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Author/s:

Kiburg, KV;Ward, GM;Vogrin, S;Steele, K;Mulrooney, E;Loh, M;McLachlan, SA;Sundararajan, V;Maclsaac, RJ

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Short title/*Authors running head*: Impact of diabetes on hospitalization/mortality in people with malignancy • K. V. Kiburg et al.

Research: Epidemiology

Impact of type 2 diabetes on hospitalization and mortality in people with malignancy

K. V. Kiburg^{1,2,3}, G. M. Ward^{1,2,4}, S. Vogrin², K. Steele¹, E. Mulrooney¹, M. Loh¹, S.-A. McLachlan^{2,5}, V. Sundararajan^{2,6} and R. J. MacIsaac^{1,2,3}

¹Department of Endocrinology and Diabetes, St Vincent's Hospital Melbourne, Fitzroy, ²Department of Medicine, University of Melbourne, Fitzroy, ³St Vincent's Institute of Medical Research, Fitzroy, ⁴Department of Clinical Biochemistry, St Vincent's Hospital Melbourne, Fitzroy, ⁵Medical Oncology, St Vincent's Hospital Melbourne, Fitzroy, and ⁶Department of Public Health, La Trobe University, Melbourne, VIC, Australia

Correspondence to: Katerina Kiburg. E-mail: katerina.kiburg@svha.org.au

What's new?

- It has been shown that a diagnosis of diabetes is associated with an increased risk of the development and progression of malignancies, and of mortality in people with

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malignancies, a number of suggested explanations for which include hyperinsulinaemia and hyperglycaemia.

- The findings of the present study highlight the increased risk of emergency department presentations, inpatient admission, longer length of hospital stay and all-cause mortality associated with a diagnosis of diabetes and malignancy.
- This work emphasizes the importance of avoiding diabetes, and highlights that people who have already developed diabetes and have a co-diagnosis of a malignancy represent a high-risk group that may benefit from additional treatment strategies.

Abstract

Aim To compare the characteristics of and outcomes for people with malignancies with and without a co-diagnosis of diabetes.

Methods Emergency department and hospital discharge data from a single centre for the period between 1 January 2015 and 31 December 2017 were used to identify people with a diagnosis of a malignancy and diabetes. Multivariate Cox regression models were used to estimate the effect of diabetes on all-cause mortality. A truncated negative binomial regression model was used to assess the impact of diabetes on length of hospital inpatient stay. Prentice–Williams–Peterson total time models were used to assess the effect of diabetes on number of emergency department re-presentations and inpatient re-admissions.

Results Of 7004 people identified with malignancies, 1195 (17.1%) were also diagnosed with diabetes. A diagnosis of diabetes was associated with a greater number of inpatient re-admissions [adjusted hazard ratio 1.13 (95% CI 1.03, 1.24)], a greater number of emergency department re-presentations [adjusted hazard ratio 1.13 (95% CI 1.05, 1.22)] and longer length of stay [adjusted hazard ratio 1.14 (95% CI 1.04, 1.25)]. A co-diagnosis of diabetes was also associated with a 48% increased risk of all-cause mortality [adjusted hazard ratio 1.48 (95% CI 1.22–1.76)].

Conclusions People with malignancies and diabetes had significantly more emergency department presentations, more inpatient admissions, longer length of hospital stay and higher rates of all-cause mortality compared to people with a malignancy without diabetes.

Introduction

The link between diabetes and rising incidence of malignancies is increasingly being recognized. A recent meta-analysis of over 20 million people has shown that men with diabetes were at a 19% increased risk (RR 1.19, 95% CI 1.13, 1.25), whilst women were at a 27% increased risk (RR 1.27, 95% CI 1.21, 1.32) of developing a malignancy [1]. This increased risk of developing a malignancy may be related to malignancy type, with pancreatic, liver and gallbladder malignancies reported to be more common in people with diabetes [2]. Furthermore, it has been suggested that people with malignancies and diabetes have higher mortality rates compared to those without diabetes [3–6]. One study has estimated that there is up to a 219% increased risk of mortality for people with malignancies and diabetes compared to such people without diabetes, depending on type of malignancy and gender [6].

