, 95% CI 1.13 to 1.33, p < 0.001), in comparison to patients without diabetes. Other factors associated with increased 90-day mortality were increasing patients age and comorbidity, deprivation, emergency surgery and benign disease as an operative indication, as well as open laparotomy.
There were no significant interactions between the exposure of interest and any of the covariates included in the multivariate model (age; p = 0.350, comorbidity; p = 0.078, deprivation; p = 0.893, operation urgency; p = 0.061, operative indication; p = 0.158, surgical access; p = 0.616).

Visual assessment of the log-log plot for survival, stratified by insulin-use, showed crossover between the group of patients with diabetes with insulin-use and the patients with diabetes without insulin-use. The functions were similar for patients with diabetes with insulin-use and patients with diabetes without insulin-use up until 2-weeks postoperatively (between mark (ln(12.18) = 2.5) and ln(20.09) = 3.0), after which there appeared to be a separation of functions and therefore difference in hazards between groups. (Figure 12). There is no crossover between either group of patients with diabetes (with or without insulin-use) and the group of patients with diabetes, with the transformed survival functions remaining proportionally reduced for patients without diabetes at all timepoints within 90 days after surgery.

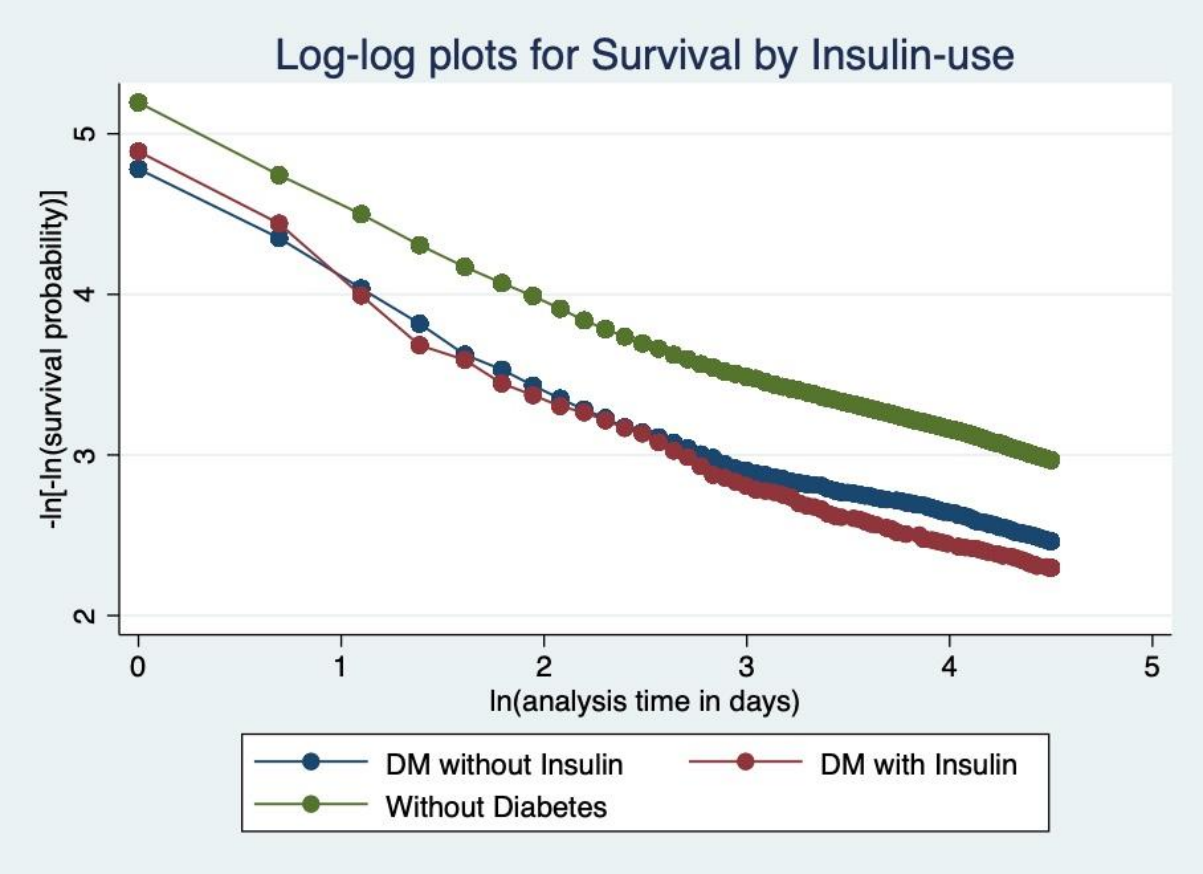


Figure 12: Log-log plots for patients with diabetes with insulin-use, patients with diabetes without insulin-use and patients without diabetes. DM = Diabetes Mellitus.

4.4.3 90-day Readmission

The odds of 90-day readmission were increased by 35% in patients with diabetes and insulin-use (26.0%), compared to patients with diabetes without insulin-use (20.7%) (OR 1.35, 95% CI 1.12 to 1.50, $p < 0.001$).

Insulin-use in patients with diabetes was associated with higher mortality rates (1453.85 per 1000-person years, 95% CI 1337.99 to 1579.74), in the context of patients with diabetes without insulin-use (1082.90 per 1000 person-years, 95% CI 11034.13 to 1133.97) and patients without diabetes (954.91 per 1000 person-years, 95% CI 941.12 to 968.91).

The cumulative risk of 90-day readmission, stratified by insulin-use are depicted in Figure 13. This demonstrates separation of the Kaplan Meier failure functions for

readmission for each group (patients with diabetes with insulin-use, patients with diabetes without Insulin-use and patients without diabetes) across 30, 60 and 90 days postoperatively.

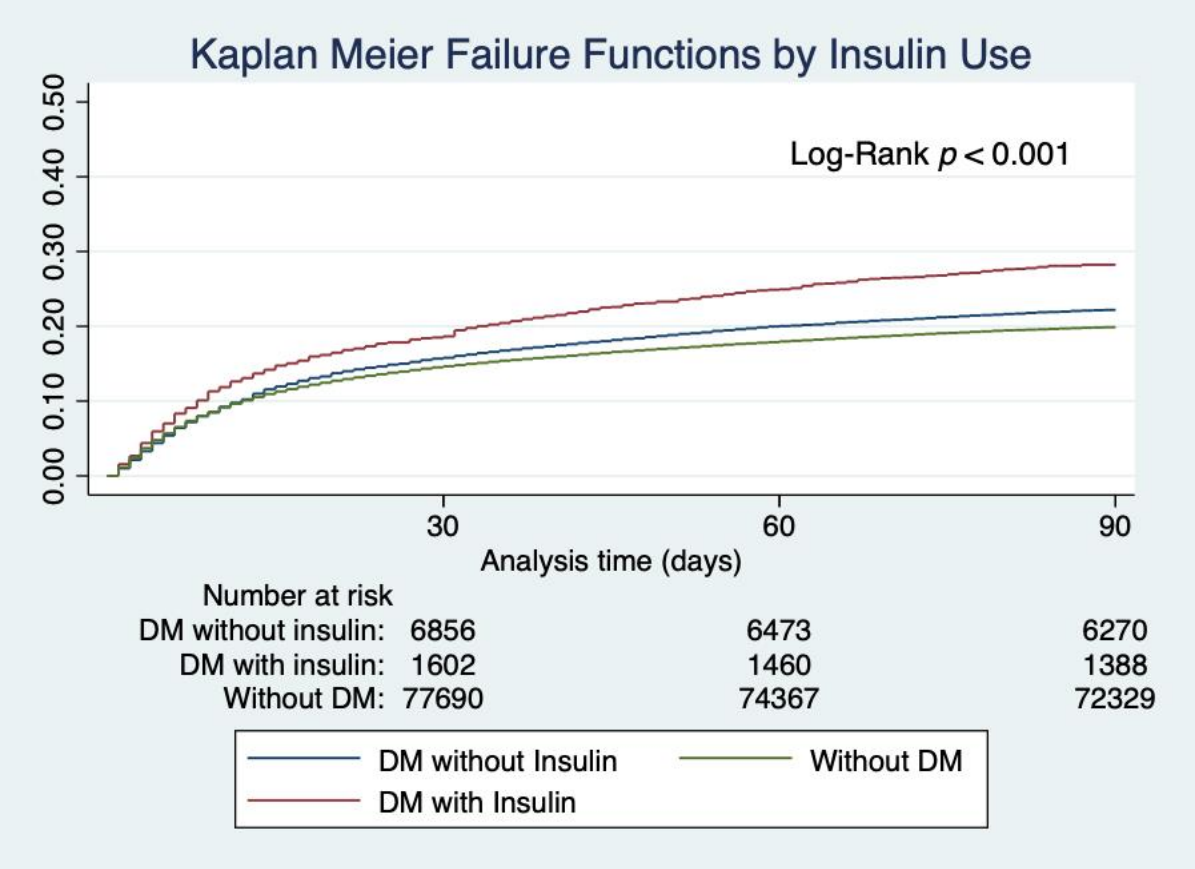


Figure 13: Kaplan Meier failure functions for readmission in patients with diabetes with insulin-use, patients with diabetes without insulin-use and patients without diabetes. DM = Diabetes Mellitus.

All covariates were significant on univariate analysis, and therefore considered in the multivariate Cox regression model for 90-day readmission, with insulin-use as the exposure of interest. The likelihood ratio test of a multivariate model with and without deprivation confirmed the overall significance of this factor variable. Results from these univariate and multivariate analyses are presented in Table 9.

Table 9: Cox Regression Model for 90-day Readmission with Insulin-use as the Exposure of Interest

Covariate	Unadjus-ted HR	95% CI	p value	Adjusted HR	95% CI	p value
Sex						
Male	1	-		1	-	-
Female	0.96	0.94 to 0.99	0.009	0.95	0.92 to 0.98	<0.001
Age						
0-50	1	-	<0.001	1	-	-
51-60	0.92	0.88 to 0.96	<0.001	0.92	0.88 to 0.97	<0.001
61-70	0.82	0.79 to 0.86	<0.001	0.83	0.80 to 0.87	<0.001
71-80	0.83	0.80 to 0.86	<0.001	0.83	0.80 to 0.87	<0.001
>80	0.84	0.80 to 0.88	<0.001	0.83	0.79 to 0.87	<0.001
Deprivation						
1	1	-	<0.001	1	-	<0.001
2	1.04	1.00 to 1.08	0.08	1.02	0.98 to 1.07	0.214
3	1.05	1.01 to 1.10	0.027	1.02	0.98 to 1.06	0.393
4	1.15	1.10 to 1.20	<0.001	1.10	1.05 to 1.15	<0.001
5	1.28	1.23 to 1.34	<0.001	1.19	1.14 to 1.25	<0.001
CCI						
0	1	-	0.001	1	-	-
1	0.98	0.92 to 1.03	0.419	1.12	1.06 to 1.19	<0.001

2	1.05	1.02 to 1.08	0.003	1.27	1.23 to 1.32	<0.001
Diabetes						
No	1	-		1	-	-
DM without Insulin-use	1.12	1.07 to 1.18	<0.001	1.17	1.12 to 1.23	<0.001
DM with Insulin-use	1.47	1.35 to 1.60	<0.001	1.46	1.34 to 1.59	<0.001
Urgency						
Elective	1	-		1	-	-
Emergency	1.39	1.35 to 1.43	<0.001	1.27	1.23 to 1.31	<0.001
Indication						
Benign	1	-		1	-	-
Malignant	0.74	0.71 to 0.76	<0.001	0.84	0.81 to 0.86	<0.001
Access						
Open	1	-		1	-	-
Minimally Invasive	0.77	0.75 to 0.80	<0.001	0.87	0.84 to 0.89	<0.001

HR = Hazard Ratio, CI = Confidence Interval, Pyrs = person-years, CCI = Charlson Comorbidity Index. Deprivation was included in the final model based on likelihood ratio test results ($p < 0.001$).