A number of hypotheses have been put forward to explain the greater prevalence and adverse outcomes associated with malignancies in people with diabetes [7]. The mechanisms linking diabetes and increased rates of malignancy are not fully understood, but hyperinsulinaemia and hyperglycaemia have been implicated in increased cell proliferation. Furthermore, once a malignancy develops, high levels of insulin and insulin-like growth factors may possibly promote malignant cell and tumour growth, and metastasis [8–10]. The development and progression of a malignancy may also possibly be influenced by various classes of glucose-lowering medications. People on metformin may have a decreased risk of malignancy development and mortality, whereas therapies such as sulfonylureas, glitazones, incretin modifiers and insulin may possibly increase the risk of developing a malignancy [11–15].

Apart from incidence and mortality studies, there is little information regarding the impact of diabetes on other clinical outcomes, such as length of hospital stay, hospital admission rates and emergency department presentations, for people with a malignancy. The aims of the present study, therefore, were to explore the impact a diagnosis of diabetes in people with a malignancy had on clinical outcomes, including length of stay, hospital admission rates, emergency department presentations and mortality after adjustment for relevant covariates after index admission.

Research design and methods

Study design

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This was a hospital-wide retrospective cohort study comparing the characteristics and outcomes of people with a diagnosis of a malignancy with and without diabetes over a 3-year period.

Case identification

Clinically coded data were used to identify all people who attended the emergency department of or were admitted as an inpatient to an Australian tertiary referral hospital between 1 January 2015 and 31 December 2017. People were selected using the following codes from the International Classifications of Diseases, version 10, Australian Modification (ICD-10-AM): C00-C96 or D00-D48 for malignancies, C77-C79 for metastatic cancer and E11 for type 2 diabetes [16]. People classified as having type 1 diabetes or intermediate hyperglycaemia were excluded because of the heterogenous nature of that population.

Outcome measures

The main outcome was all-cause mortality ($n=633$). The date of death was based on information available in the hospital electronic database. Other outcomes of interest included number of emergency department presentations ($n=9916$), length of any hospital stay and inpatient admission rates ($n=9029$).

Chart review to assess steroid use

As steroids are often part of malignancy treatment and are a risk factor for hyperglycaemia, the temporal relationship between malignancy diagnosis, steroid use and diabetes diagnosis required further investigation as no information on steroid use was available in the databases used in the present study; therefore, in order to investigate the potential difference in steroid use between people with and without diabetes a chart review was conducted. Our preliminary results suggested that people with diabetes and haematological and lymphoid malignancies, in particular, were at an increased risk of mortality. In addition to the above chart review, therefore, we specifically reviewed all clinical records of people with diabetes and these malignancies ($n=110$) to assess the possible influence of steroid use on hyperglycaemia and the outcomes of interest of this study.

Statistical analysis

Normality was assessed visually using normal probability plots. Normally distributed continuous variables are presented as mean \pm SD, non-normally distributed continuous

variables as median and interquartile range and categorical variables as total number and percentage. Individuals' characteristics by diabetes status were compared using independent sample *t*-tests for continuous variables, Pearson's chi-squared test for categorical variables and Wilcoxon's rank-sum test for variables without a normal distribution.

Three different approaches were taken to fit models for mortality, length of hospital stay and hospital utilization numbers: 1) multivariate Cox regression models were used to estimate the effect of diabetes on all-cause mortality; 2) truncated negative binomial regression models were used to assess the impact of diabetes on length of hospital inpatient stay; and 3) Prentice–Williams–Peterson total time models were used to assess the effect of diabetes on the number of emergency department presentations and inpatient admissions following a individual's index admission of presentation [17]. All models accounted for baseline characteristics including: age, gender, diabetes, ischaemic heart disease, chronic kidney disease, BMI (kg/m²), BMI < 18.5 kg/m², 18.5–25 kg/m² and >25 kg/m², type of malignancy, metastatic disease, and, for the length-of-stay model, vital status at discharge. The proportional hazards assumption was assessed visually using log-log plots for individual covariates. The presence of multicollinearity was assessed by the variance inflation factor. Propensity scores were estimated to evaluate the average treatment effect of the treated individuals for the above outcomes as an additional analysis (Tables S6 and S7; Figure S1).

As mentioned above, two chart reviews were conducted: one to examine potential differences in steroid use in people with and without diabetes and another to examine the temporal relationship between diabetes and malignancy diagnosis for people with lymphoid and haematological malignancies (a group of people with a high proportion of steroid use).

Ethics

Ethics approval for this study was granted by the St Vincent's Hospital Melbourne ethics committee (LNR 176/18).