Patients with diabetes and insulin-use had an increased hazard rate for 90-day readmission (adjusted HR 1.46, 95% CI 1.34 to 1.59, $p < 0.001$), over and above patients with diabetes without insulin-use (adjusted HR 1.17, 95% CI 1.12 to 1.23, $p < 0.001$), compared to patients without diabetes (reference group).

The log-log plots for readmission by insulin-use are presented in Figure 13. The functions for the patients without diabetes and those with diabetes without insulin-use run closely together, with differences only becoming apparent later in the postoperative phase. There is no crossover between the group of patients with diabetes with insulin-use and those without insulin-use.

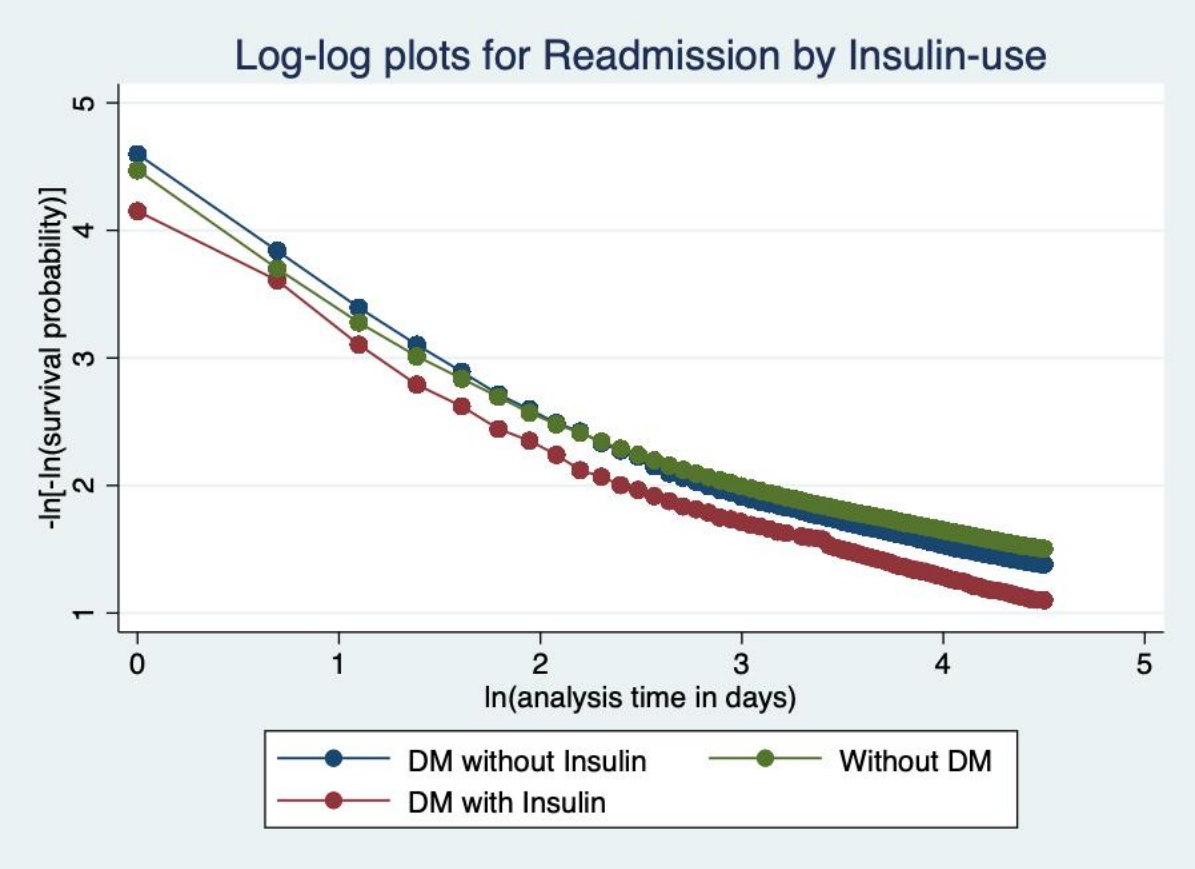


Figure 14: Log-log plots for readmission for patients with diabetes with insulin-use, patients with diabetes without insulin-use and patients without diabetes. DM = Diabetes Mellitus.

5 Chapter 5. Discussion

5.1 Summary

In this large contemporary population based study of patients undergoing colorectal resectional surgery for any benign or malignant indication, patients with diabetes experienced a significantly increased risk of 90-day mortality, prolonged length of stay and 90-day readmission, compared to patients without diabetes. Patients with diabetes and insulin-use appear to incur an increased risk of poor postoperative outcomes compared to patients with diabetes without insulin-use and patients without diabetes.

Other predictors of poor outcomes include increasing patient age, increasing comorbidity, deprivation, emergency surgery, benign indications and open laparotomy.

5.2 Strengths and Limitations

This study represents the first analysis of a national cohort encompassing a substantial number of patients, followed over a ten-year period, with linked data captured through national primary and secondary care databases. To our knowledge, this study describes the largest cohort of diabetic patients undergoing colorectal surgery, and their subsequent postoperative outcomes, to date. It also captures the rate of preoperative HbA1c measurement over a 10-year period in a national cohort of colorectal surgical patients.

This study encompasses a long period of time, throughout which there have been developments in perioperative care, surgical approach and guidelines relating to patients with diabetes undergoing colorectal surgery. These changes may have selectively affected the cohort of patients undergoing colorectal surgery and subsequent postoperative outcomes. Data pertaining to perioperative factors such as inpatient prescribing during hospital stay or ERAS implementation and compliance are not recorded in HES and were therefore not included in our analysis.

Additionally, we did not have enough numbers of events to conduct subgroup analysis for patients with diabetes based on operative urgency or indication, as this would have led to underpowered results. The postoperative outcomes for patients with diabetes may differ between these groups and warrants further investigation when larger numbers are available.

Lastly, although there is no crossover in the log-log plots for the primary outcome, there is some overlap in the log-log plots for readmission and for 90-day mortality using insulin-use as the exposure of interest. This is visible between one to two weeks postoperatively, whereafter the plots diverge and remain separate. The initial weeks after surgery include rapid developments and adjustments in the recovery process of each patient, before reaching a more stable physical steady-state. Simultaneously, the outcome of readmission in particular, is less common in the first few days after discharge, compared to the remaining postoperative period when potential complications requiring readmission tend to manifest. With fewer outcome events occurring in the early postoperative period, the variance is higher, potentially obscuring the true effect and accounting for the seeming early overlap in the log-log plots. Clinically, there is no reasoning to indicate that the increased hazard rate for patients with diabetes should be different in the first few weeks postoperatively compared to the remaining postoperative period of a total 90-days.
Although this issue may have been further addressed by creating models stratified by time-periods or by including time-varying interaction terms in the models, this would have reduced the study power and resulted in underpowered effect sizes. Modelling of 90-day mortality separately for patients stratified by operative indication (a variable for which the proportional hazards assumption was not met on testing of the Schoenfeld residuals in section 4.3.2) was attempted, but abandoned due to the low number of patients with the outcome of interest remaining across covariates, insufficient absolute outcome numbers per group and underpowered results.
Given the importance and clinical use of outcomes measured during the 90-day postoperative timeframe in current evidence-based medicine, we believe our choice of outcome measures remains justified.

5.3 Current Literature

The overall 5.7% 90-day mortality rate described in this cohort lies within the range described in current literature (4.4 – 11.3%).[35–39] Birch et al.[13] investigated postoperative outcomes for patients with diabetes undergoing surgery for colorectal malignancy and found an increased 90-day mortality risk limited to patients with complicated diabetes (6.6% vs 3.2% in patients without diabetes), but not for patients with uncomplicated diabetes. This finding was reiterated in their adjusted analysis of 1-year postoperative mortality (adjusted OR 1.05, 95% CI 0.99 to 1.11 for patients with uncomplicated diabetes, adjusted OR 1.58, 95% CI 1.51 to 1.66 for patients with complicated diabetes), which adjusted for patient age, sex, socioeconomic status, stage of disease, tumour site and year of colorectal cancer diagnosis. Patient comorbidity and surgical access were not considered in their regression model, which was limited to patients undergoing colorectal resections for malignant disease only. Of note, almost half (49.2%) of their diabetic population was classed as having complicated diabetes (limited to vascular complications), which may have contributed to 1-year mortality independently of their surgical intervention. This cohort also represents a period of time (2005 – 2016) which only partially includes diabetic-specific guidelines in colorectal surgery, which were introduced from 2012 onwards.[18,23,24,32] It is conceivable that these guidelines resulted in improved perioperative optimisation and care, as well as patient selection, leading to a more homogenous group of patients with diabetes undergoing colorectal surgery. Nevertheless, consideration of diabetic complications may be important in the ongoing care for patients with diabetes undergoing colorectal surgery.

A recent meta-analysis by Tan et al.[12] concluded that there was no statistically significant difference in 30-day mortality (OR 2.65, 95% CI 0.80 to 8.70, p = 0.109) after colorectal surgery for patients with diabetes compared to patients without diabetes, based on a pooled analysis of three studies (n = 3,526 (11.3%) with diabetes). However, these results may not represent the true risk, as the three combined studies appear to be underpowered to detect a difference in 30-day mortality (a more infrequent outcome), based on a relatively small pooled sample

size and indicated by the wide confidence intervals surrounding the pooled effect size.

Tan et al. also conducted a pooled meta-analysis of hospital readmission rates following colorectal surgery, derived from two studies (n = 181,876 total patients, n = 24,396 (13.4%) with diabetes), and reported an increased risk of readmission after colorectal surgery for patients with diabetes (OR 1.41, 95% CI 1.35 to 1.47, p < 0.001). Although there is limited evidence describing the readmission rates after colorectal surgery for patients with diabetes, an increased risk compared to patients without diabetes has been consistently described in other surgical [20,21,50] and medical[51,52] specialities. An increased 30-day and 90-day readmission risk has also been demonstrated for patients with diabetes and insulin-use over and above patients with diabetes without insulin-use.[20,53] These findings are consistent with our results.

Lastly, length of stay has shown to be increased for patients with diabetes in other non-cardiac surgical specialties.[20,22] Within colorectal surgery, Cologne et al.[54] reported an increased hospital stay in patients with diabetes hospitalised with diverticulitis (mean 7.29 vs 5.81 days, p = 0.05), although their study is not limited to surgical patients and does not report an adjusted effect size. It has also been shown that general surgical patients with diabetes and insulin-use are prone to increased length of stay (excess LOS 1.2 days) compared to those with diabetes and without insulin-use (excess LOS 0.9 days) and patients without diabetes.[22] The clinical importance of one additional day in hospital before discharge is, however, debatable.

5.4 HbA1c Measurement Rates

The measurement rate of preoperative HbA1c in our national cohort of colorectal surgical patients has remained relatively stable for 10 years. The overall rate of HbA1c measurement within one year before surgery was 69.9%. Patients with type 1 diabetes were less likely to have a recent HbA1c compared to patients with type 2 diabetes. These findings fall approximately 15% below the recent national average for patients with both type 1 (59.3% vs 75.8%) and type 2 diabetes (70.5% vs

86.2%), as documented by the National Diabetes Audit for the years of 2020/2021.[30] This is likely an underestimate of the shortcomings in timely preoperative measurement of HbA1c shown in our cohort, given that the nationally recorded average rates of timely HbA1c measurement for the years of 2015 to 2020 are around 85% for type 1 diabetes and 95% for type 2 diabetes.

The perioperative guidelines for patients with diabetes undergoing surgery clearly advise for up to date HbA1c values to be recorded in any surgical referrals. A recent national review of the management of patients with diabetes undergoing surgery showed that an HbA1c value within 3 months was only provided in 42% of all surgical referrals, whilst 41% of all surgical referrals did not include any information on the patient's diabetic management in the community.[17]
Patients with diabetes for whom this is not included may have their HbA1c measured during preoperative clinic appointments, anaesthetic assessments or on admission prior to their surgery. Our primary analysis did not include any HbA1c values measured in secondary care before the index surgery (unless these were subsequently submitted to the patient's primary care provider for their records), as HES does not provide these results. In contrast, the completed audit, which was based on records obtained from a local secondary-care database, showed higher rates of HbA1c measurement within three and six months of surgery. These are closer to the 3-month HbA1c measurement rates quoted by the NCEPOD "Highs and Lows" report. The true preoperative HbA1c measurement rates in patients undergoing colorectal surgery may therefore be higher at three and six months preceding surgery than estimated in our primary analysis, but remain substandard overall.

5.5 Clinical Significance

Diabetes significantly increases the risk of 90-day mortality by 28% and 90-day emergency readmission by 23% in patients undergoing colorectal resections, whilst also increasing the length of hospital stay by 10%. The use of insulin in patients with diabetes undergoing colorectal surgery predicts an additional risk of worse outcomes across all three measures. Both increased readmission rates and prolonged hospital

stay translate not only to delayed patient recovery and increased morbidity, but also to decreased bedspace availability in hospitals and increased healthcare expenditure. This, in turn, will impact on preoperative planning of service provision and resource allocation for colorectal patients.

Meanwhile, HbA1c remains an underutilised tool for perioperative optimisation and risk stratification in patients with diabetes undergoing colorectal surgery. A significant proportion of patients with diabetes do not reach their treatment target of HbA1c less than 58mmol/mol before undergoing colorectal surgery. Patients with type 1 diabetes are at greater risk of not having a timely HbA1c measurement, and of not reaching target levels of glycaemic control before surgery, compared to patients with type 2 diabetes. Given that hba1c regulation and subsequent long-term diabetic control is a cornerstone of risk reduction in patients with diabetes undergoing surgery, this highlights an important area for improvement. Close collaboration with primary care and preoperative assessment services is required to ensure timely Hba1c measurement for elective procedures, to allow for targeted preoperative risk prevention and modification in patients with diabetes. In patients with diabetes undergoing emergency colorectal surgery, Hba1c measurement can inform risk stratification and highlight patients for whom intra- and postoperative glucose control may require particular attention.

The perioperative period should be used to target modifiable risk factors, such as patients with type 2 diabetes with insulin-use (14.5% in this cohort), patients with poor long-term glycaemic control and patients with undiagnosed diabetes, which should ideally be addressed and optimised before surgery in line with current guidelines. Based on findings from this study, patients with diabetes and insulin-use should be considered particularly vulnerable to poorer postoperative outcomes, with insulin-use being taken into account when assessing and determining the risk of patients with diabetes undergoing colorectal surgery. This may also guide consent discussions and the patient selection process.

The recent NCEPOD “Highs and Lows” report[17] found that 43.4% of pre-operative assessment clinics did not have a specific policy for the management of patients with diabetes undergoing surgery, and advised the implementation and audit of diabetes-

specific perioperative care policies to address many of the issues described in this study. These local policies should take into account recommendations provided by current perioperative care guidelines as described in chapter 1.2. Our results support this conclusion and additionally emphasises the importance of cooperation between primary care, secondary care and diabetes specialist services, to ensure sustainable improvement to referral communications and preoperative risk modification in patients with diabetes undergoing colorectal surgery.

5.6 Further Research

This study provides baseline estimates of the increased risk of poor postoperative outcomes incurred by patients with diabetes undergoing colorectal surgery. Further investigation is warranted into whether measures of disease severity and diabetic control, such as diabetic complications and HbA1c levels, are able to additionally stratify the mortality risk of patients with diabetes undergoing colorectal surgery, to help guide clinical decision making in daily practice. Additionally, there would be value in exploring the longer-term impact of diabetes on postoperative outcomes in patients undergoing colorectal resections. Lastly, local or regional audit of compliance with perioperative guidelines regarding the management of patients with diabetes undergoing colorectal surgery is encouraged, to further understand and address the issue of poor preoperative HbA1c measurement rates in these patients.

6 Chapter 6. Conclusions

Patients with diabetes undergoing surgery for colorectal resections are at a greater risk of 90-day mortality, prolonged length of stay and 90-day readmissions, compared to patients without diabetes. Insulin-use in patients with diabetes confers an added risk of poor postoperative outcomes. Despite timely preoperative HbA1c measurement being recommended for all patients with diabetes to guide risk stratification and modification, it remains underutilised in the colorectal surgical cohort.

Awareness of these increased risks should be considered during the perioperative optimisation and care of the patient, as well as in consent discussions and patient selection processes.

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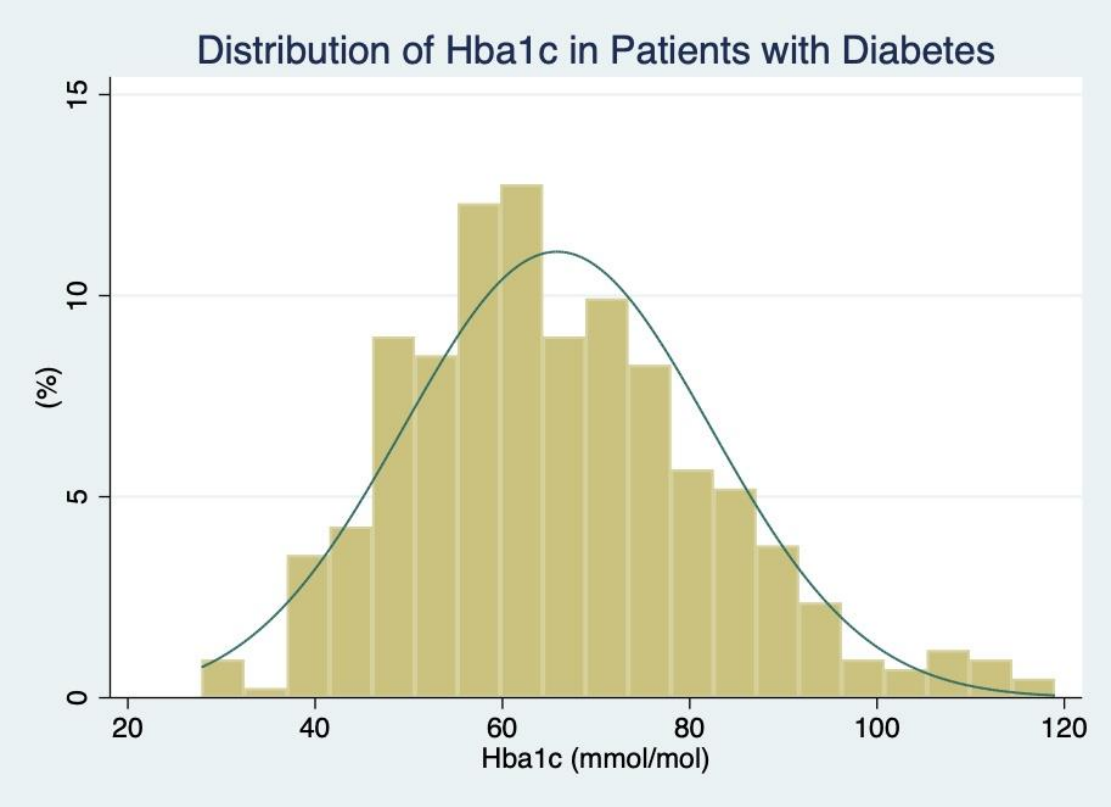
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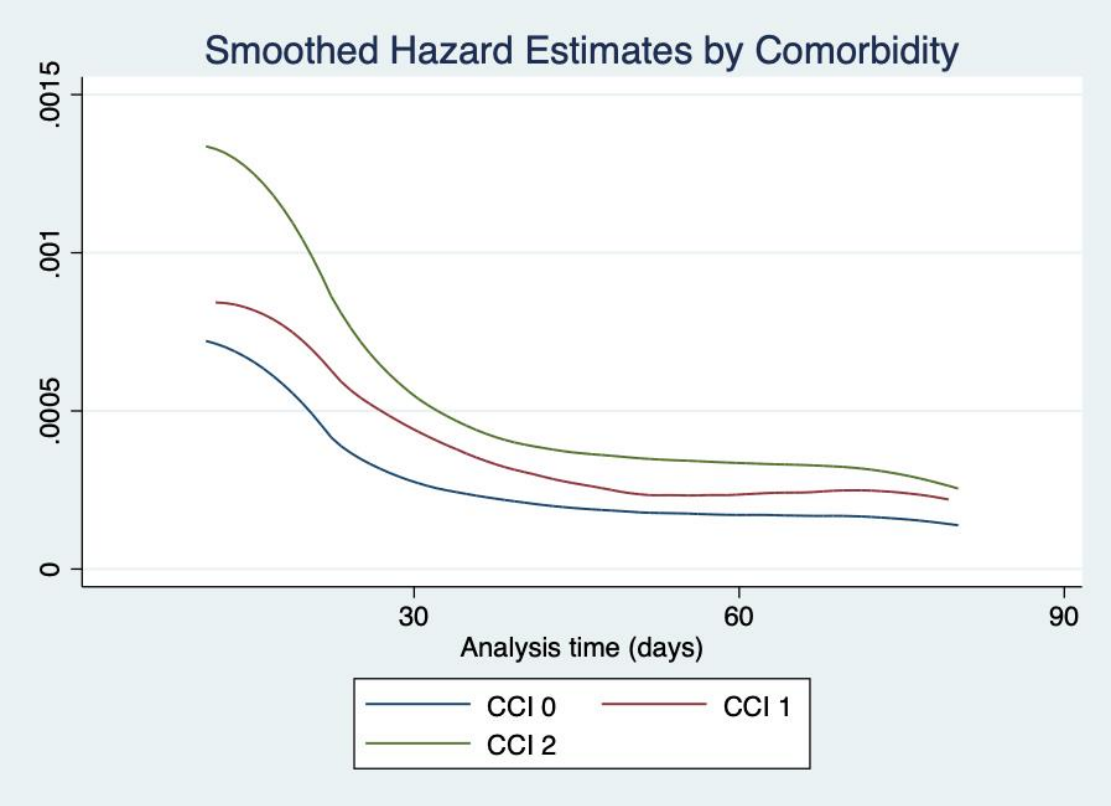
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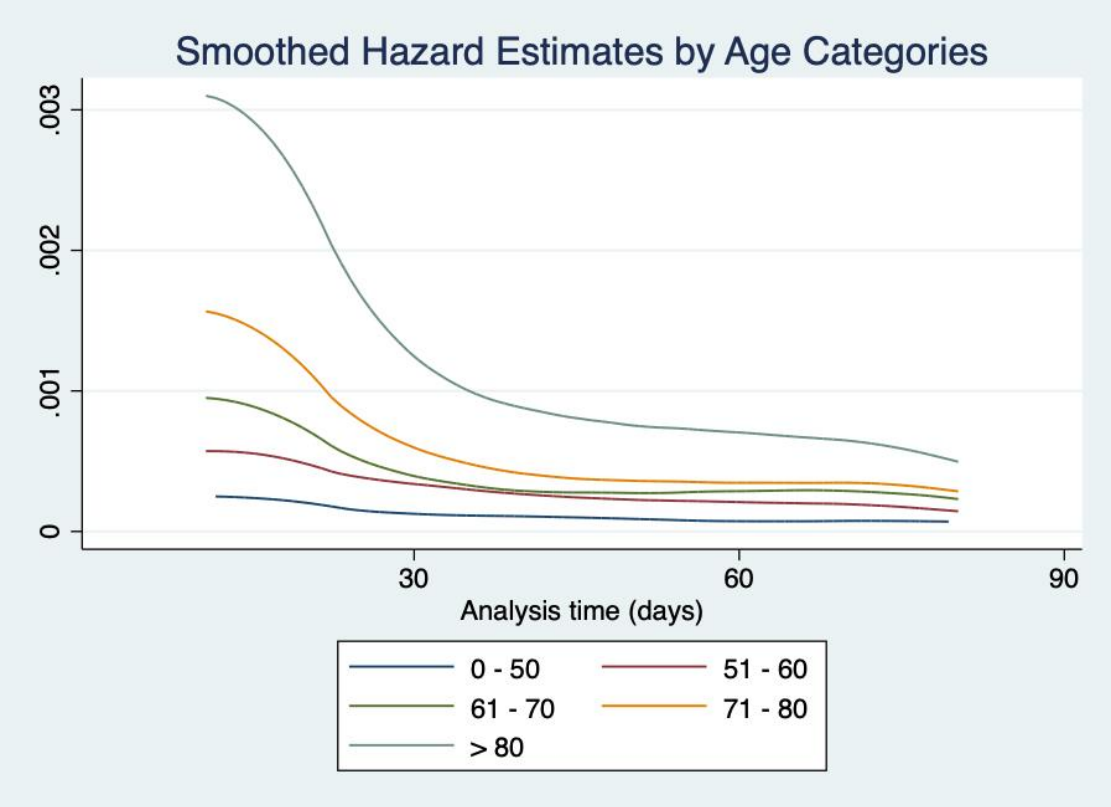
8 Appendices



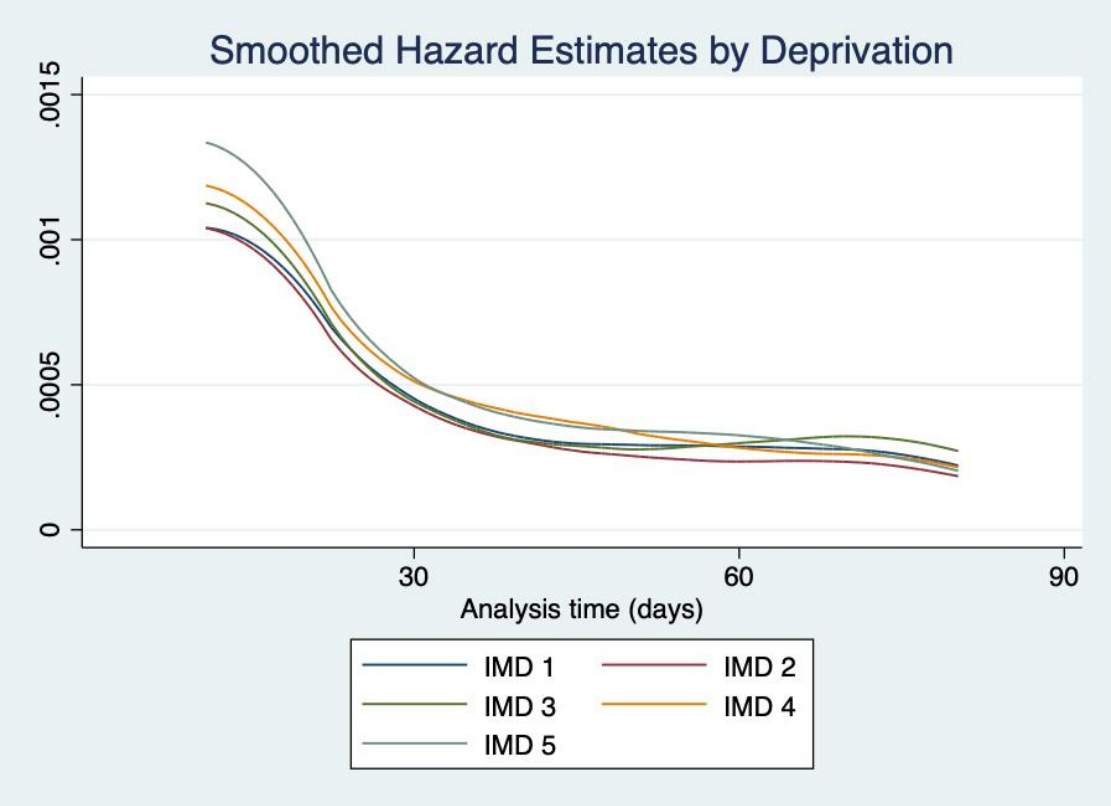
Appendix 1 Figure 1: Distribution of HbA1c values in all patients with diabetes.



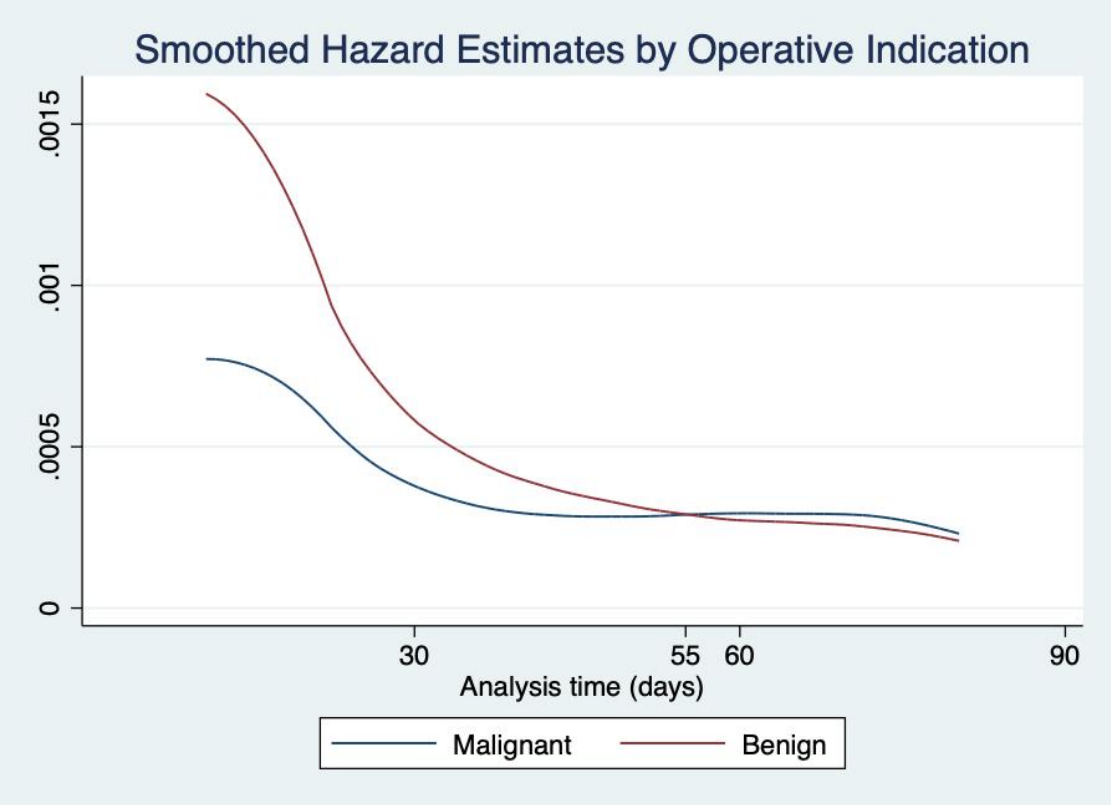
Appendix 2 Figure 2: Smoothed hazard functions stratified by comorbidity group. CCI = Charlson Comorbidity Index



Appendix 3 Figure 3: Smoothed hazard functions by age category in years.



Appendix 4 Figure 4: Smoothed hazard functions stratified by deprivation. IMD = Index of Multiple Deprivation 2015



Appendix 5 Figure 5: Smoothed hazard functions stratified by operative indication.

Appendix 6 Table 1: HES and ICD-10 Codelists

Codes used to identify colectomy, inflammatory bowel disease (IBD), diverticular disease (DD), minimally-invasive surgery (MIS) and diabetes mellitus (DM):
Colectomy (OPCS-4 and ICD-10 codes) H041, H042, H043, H048, H049, H051, H052, H053, H058, H059, H061, H062, H063, H064, H068, H069, H071, H072, H073, H074, H078, H079, H081, H082, H083, H084, H085, H088, H089, H091, H092, H093, H094, H095, H098, H099, H101, H102, H103, H104, H105, H108, H109, H111, H112, H113, H114, H115, H118, H119, H291, H292, H293, H294, H298, H299, H331, H332, H333, H334, H335, H336, H337, H338, H339
IBD (OPCS-4 and ICD-10 codes) K50, K500, K501, K508, K509, K51, K510, K512, K513, K514, K515, K518, K519, K520, K521, K522, K523, K528, K529
DD (OPCS-4 and ICD-10 codes) K57, K570, K571, K572, K573, K574, K575, K578, K579
MIS (OPCS-4 codes) Y50.8, Y57.1, Y75.2, Y75.3
DM (ICD-10) E100, E101, E102, E103, E104, E105, E106, E107, E108, E109, E110, E111, E112, E113, E114, E115, E116, E117, E118, E119, E120, E121, E122, E123, E124, E125, E126, E127, E128, E129, E130, E131, E132, E133, E134, E135, E136, E137, E138, E139, E140, E141, E142, E143, E144, E145, E146, E147, E148, E149, O240, O241, O242, O243, O244, O249

Appendix 7 Table 2: CPRD Codelists for Diabetes

Read Code	Term
66AJ1	Brittle diabetes
C10E	Type 1 diabetes mellitus
F4201	Proliferative diabetic retinopathy
66A8	Has seen dietician - diabetes
C10F	Type 2 diabetes mellitus
1434	H/O: diabetes mellitus
8H3O	Non-urgent diabetic admission
C10F4-1	Type II diabetes mellitus with ulcer
C10A1	Malnutrition-related diabetes mellitus with ketoacidosis
C10E5-1	Type I diabetes mellitus with ulcer
C10E9	Type 1 diabetes mellitus maturity onset
9OL2	Refuses diabetes monitoring
C10E9-1	Type I diabetes mellitus maturity onset
C10F3	Type 2 diabetes mellitus with multiple complications
C10A7	Malnutrition-related diabetes mellitus without complications
9OL1	Attends diabetes monitoring
F3721	Chronic painful diabetic neuropathy
C10F3-1	Type II diabetes mellitus with multiple complications
F3720	Acute painful diabetic neuropathy
F3722	Asymptomatic diabetic neuropathy
66AD	Fundoscopy - diabetic check
C10E5	Type 1 diabetes mellitus with ulcer
C10F4	Type 2 diabetes mellitus with ulcer
K01x1	Nephrotic syndrome in diabetes mellitus
66A9	Understands diet - diabetes
66AT	Annual diabetic blood test
F4203	Advanced diabetic maculopathy
L1806	Pre-existing diabetes mellitus, non-insulin-dependent
L1807	Pre-existing malnutrition-related diabetes mellitus
M2711	Neuropathic diabetic ulcer - foot
M0372	Cellulitis in diabetic foot
M2710	Ischaemic ulcer diabetic foot
M2712	Mixed diabetic ulcer - foot
K08yA-1	Clinical diabetic nephropathy
9N2i	Seen by diabetic liaison nurse

K08yA	Proteinuric diabetic nephropathy
C10F9	Type 2 diabetes mellitus without complication
C10EA-1	Type I diabetes mellitus without complication
C10EE-1	Type I diabetes mellitus with hypoglycaemic coma
C10EH-1	Type I diabetes mellitus with arthropathy
C10FF	Type 2 diabetes mellitus with peripheral angiopathy
C10E4-1	Unstable type I diabetes mellitus
C10E4	Unstable type 1 diabetes mellitus
C10EA	Type 1 diabetes mellitus without complication
C10FG	Type 2 diabetes mellitus with arthropathy
C10EH	Type 1 diabetes mellitus with arthropathy
C10D-1	Maturity onset diabetes in youth type 2
2G5A	O/E - Right diabetic foot at risk
3881	Education score - diabetes
C10FH-1	Type II diabetes mellitus with neuropathic arthropathy
C10FH	Type 2 diabetes mellitus with neuropathic arthropathy
2BBV	O/E - left eye proliferative diabetic retinopathy
F3813	Myasthenic syndrome due to diabetic amyotrophy
9N1v	Seen in diabetic eye clinic
C109G	Non-insulin dependent diabetes mellitus with arthropathy
2BBT	O/E - right eye proliferative diabetic retinopathy
F4206	Non proliferative diabetic retinopathy
2G5B	O/E - Left diabetic foot at risk
14F4	H/O: Admission in last year for diabetes foot problem
9OLB	Attended diabetes structured education programme
C109J-1	Insulin treated non-insulin dependent diabetes mellitus
2G5E	O/E - Right diabetic foot at low risk
2BBQ	O/E - left eye background diabetic retinopathy
7276	Pan retinal photocoagulation for diabetes
8CP2	Transition of diabetes care options discussed
2G5G	O/E - Right diabetic foot at high risk
F4207	High risk proliferative diabetic retinopathy
2G5J	O/E - Left diabetic foot at moderate risk
8Hj0	Referral to diabetes structured education programme
2G5W	O/E - left chronic diabetic foot ulcer
2BBS	O/E - left eye preproliferative diabetic retinopathy
C10FK	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10F-1	Type II diabetes mellitus

C10E-1	Type I diabetes mellitus
C10EL	Type 1 diabetes mellitus with persistent microalbuminuria
2G5H	O/E - Right diabetic foot - ulcerated
2G5L	O/E - Left diabetic foot - ulcerated
9NN8	Under care of diabetologist
8HHy	Referral to diabetic register
9M00	Informed consent for diabetes national audit
8HTi	Referral to multidisciplinary diabetic clinic
9N4p	Did not attend diabetic retinopathy clinic
9N0o	Seen in community diabetic specialist nurse clinic
2G5F	O/E - Right diabetic foot at moderate risk
9N1i	Seen in diabetic foot clinic
9360	Patient held diabetic record issued
C10M0	Lipoatrophic diabetes mellitus without complication
9N0n	Seen in community diabetes specialist clinic
9NND	Under care of diabetic foot screener
8Hj4	Referral to DESMOND diabetes structured education programme
9OLJ	DAFNE diabetes structured education programme completed
9OLG	Attended XPERT diabetes structured education programme
8I82	Did not complete DAFNE diabetes structured education program
8I81	Did not complete diabetes structured education programme
8Hj3	Referral to DAFNE diabetes structured education programme
9NiA	Did not attend diabetes structured education programme
9NiC	Did not attend DAFNE diabetes structured education programme
C10FS	Maternally inherited diabetes mellitus
9OLL	XPERT diabetes structured education programme completed
2BBr	Impaired vision due to diabetic retinopathy
9m06	Excluded from diabetic retinopathy screening as deceased
9m08	Excluded from diabetic retinopathy screening as blind
9N0m	Seen in diabetic nurse consultant clinic
EMISR4QIN2	Ins-treat non-ins-dep diab mel
L180-99	Preg.+ diabetes mellitus
EMISQLE12	Left diabetic maculopathy
EMISQLE17	Left diabetic foot low current risk
EMISQLE9	Left preproliferative diabetic retinopathy
EMISQRI13	Right advanced diabetic retinal disease
EMISQRI14	Right diabetic foot active ulceration
EMISQLA1	Laser treated diabetic retinopathy

EMISQLE11	Left laser treated diabetic retinopathy
EMISQRI15	Right diabetic foot high risk
EMISQLE13	Left advanced diabetic retinal disease
EMISQRI8	Right non-proliferative diabetic retinopathy
EMISQLE15	Left diabetic foot high risk
EMISQLE8	Left non-proliferative diabetic retinopathy
EMISQRI16	Right diabetic foot moderate risk
EMISQRI17	Right diabetic foot low current risk
EMISQRI11	Right laser treated diabetic retinopathy
EMISQLE10	Left proliferative diabetic retinopathy
EMISQLE16	Left diabetic foot moderate risk
EMISQRI12	Right diabetic maculopathy
ALLERGY3148	Adverse reaction to Minodiab
C10A-1	Jamaica type diabetes
EMISNQIN24	Ineligibility for diabetic eye screening: No contact details
66AQ1	Declined consent for diabetes year of care programme
66At1-1	Type 2 diabetic dietary review
66At0	Type I diabetic dietary review
66At1	Type II diabetic dietary review
2G5e	O/E - Right diabetic foot at increased risk
EMISNQRE56	Referral for diabetic retinopathy screening
EMISNQIN23	Ineligibility for diabetic eye screening: Persistent DNA
EMISNQIN25	Ineligibility for diab. eye screening: Declined to participate
EMISNQIN27	Ineligibility for diab. eye screen: Blind (screening contraind)
EMISNQIN33	Ineligibility for diabetic eye screening: Physical disability
9NiZ	Did not attend diabetes foot screening
EMISNQSE63	Seen in in-house nurse-led diabetic clinic
EMISNQDI79	DIDMOAD - Diabetes insip, diabetes mell, optic atrophy, deafness
EMISNQIN165	In-house diabetes foot screen discharge
EMISNQIN162	In-house diabetes foot screening
EMISNQDA12	Date other antidiabetic drug started
EMISNQAD61	Advised about diabetes and driving
EMISNQHO54	Home visit for diabetes monitoring
EMISNQAC841	Access to online patient diabetes education given
EMISNQIN163	In-house diabetes foot screen first appointment
EMISNQIN164	In-house diabetes foot screen follow-up appointment
EMISNQUN46	Unsuitable for DESMOND diabetes structured education programme
EMISNQPA381	Patient in diabetes study

8HTE1	Referral to community diabetes clinic
8OA3	Provision of written information about diabetes and driving
K27y7	Erectile dysfunction due to diabetes mellitus
9NJy	In-house diabetic foot screening
8Hlc	Referral to community diabetes service
679L2	Education about diabetes and driving
9NJy0	In-house diabetic foot screening first appointment
66o3	Has diabetes identity card
EMISNQ3D9	3D study - problems with diabetes management
66o1	Enquiry about diabetic erectile dysfunction declined
EMISNQLI60	Liverpool diabetes pilot - support option 4
9NJy1	In-house diabetic foot screening follow-up appointment
66AH2	Conversion to insulin by diabetes specialist nurse
ESCTSE11	Secondary endocrine diabetes mellitus
ESCTMA7	Malnutrition-related diabetes mellitus - fibrocalculous
ESCTDI18-1	Genetic syndromes of diabetes mellitus
ESCTPH1	Photomyoclonus, diabetes mellitus, deafness, nephropathy and cerebral dysfunction
ESCTIN27	Insulin-dependent diabetes mellitus secretory diarrhoea syndrome
ESCTME15	Megaloblastic anaemia, thiamine-responsive, with diabetes mellitus and sensorineural deafness
ESCTLI13	Lipodystrophy, partial, with Rieger anomaly, short stature, and insulinopenic diabetes mellitus
9NlP1	Seen by diabetes specialist nurse
EMISNQNE23	Newly diagnosed diabetes
ESCTAB10	Abnormal metabolic state in diabetes mellitus
ESCTIN27-1	Congenital insulin-dependent diabetes mellitus with fatal secretory diarrhoea
67HA	Lifestyle education for diabetes
9NN91	Under care of community-based diabetes specialist nurse
67D8	Provision of diabetes clinical summary
EMISNQLI56	Liverpool diabetes pilot administration
EMISNQLI58	Liverpool diabetes pilot - support option 2
ESCTHY3	Hyperglycaemic crisis in diabetes mellitus
EMISNQLI59	Liverpool diabetes pilot - support option 3
9NN90	Under care of hospital-based diabetes specialist nurse
ESCTHY2	Hypogonadism, diabetes mellitus, alopecia, mental retardation and electrocardiographic abnormalities
C1001-2	Non-insulin dependent diabetes mellitus
EMISNQHO137	H/O: hypoglycaemic event in diabetes

C10F7-1	Type II diabetes mellitus - poor control
C10E8-1	Type I diabetes mellitus - poor control
EMISNQKE155	Keele ENHANCE trial - diabetic review
Lyu29	[X]Pre-existing diabetes mellitus, unspecified
R0542	[D]Gangrene of toe in diabetic
EMISNQLI57	Liverpool diabetes pilot - support option 1
Kyu03	[X]Glomerular disorders in diabetes mellitus
C104y	Other specified diabetes mellitus with renal complications
C10C-2	Maturity onset diabetes in youth type 1
R0543	[D]Widespread diabetic foot gangrene
C10EJ-1	Type I diabetes mellitus with neuropathic arthropathy
C10E8	Type 1 diabetes mellitus - poor control
Cyu20	[X]Other specified diabetes mellitus
C108-2	Type 1 diabetes mellitus
C108E-2	Type 1 diabetes mellitus with hypoglycaemic coma
C1083-2	Type 1 diabetes mellitus with multiple complications
C108D-2	Type 1 diabetes mellitus with nephropathy
C1080-2	Type 1 diabetes mellitus with renal complications
C1087-2	Type 1 diabetes mellitus with retinopathy
C1089-2	Type 1 diabetes mellitus maturity onset
C109-2	Type 2 diabetes mellitus
C1099-2	Type 2 diabetes mellitus without complication
C1082-1	Type I diabetes mellitus with neurological complications
C1080-1	Type I diabetes mellitus with renal complications
C109G-1	Type II diabetes mellitus with arthropathy
C108y	Other specified diabetes mellitus with multiple comps
C109C-2	Type 2 diabetes mellitus with nephropathy
C1091-2	Type 2 diabetes mellitus with ophthalmic complications
C108D-1	Type I diabetes mellitus with nephropathy
C1090-1	Type II diabetes mellitus with renal complications
9h42	Excepted from diabetes quality indicators: Informed dissent
C109B	Non-insulin dependent diabetes mellitus with polyneuropathy
C109	Non-insulin dependent diabetes mellitus
C10FR	Type 2 diabetes mellitus with gastroparesis
C10zy	Other specified diabetes mellitus with unspecified comps
C11y0	Steroid induced diabetes
679L	Health education - diabetes
C1088-2	Type 1 diabetes mellitus - poor control

C109B-2	Type 2 diabetes mellitus with polyneuropathy
C1083-1	Type I diabetes mellitus with multiple complications
C108A-1	Type I diabetes mellitus without complication
C109-3	Type II diabetes mellitus
C1094-1	Type II diabetes mellitus with ulcer
C108H-2	Type 1 diabetes mellitus with arthropathy
C108C-2	Type 1 diabetes mellitus with polyneuropathy
C108A-2	Type 1 diabetes mellitus without complication
C1097-2	Type 2 diabetes mellitus - poor control
C1096-2	Type 2 diabetes mellitus with retinopathy
C108E-1	Type I diabetes mellitus with hypoglycaemic coma
C108C-1	Type I diabetes mellitus with polyneuropathy
C1085-1	Type I diabetes mellitus with ulcer
C1096-1	Type II diabetes mellitus with retinopathy
C1097	Non-insulin dependent diabetes mellitus - poor control
C108J-2	Type 1 diabetes mellitus with neuropathic arthropathy
C109G-2	Type 2 diabetes mellitus with arthropathy
C109F-2	Type 2 diabetes mellitus with peripheral angiopathy
C1088-1	Type I diabetes mellitus - poor control
C108H-1	Type I diabetes mellitus with arthropathy
C109E-1	Type II diabetes mellitus with diabetic cataract
8CA41	Pt advised re diabetic diet
Q440	'Infant of a diabetic mother' syndrome
C10G0	Secondary pancreatic diabetes mellitus without complication
C109D-2	Type 2 diabetes mellitus with hypoglycaemic coma
C1090-2	Type 2 diabetes mellitus with renal complications
C1094	Non-insulin dependent diabetes mellitus with ulcer
C109E	Non-insulin depend diabetes mellitus with diabetic cataract
L180X	Pre-existing diabetes mellitus, unspecified
C1094-2	Type 2 diabetes mellitus with ulcer
C108B-1	Type I diabetes mellitus with mononeuropathy
C109F-1	Type II diabetes mellitus with peripheral angiopathy
C109A	Non-insulin dependent diabetes mellitus with mononeuropathy
C1085-2	Type 1 diabetes mellitus with ulcer
C1092-2	Type 2 diabetes mellitus with neurological complications
C108F-1	Type I diabetes mellitus with diabetic cataract
C1093-1	Type II diabetes mellitus with multiple complications
C109C-1	Type II diabetes mellitus with nephropathy

C10FD	Type 2 diabetes mellitus with hypoglycaemic coma
TJ23	Adverse reaction to insulins and antidiabetic agents
Cyu22	[X]Malnutrit-related diabetes mellitus with unspec complics
C1096	Non-insulin-dependent diabetes mellitus with retinopathy
2BBF	Retinal abnormality - diabetes related
C10N0	Secondary diabetes mellitus without complication
C1090	Non-insulin-dependent diabetes mellitus with renal comps
66AA-1	Injection sites - diabetic
C10EQ-1	Type I diabetes mellitus with gastroparesis
9m07	Excluded diabetc retinop screen as under care ophthalmolgist
PKyP	Diab insipidus,diab mell,optic atrophy and deafness
8I84	Did not complete XPERT diabetes structured education program
9m0D	Excluded from diabetic retinopthy screen as learn disability
C1091	Non-insulin-dependent diabetes mellitus with ophthalm comps
67W1	Recommendation self-refer for diabetes structured education
C10Q	Maturity onset diabetes of the young type 5
L1805	Pre-existing diabetes mellitus, insulin-dependent
C10EA-2	Insulin-dependent diabetes without complication
C108E	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10ED-2	Insulin dependent diabetes mellitus with nephropathy
C10EH-2	Insulin dependent diabetes mellitus with arthropathy
C108F	Insulin dependent diabetes mellitus with diabetic cataract
C108J	Insulin dependent diab mell with neuropathic arthropathy
C108-1	IDDM-Insulin dependent diabetes mellitus
C10E3-2	Insulin dependent diabetes mellitus with multiple complicat
C108B	Insulin dependent diabetes mellitus with mononeuropathy
C108C	Insulin dependent diabetes mellitus with polyneuropathy
C108G	Insulin dependent diab mell with peripheral angiopathy
C10E9-2	Insulin dependent diabetes maturity onset
C10EB-2	Insulin dependent diabetes mellitus with mononeuropathy
C10EJ-2	Insulin dependent diab mell with neuropathic arthropathy
C1087	Insulin dependent diabetes mellitus with retinopathy
C10E7-2	Insulin dependent diabetes mellitus with retinopathy
C10FR-1	Type II diabetes mellitus with gastroparesis
8I83	Did not complete DESMOND diabetes structured educat program
9NiD	Did not attend DESMOND diabetes structured education program
8IEa	Referral to DAFNE diabetes structured educn prog declined
679L2-1	Advice about diabetes and driving

C108z	Unspecified diabetes mellitus with multiple complications
C108A	Insulin-dependent diabetes without complication
C1089	Insulin dependent diabetes maturity onset
C10ED-1	Type I diabetes mellitus with nephropathy
C10FM	Type 2 diabetes mellitus with persistent microalbuminuria
C10EP	Type 1 diabetes mellitus with exudative maculopathy
C10E7	Type 1 diabetes mellitus with retinopathy
C10EF-1	Type I diabetes mellitus with diabetic cataract
C10FD-1	Type II diabetes mellitus with hypoglycaemic coma
C10F0-1	Type II diabetes mellitus with renal complications
C10F2	Type 2 diabetes mellitus with neurological complications
C10FA-1	Type II diabetes mellitus with mononeuropathy
C10FB-1	Type II diabetes mellitus with polyneuropathy
^ESCTNO698127	Non-ketotic non-hyperosmolar coma associated with diabetes mellitus
C10M	Lipoatrophic diabetes mellitus
C10EE-2	Insulin dependent diabetes mellitus with hypoglycaemic coma
2G510	Foot abnormality - diabetes related
C108H	Insulin dependent diabetes mellitus with arthropathy
C10EG	Type 1 diabetes mellitus with peripheral angiopathy
C1084	Unstable insulin dependent diabetes mellitus
C1081-1	Type I diabetes mellitus with ophthalmic complications
C108G-1	Type I diabetes mellitus with peripheral angiopathy
9OLP	X-PERT First Steps diabetes self-management programme complt
Cyu23	[X]Unspecified diabetes mellitus with renal complications
C10EG-2	Insulin dependent diab mell with peripheral angiopathy
2G5C	Foot abnormality - diabetes related
C1082	Insulin-dependent diabetes mellitus with neurological comps
C1080	Insulin-dependent diabetes mellitus with renal complications
C108	Insulin dependent diabetes mellitus
C10E1-2	Insulin-dependent diabetes mellitus with ophthalmic comps
C10EC-2	Insulin dependent diabetes mellitus with polyneuropathy
C10EF-2	Insulin dependent diabetes mellitus with diabetic cataract
C10E6-1	Type I diabetes mellitus with gangrene
^ESCTHY812040	Hyperosmolar coma due to secondary diabetes mellitus
8H2J	Admit diabetic emergency
^ESCTLU786380	Lumbosacral plexopathy co-occurrent and due to diabetes mellitus
C10F0	Type 2 diabetes mellitus with renal complications
C10FC	Type 2 diabetes mellitus with nephropathy

C10FC-1	Type II diabetes mellitus with nephropathy
C10EK-1	Type I diabetes mellitus with persistent proteinuria
C10EL-1	Type I diabetes mellitus with persistent microalbuminuria
C10FL	Type 2 diabetes mellitus with persistent proteinuria
C1083	Insulin dependent diabetes mellitus with multiple complication
C1000-1	Insulin dependent diabetes mellitus
C10E0-2	Insulin-dependent diabetes mellitus with renal complications
2BBW	O/E - right eye diabetic maculopathy
679R	Patient offered diabetes structured education programme
^ESCTLU786381	Lumbosacral plexopathy with diabetes mellitus
^ESCTPR351158	Pretibial pigmental patches in diabetes
^ESCTDE781181	DEND (developmental delay, epilepsy, neonatal diabetes) syndrome
C109J-2	Insulin treated Type II diabetes mellitus
C10E3-1	Type I diabetes mellitus with multiple complications
C10EK	Type 1 diabetes mellitus with persistent proteinuria
C10FN	Type 2 diabetes mellitus with ketoacidosis
2BBl	O/E - left eye stable treated prolif diabetic retinopathy
ZV653-2	[V]Dietary counselling in diabetes mellitus
C10F5-1	Type II diabetes mellitus with gangrene
F4208	High risk non proliferative diabetic retinopathy
C109K	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10ED	Type 1 diabetes mellitus with nephropathy
C10F6-1	Type II diabetes mellitus with retinopathy
C10FE	Type 2 diabetes mellitus with diabetic cataract
C10EF	Type 1 diabetes mellitus with diabetic cataract
C10FQ	Type 2 diabetes mellitus with exudative maculopathy
C10E1	Type 1 diabetes mellitus with ophthalmic complications
C1095-2	Type 2 diabetes mellitus with gangrene
C109J	Insulin treated Type 2 diabetes mellitus
66AX	Diabetes: shared care in pregnancy - diabetol and obstet
C10E3	Type 1 diabetes mellitus with multiple complications
C10E7-1	Type I diabetes mellitus with retinopathy
C10EC	Type 1 diabetes mellitus with polyneuropathy
C10F1	Type 2 diabetes mellitus with ophthalmic complications
C10F2-1	Type II diabetes mellitus with neurological complications
C10FN-1	Type II diabetes mellitus with ketoacidosis
C10EP-1	Type I diabetes mellitus with exudative maculopathy
C1095-1	Type II diabetes mellitus with gangrene

C1085	Insulin dependent diabetes mellitus with ulcer
^ESCTRA786157	Radiculoplexoneuropathy due to diabetes mellitus
^ESCT1169219	Acute complication with diabetes mellitus
^ESCTDI796695	Diabetic angina pectoris associated with type 2 diabetes mellitus
C10E6	Type 1 diabetes mellitus with gangrene
C10AW	Malnutrit-related diabetes mellitus with unspec complics
^ESCTAT1163321	Atypical diabetes mellitus
^ESCT1169220	Acute complication co-occurrent and due to diabetes mellitus
^ESCTPR803330	Pre-existing diabetes mellitus in childbirth
C10A4	Malnutrition-related diabetes mellitus wth neuro complicatns
C10A5	Malnutritn-relat diabetes melitus wth periph circul complctn
C10EB	Type 1 diabetes mellitus with mononeuropathy
C10FA	Type 2 diabetes mellitus with mononeuropathy
C1086-2	Type 1 diabetes mellitus with gangrene
^ESCTGI764468	Gingivitis co-occurrent with diabetes mellitus
C10A2	Malnutrition-related diabetes mellitus with renal complicatn
^ESCTAD1163322	ADM - atypical diabetes mellitus
^ESCTAN796694	Angina associated with type II diabetes mellitus
66Af	Patient diabetes education review
C106y	Other specified diabetes mellitus with neurological comps
2BBX	O/E - left eye diabetic maculopathy
C109D	Non-insulin dependent diabetes mellitus with hypoglyca coma
C10EQ	Type 1 diabetes mellitus with gastroparesis
C109H-1	Type II diabetes mellitus with neuropathic arthropathy
C10A	Malnutrition-related diabetes mellitus
L180B	Pre-existing type 2 diabetes mellitus in pregnancy
C10FP-1	Type II diabetes mellitus with ketoacidotic coma
EMISNQLI61	Liverpool diabetes pilot - support option 5
^ESCTPR750021	Pre-existing diabetes mellitus in pregnancy
C10A3	Malnutrit-related diabetes mellitus wth ophthalmic complicat
C10AX	Malnutrit-relat diabetes mellitus with other spec comps
C10FG-1	Type II diabetes mellitus with arthropathy
F1711	Autonomic neuropathy due to diabetes
EMISNQNE127	New diabetic foot ulcer
ESCTPR17	Protein-deficient diabetes mellitus
C10F6	Type 2 diabetes mellitus with retinopathy
C10EM-1	Type I diabetes mellitus with ketoacidosis
C10EN-1	Type I diabetes mellitus with ketoacidotic coma

C10FL-1	Type II diabetes mellitus with persistent proteinuria
C10FM-1	Type II diabetes mellitus with persistent microalbuminuria
C10FP	Type 2 diabetes mellitus with ketoacidotic coma
C10FQ-1	Type II diabetes mellitus with exudative maculopathy
C109B-1	Type II diabetes mellitus with polyneuropathy
C1081	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E8-2	Insulin dependent diabetes mellitus - poor control
C10EG-1	Type I diabetes mellitus with peripheral angiopathy
8OAL	Provision of diabetes identity card
8Hj5	Referral to XPERT diabetes structured education programme
66AN	Date diabetic treatment start
C1084-1	Unstable type I diabetes mellitus
C109E-2	Type 2 diabetes mellitus with diabetic cataract
C10FF-1	Type II diabetes mellitus with peripheral angiopathy
F4200	Background diabetic retinopathy
2BBP	O/E - right eye background diabetic retinopathy
C10E2	Type 1 diabetes mellitus with neurological complications
C10F7	Type 2 diabetes mellitus - poor control
C1087-1	Type I diabetes mellitus with retinopathy
9m0C	Excluded frm diabetic retinopathy screen as terminal illness
C10E-2	Insulin dependent diabetes mellitus
C10E2-2	Insulin-dependent diabetes mellitus with neurological comps
C108B-2	Type 1 diabetes mellitus with mononeuropathy
C1092	Non-insulin-dependent diabetes mellitus with neuro comps
C108J-1	Type I diabetes mellitus with neuropathic arthropathy
C103y	Other specified diabetes mellitus with coma
C108-3	Type I diabetes mellitus
C10EC-1	Type I diabetes mellitus with polyneuropathy
C10EN	Type 1 diabetes mellitus with ketoacidotic coma
C105y	Other specified diabetes mellitus with ophthalmic complicatn
EMISNQIN28	Ineligibility for diabetic eye screening: Under ophthalmic care
C1086	Insulin dependent diabetes mellitus with gangrene
C10E6-2	Insulin dependent diabetes mellitus with gangrene
C10F1-1	Type II diabetes mellitus with ophthalmic complications
C10F5	Type 2 diabetes mellitus with gangrene
C1089-1	Type I diabetes mellitus maturity onset
C109D-1	Type II diabetes mellitus with hypoglycaemic coma
66At0-1	Type 1 diabetic dietary review

2G5d	O/E - Left diabetic foot at increased risk
8BL2	Patient on maximal tolerated therapy for diabetes
93C4	Patient consent given for addition to diabetic register
9NN9	Under care of diabetes specialist nurse
2G5I	O/E - Left diabetic foot at low risk
EMISNQRE335	Reason for influenza vaccine - diabetes mellitus
C10yz-97	Hypo states in diabetes
2BBL	O/E - diabetic maculopathy present both eyes
9M10	Informed dissent for diabetes national audit
C10FJ-1	Insulin treated Type II diabetes mellitus
F372	Polyneuropathy in diabetes
C108D	Insulin dependent diabetes mellitus with nephropathy
C10N	Secondary diabetes mellitus
9OLK	DESMOND diabetes structured education programme completed
EMISTO1	Patient has been told has diabetes
EMISNQSI2	Six month diabetic review
C10E5-2	Insulin dependent diabetes mellitus with ulcer
^ESCTPR803329	Pre-existing diabetes mellitus in mother complicating childbirth
^ESCTAN796693	Angina associated with type 2 diabetes mellitus
C10EJ	Type 1 diabetes mellitus with neuropathic arthropathy
C10FJ	Insulin treated Type 2 diabetes mellitus
^ESCTGI774616	Gingival disease co-occurrent with diabetes mellitus
C108F-2	Type 1 diabetes mellitus with diabetic cataract
C1095	Non-insulin dependent diabetes mellitus with gangrene
ESCTPR17-1	Malnutrition-related diabetes mellitus - protein-deficient
EMISNQIN34	Ineligib for diab. eye screening: Learning or mental disability
C109H-2	Type 2 diabetes mellitus with neuropathic arthropathy
C109A-1	Type II diabetes mellitus with mononeuropathy
C10N1	Cystic fibrosis related diabetes mellitus
L180A	Pre-existing type 1 diabetes mellitus in pregnancy
C109A-2	Type 2 diabetes mellitus with mononeuropathy
C10C-1	Maturity onset diabetes in youth
C107y	Other specified diabetes mellitus with periph circ comps
Cyu21	[X]Malnutrit-relat diabetes mellitus with other spec comps
C1091-1	Type II diabetes mellitus with ophthalmic complications
C1099-1	Type II diabetes mellitus without complication
67IJ1	Pre-conception advice for diabetes mellitus
2BBk	O/E - right eye stable treated prolif diabetic retinopathy

C10yy	Other specified diabetes mellitus with other spec comps
C10E4-2	Unstable insulin dependent diabetes mellitus
C1082-2	Type 1 diabetes mellitus with neurological complications
C1086-1	Type I diabetes mellitus with gangrene
C10A6	Malnutrition-related diabetes mellitus with multiple comps
EMISQRI9	Right preproliferative diabetic retinopathy
9N1o	Seen in multidisciplinary diabetic clinic
C10FK-1	Hyperosmolar non-ketotic state in type II diabetes mellitus
9OLH	Attended DAFNE diabetes structured education programme
U6023-E	[X] Adverse reaction to insulins and antidiabetic agents NOS
9m0E	Excluded from diabetic retinopathy screen physical disorder
C10E0-1	Type I diabetes mellitus with renal complications
C10E2-1	Type I diabetes mellitus with neurological complications
C1081-2	Type 1 diabetes mellitus with ophthalmic complications
C10E1-1	Type I diabetes mellitus with ophthalmic complications
TJ23z	Adverse reaction to insulins and antidiabetic agents NOS
C1093-2	Type 2 diabetes mellitus with multiple complications
C1097-1	Type II diabetes mellitus - poor control
C10E0	Type 1 diabetes mellitus with renal complications
C10FB	Type 2 diabetes mellitus with polyneuropathy
C10A0	Malnutrition-related diabetes mellitus with coma
F4205	Advanced diabetic retinal disease
EMISNQIN35	Ineligibility for diabetic eye screening: Terminal illness
EMISNQDE12	Declined referral to DESMOND diabet. structured educat programme
F4202	Preproliferative diabetic retinopathy
8H7r	Refer to diabetic foot screener
C10F9-1	Type II diabetes mellitus without complication
C10G	Secondary pancreatic diabetes mellitus
2BBR	O/E - right eye preproliferative diabetic retinopathy
9m0B	Excluded frm diab retinop screen as no currnt contct details
EMISNQIN30	Ineligibility for diabetic eye screening: Moved away
C10EB-1	Type I diabetes mellitus with mononeuropathy
C10FE-1	Type II diabetes mellitus with diabetic cataract
C10EM	Type 1 diabetes mellitus with ketoacidosis
9m0A	Declined diabetic retinopathy screening
EMISQRI10	Right proliferative diabetic retinopathy
9m05	Excluded from diabetic retinopathy screening as moved away
C10EE	Type 1 diabetes mellitus with hypoglycaemic coma

2BBo	O/E - sight threatening diabetic retinopathy
2G5V	O/E - right chronic diabetic foot ulcer
2BBG	Retinal abnormality - non-diabetes
TJ23-99	Reaction: insulin/antidiabetic
C1099	Non-insulin-dependent diabetes mellitus without complication
C101y	Other specified diabetes mellitus with ketoacidosis
C1093	Non-insulin-dependent diabetes mellitus with multiple comps
U6023-1	[X] Adverse reaction to insulins and antidiabetic agents
C108G-2	Type 1 diabetes mellitus with peripheral angiopathy
C1088	Insulin dependent diabetes mellitus - poor control
679L0	Education in self management of diabetes
EMISQLE14	Left diabetic foot active ulceration
66AJ-1	Unstable diabetes
C1084-2	Unstable type 1 diabetes mellitus
EMISNQCO167	Conversion to insulin by diabetic specialist nurse
8HTk	Referral to diabetic eye clinic
2G5K	O/E - Left diabetic foot at high risk
9N2d	Seen by diabetologist
8Hl1	Referral for diabetic retinopathy screening
9m00	Eligible for diabetic retinopathy screening
C109-1	NIDDM - Non-insulin dependent diabetes mellitus

Appendix 8 Table 3: CPRD Codelists for Type 1, Type 2 Diabetes and HbA1c

Codes used to identify type 1 diabetes (T1DM), type 2 diabetes (T2DM) and HbA1c:
T1DM (Read Codes) C10E4-1, C1084-1, C10E4, C1084-2, C1084, C10E4-2, 66At0, C10EA-1, C108A-1, C10E5-1, C1085-1, C10E7-1, C1087-1, C1080-1, C10E0-1, C108C-1, C10EC-1, C10EK-1, C10EL-1, C108G-1, C10EG-1, C1081-1, C10E1-1, C10EJ-1, C108J-1, C1082-1, C10E2-1, C108D-1, C10ED-1, C1083-1, C10E3-1, C108B-1, C10EB-1, C10EN-1, C10EM-1, C10EE-1, C108E-1, C10EQ-1, C10E6-1, C1086-1, C10EP-1, C108F-1, C10EF-1, C10EH-1, C108H-1, C10E9-1, C1089-1, C10E8-1, C1088-1, C10E-1, C108-3, 66At0-1, C10EA, C108A-2, C10E5, C1085-2, C1087-2, C10E7, C1080-2, C10E0, C108C-2, C10EC, C10EK, C10EL, C10EG, C108G-2,

C10E1, C1081-2, C108J-2, C10EJ, C10E2, C1082-2, C108D-2, C10ED, C1083-2, C10E3, C10EB, C108B-2, C10EN, C10EM, C108E-2, C10EE, C10EQ, C10E6, C1086-2, C10EP, C10EF, C108F-2, C10EH, C108H-2, C10E9, C1089-2, C10E8, C1088-2, C10E, C108-2, L180A, L1805, C10EA-2, C108A, C1080, C10E0-2, C10E1-2, C1081, C1082, C10E2-2, ESCTIN27, C1085, C10E5-2, C1087, C10E7-2, C108C, C10EC-2, C10ED-2, C108D, C1083, C10E3-2, C108B, C10EB-2, C108E, C10EE-2, C1086, C10E6-2, C108F, C10EF-2, C10EH-2, C108H, C10E8-2, C1088, C108, C1000-1, C10E-2, C10E9-2, C1089, C108G, C10EG-2, C108J, C10EJ-2, C108-1, ESCTIN27-1
T2DM (Read Codes) 66At1, C1099-1, C10F9-1, C10F4-1, C1094-1, C1096-1, C10F6-1, C1090-1, C10F0-1, C10FB-1, C109B-1, C10FL-1, C10FM-1, C109F-1, C10FF-1, C10F1-1, C1091-1, C10FH-1, C109H-1, C10F2-1, C109C-1, C10FC-1, C10F3-1, C1093-1, C10FA-1, C109A-1, C10FP-1, C10FN-1, C10FD-1, C109D-1, C10FR-1, C10F5-1, C1095-1, C10FQ-1, C109E-1, C10FE-1, C109G-1, C10FG-1, C10F7-1, C1097-1, C10F-1, C109-3, 66At1-1, C10F9, C1099-2, C10F4, C1094-2, C1096-2, C10F6, C1090-2, C10F0, C109B-2, C10FB, C10FL, C10FM, C10FF, C109F-2, C1091-2, C10F1, C10FH, C109H-2, C1092-2, C10F2, C109C-2, C10FC, C10F3, C1093-2, C10FA, C109A-2, C10FP, C10FN, C109D-2, C10FD, C10FR, C1095-2, C10F5, C10FQ, C10FE, C109E-2, C10FG, C109G-2, C1097-2, C10F7, C10F, C109-2, L180B, L1806, C1099, C1096, C1090, C1091, C1092, C1093, C1094, C109B, C109A, C109D, C1095, C109G, C1097, C1001-2, C109, C109E, C109-1, C109J-2, C10FJ-1, C109J, C10FJ, C109J-1, EMISR4QIN2, C10FK-1, C10FK, C109K, ^ESCTDI796695, ^ESCTAN796694, ^ESCTAN796693
HbA1c (Medcode ID) 129761000000114, 1700711000006113, 1753211000006115, 1927791000006119, 1986181000006111, 1986191000006114, 2154205011, 2160141012, 2397571000000119, 2397611000000111, 257619018, 257620012 257621011, 257623014, 3199161000006117, 404444016, 451418011, 453910015, 457953019, 457954013, 803891000006119, 804121000006112, 817471000006110, 817481000006113, 817491000006111

Appendix 9 Table 4: CPRD Directory of Medicines and Devices (DMD) Codelist for Insulin

DMDCode	Drug Name
3284211000001102	Insulin glargine
10250211000001100	Insulin glargine
400780006	Insulin glargine
30172211000001104	Insulin glargine
11933011000001106	Insulin glargine
3283211000001100	Insulin glargine
400877001	Insulin glargine
30171811000001104	Insulin glargine
36082811000001104	Insulin glargine
3468611000001108	Insulin aspart
3279211000001105	Insulin aspart
34043211000001100	Insulin aspart
3281611000001102	Insulin aspart
3282211000001106	Insulin aspart
3468711000001104	Insulin aspart
19570211000001104	Insulin aspart
34043011000001104	Insulin aspart
3277811000001103	Insulin aspart/ Insulin aspart protamine
3277211000001104	Insulin aspart/ Insulin aspart protamine
3268711000001103	Insulin isophane human/ Insulin soluble human
3264711000001106	Insulin isophane human/ Insulin soluble human
3269711000001107	Insulin isophane human/ Insulin soluble human
3273911000001104	Insulin isophane human/ Insulin soluble human
3270211000001103	Insulin isophane human/ Insulin soluble human
3271711000001102	Insulin isophane human/ Insulin soluble human
3267811000001107	Insulin isophane human/ Insulin soluble human
3264411000001100	Insulin isophane human/ Insulin soluble human
3263611000001100	Insulin isophane human/ Insulin soluble human
3266111000001103	Insulin isophane human/ Insulin soluble human
3264111000001105	Insulin isophane human/ Insulin soluble human
3259811000001109	Insulin isophane human/ Insulin soluble human
18150311000001108	Insulin isophane human/ Insulin soluble human
3263011000001107	Insulin isophane human/ Insulin soluble human
3275311000001104	Insulin isophane human/ Insulin soluble human

3274811000001107	Insulin isophane human/ Insulin soluble human
3275011000001102	Insulin isophane human/ Insulin soluble human
3273111000001102	Insulin isophane human/ Insulin soluble human
3273611000001105	Insulin isophane human/ Insulin soluble human
3271611000001106	Insulin isophane human/ Insulin soluble human
3272211000001102	Insulin isophane human/ Insulin soluble human
3270511000001100	Insulin isophane human/ Insulin soluble human
9437511000001100	Insulin isophane human/ Insulin soluble human
17609511000001108	Insulin isophane human/ Insulin soluble human
3285511000001103	Insulin isophane human/ Insulin soluble human
3281211000001104	Insulin isophane human/ Insulin soluble human
3272011000001107	Insulin isophane human/ Insulin soluble human
3273411000001107	Insulin isophane human/ Insulin soluble human
3271011000001104	Insulin isophane human/ Insulin soluble human
3272411000001103	Insulin isophane human/ Insulin soluble human
3272811000001101	Insulin isophane human/ Insulin soluble human
3278611000001103	Insulin isophane human/ Insulin soluble human
3278311000001108	Insulin isophane human/ Insulin soluble human
3274511000001109	Insulin isophane human/ Insulin soluble human
3277711000001106	Insulin isophane porcine/ Insulin soluble porcine
3266811000001105	Insulin isophane porcine/ Insulin soluble porcine
3267911000001102	Insulin isophane porcine/ Insulin soluble porcine
3280011000001100	Insulin isophane bovine
3472311000001106	Insulin isophane bovine
3259411000001107	Insulin isophane human
3255911000001101	Insulin isophane human
3256111000001105	Insulin isophane human
3472511000001100	Insulin isophane human
3258411000001104	Insulin isophane human
3473011000001104	Insulin isophane porcine
3284011000001107	Insulin isophane porcine
3333111000001107	Insulin isophane porcine
3276011000001106	Insulin lispro/ Insulin lispro protamine
13884711000001104	Insulin lispro/ Insulin lispro protamine
13884911000001102	Insulin lispro/ Insulin lispro protamine
3276911000001105	Insulin lispro/ Insulin lispro protamine
3275711000001100	Insulin lispro/ Insulin lispro protamine
3280611000001107	Insulin zinc suspension mixed bovine

4029411000001100	Insulin isophane porcine/ Insulin soluble porcine
4028311000001101	Insulin isophane bovine
4033211000001103	Insulin isophane bovine
4028811000001105	Insulin soluble bovine
4053611000001100	Insulin isophane porcine
4034311000001108	Insulin isophane porcine
4034911000001109	Insulin soluble porcine
7594211000001102	Insulin detemir
7589411000001100	Insulin detemir
11148111000001100	Insulin detemir
7597611000001106	Insulin detemir
7589911000001108	Insulin detemir
9532111000001100	Insulin glulisine
9528311000001104	Insulin glulisine
10898411000001104	Insulin glulisine
10097211000001102	Insulin glulisine
10093311000001104	Insulin glulisine
12144611000001100	Insulin glulisine
10344911000001108	Insulin lispro/ Insulin lispro protamine
10690511000001104	Insulin human
10690811000001108	Insulin human
13859411000001100	Insulin human
18030311000001100	Insulin human
15603111000001104	Insulin human
16530311000001108	Insulin lispro/ Insulin lispro protamine
18083911000001104	Insulin human
18046311000001104	Insulin human
21939511000001100	Insulin degludec
21928511000001108	Insulin degludec
21930011000001100	Insulin degludec
21939611000001100	Insulin degludec
21939711000001104	Insulin degludec
21931911000001108	Insulin degludec
26655811000001104	Insulin aspart
26209611000001108	Insulin aspart
28279611000001108	Insulin degludec/ Liraglutide
28054311000001104	Insulin degludec/ Liraglutide
28989711000001104	Insulin lispro

28926811000001100	Insulin lispro
29903611000001104	Insulin glargine
29866811000001104	Insulin glargine
35214311000001104	Insulin human
3280711000001103	Insulin aspart
36047011000001104	Insulin aspart
34043411000001104	Insulin aspart
3287911000001100	Insulin glargine
36047111000001104	Insulin glargine
9528811000001108	Insulin glulisine
36047211000001104	Insulin glulisine
3263711000001109	Insulin isophane human
3264211000001104	Insulin isophane human
3265011000001108	Insulin isophane human
3261411000001102	Insulin isophane human
3262511000001106	Insulin isophane human
3262011000001103	Insulin isophane human
3260611000001109	Insulin isophane human
3260811000001108	Insulin isophane human
17608511000001104	Insulin isophane human
19354411000001104	Insulin isophane human
3282711000001104	Insulin lispro
36047511000001104	Insulin lispro
3280111000001104	Insulin lispro
36047611000001104	Insulin lispro
35776411000001104	Insulin lispro
3284311000001105	Insulin lispro
35776511000001104	Insulin lispro
36047711000001104	Insulin lispro
3278511000001102	Insulin lispro
13877811000001104	Insulin lispro
36047811000001104	Insulin lispro
35776811000001100	Insulin lispro
35216811000001100	Insulin lispro
3269911000001109	Insulin protamine zinc bovine
36047911000001110	Insulin protamine zinc bovine
3271311000001101	Insulin soluble bovine
3309511000001105	Insulin soluble human

3312111000001108	Insulin soluble human
3312411000001103	Insulin soluble human
3312611000001100	Insulin soluble human
3310711000001105	Insulin soluble human
3311311000001101	Insulin soluble human
3311611000001106	Insulin soluble human
3291711000001105	Insulin soluble human
3288511000001106	Insulin soluble human
3290411000001108	Insulin soluble human
3294911000001105	Insulin soluble human
3285011000001106	Insulin soluble porcine
3285611000001104	Insulin soluble porcine
36048711000001104	Insulin soluble porcine
3282311000001103	Insulin zinc suspension crystalline human
3281811000001103	Insulin zinc suspension crystalline human
3284911000001106	Insulin zinc suspension mixed human
3284111000001108	Insulin zinc suspension mixed human
36620611000001104	Insulin glargine/ Lixisenatide
36630511000001104	Insulin glargine/ Lixisenatide
36630611000001110	Insulin glargine/ Lixisenatide
36618311000001110	Insulin glargine/ Lixisenatide
36911311000001104	Insulin glargine
36931811000001104	Insulin glargine

Appendix 10 Table 5: Excluded CPRD Diabetes Terms

Diabetic assessment (Initial, follow up)
Attending diabetes clinic
Referral to diabetes nurse
Diabetic maculopathy absent – both eyes
No evidence of diabetic nephropathy
Latent autoimmune diabetes mellitus in adult
Referral to diabetes preconception counselling clinic
Referral to diabetes specialist interest GP
Referral to community diabetes specialist nurse
Ineligible for diabetic retinopathy screening
Excluded from diabetic retinopathy screening
Unsuitable for diabetes year of care programme
Ineligibility for diabetes eye screening (deceased)

Discharged from diabetes shared care programme
No evidence of diabetic peripheral neuropathy
No evidence of diabetic nephropathy
Care contact service: diabetes
Type 1/2 diabetes mellitus in remission
Discharge from secondary care diabetes services
Drug induced diabetes mellitus
Insulin or antidiabetic poisoning
Steroid induced diabetes mellitus
DNA diabetic clinic
Refer diabetic liaison nurse
Health education – diabetes
Exception reporting – diabetes quality indicator
Date diabetic treatment stop
Provision of written information about diabetes and hypertension/high cholesterol/high bp
Eligibility temporarily/permanently inactive for diabetic retinopathy screening
Joint consultation practice nurse/GP & comm diabetes specialist nurse
Exclusion from diabetes quality indicators: service unavailable
Exempted from diabetes qual indicators: patient unsuitable
Patient held diabetic record declined
Provision written information diabetes & high Hb1ac level
Discharge from in house diabetic foot screening
Patient advised re diabetic diet
Discharged from care of DSN/diabetic liaison nurse
Referral to community DSN declined
Further diabetic monitoring
DNA XPERT diabetes structured education programme

Appendix 11 Table 6: Test of Proportional Hazards Assumption using Schoenfeld Residuals

Covariate	**Rho Correlation Coefficient**	**Chi squared**	**p value**
Age			
0-50	-	-	-
51-60	-0.01	0.64	0.423
61-70	-0.03	6.70	0.010

71-80	-0.06	22.48	<0.001
>80	-0.06	19.13	<0.001
Deprivation Quintiles			
1	-	-	-
2	-0.03	5.47	0.019
3	0.00	0.00	0.984
4	-0.02	2.03	0.154
5	-0.04	7.15	0.008
CCI			
0	-	-	-
1	0.03	4.07	0.044
2	0.02	2.30	0.129
Diabetes			
No	-	-	-
Yes	-0.02	1.64	0.201
Urgency			
Elective	-	-	-
Emergency	-0.05	14.13	<0.001
Indication			
Benign	-	-	-
Malignant	0.15	129.43	<0.001
Access			
Open	-	-	-
MIS	0.01	0.22	0.658
CCI = Charlson Comorbidity Index, MIS = Minimally-invasive surgery.			

Appendix 12 Table 7: Record of Taught Credits (MRes 2022/2023)

Module	Provider	Time	Credits	Mark
Data Organisation and Management in Epidemiology (EPID4022 UNUK)	University of Nottingham	1 Semester (SPR2 22-23)	10	77
Further Medical Statistics (EPID4017 UNUK)	University of Nottingham	1 Semester (SPR1 22-23)	10	80
Using Posters to Communicate your Research	Researcher Academy	3 hrs	1	-
Introduction to Writing for Academic Journals	Researcher Academy	4-5 hrs	2	-
Research Data Management	University of Nottingham	3 hrs	1	-
Research Integrity: Concise	Researcher Academy	1 hr	1	-
Introduction to the Code of Research Conduct and Research Ethics	Researcher Academy	2.5 hrs	1	-
Microsoft Word: Managing Long Documents	Researcher Academy	1 day (7 hrs)	2	-