Results

A total of 7004 people, who attended our hospital between 1 January 2015 and 31 December 2017, were identified with a diagnosis of a malignancy of whom 1195 (17.1%) also had a diagnosis of diabetes (Table 1). People with diabetes were more likely to be male, to be older, to have ischaemic heart disease, to have chronic kidney disease and to have a BMI of > 25 kg/m², compared to those without diabetes (Table 1).

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People with diabetes were more likely to have certain types of malignancies compared to those without diabetes. In particular, malignant neoplasms of the respiratory, intrathoracic organs, digestive organs, and ill-defined, secondary and unspecified sites were more common (Table 2). In contrast, malignancies of the eye, brain and other parts of the central nervous system were less common in people with diabetes compared to those without diabetes.

Our overall chart review suggested that for our cohort of people with malignancy, there was no significant difference in steroid use between people with and without diabetes (25% vs 23%; $P=0.74$).

People with malignancies and diabetes had significantly more emergency department presentations and inpatient admissions and longer length of hospital stays compared to people without diabetes (Table 3). Analysis of the data showed that the Cox regression models for all-cause mortality, emergency department re-presentations and inpatient re-admissions fulfilled the proportional hazards assumption, and no multicollinearity existed. A Prentice–Williams–Peterson total time model was then used to investigate possible factors, in addition to diabetes status, that were associated with greater number of emergency department re-presentations and inpatient re-admissions in the cohort. The model revealed that the risk of subsequent hospitalization following an index admission for people with a diagnosis of diabetes compared to people without diabetes was increased by 14% [hazard ratio 1.14 (95% CI 1.04, 1.25); Table S1]. We also found that certain malignancy types were associated with more hospital admissions (Table S1). A similar relationship between diabetes [hazard ratio 1.19 (95% CI 1.11, 1.28)], and malignancy type was also seen for the risk of emergency department re-presentations (Table S2).

Factors that influenced length of hospital stay were further assessed using a truncated negative binomial regression model. This model confirmed that diabetes was independently and significantly associated with longer length of hospital stay [IRR 1.14 (95% CI 1.04, 1.25)]. This model also showed that type of malignancy, BMI > 25 kg/m² and Charlson comorbidity score was associated with longer length of hospital stay (Table S3). After adjustment for covariates, the expected length of hospital stay for people with diabetes compared to those without diabetes was 4.98 days (95% CI 4.49, 5.46) vs 4.36 days (95% CI 4.06, 4.66).

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A univariate Cox regression model showed a strong and statistically significant increased risk of all-cause mortality for people with malignancy and diabetes compared to those without diabetes [hazard ratio 1.99 (95% CI 1.67, 2.37)]. A Kaplan–Meier curve illustrating this relationship is shown in Fig. 1. The increased risk of death for people with a malignancy and diabetes compared to those without diabetes remained significant when assessed using multivariate Cox regression analysis [hazard ratio 1.48 (95% CI 1.23, 1.77); Table S4]. This analysis also revealed that increasing age, end-stage kidney disease, metastatic disease, Charlson comorbidity score and type of malignancy were significantly associated with an increased risk of mortality. A low BMI (< 18.5 kg/m²) was also found to be associated with an increased risk of all-cause mortality [hazard ratio 1.45 (95% CI 0.99, 2.12)].

Results obtained using propensity score weighting were similar to those obtained in the original analyses for all-cause mortality, emergency department re-presentation, inpatient re-admission and length of hospital stay. The results were similar in the trimmed sample (Table S8).

We investigated the relationship between different types of malignancy and risk of all-cause mortality in people with and without diabetes. Because of the limited number of deaths for each type of malignancy, the analysis was limited to people with malignant neoplasms of the digestive, respiratory and intrathoracic organs and lymphoid and haematological malignancies. The only significant difference for mortality associated with a diagnosis of diabetes was seen in those with lymphoid and haematological malignancies. For people with lymphoid and haematological malignancies, a co-diagnosis of diabetes was associated with an 127% increased risk of mortality [hazard ratio 2.27 (95% CI 1.41, 3.66); Table S5]. Our chart review of people with lymphoid and haematological malignancies suggested that the diagnosis of diabetes in these people was not influenced by steroid use. For this group of people only 9% (10/110) were classified as having diabetes after the commencement of steroid therapy during the course of their malignancy treatment. It was hypothesized that diabetes may merely be a marker of more severe pancreatic cancer. For this reason we conducted a sensitivity analysis in which we excluded all cases of pancreatic cancer from the survival analysis. This resulted in 43 people with diabetes and 55 people without diabetes being excluded and a change in the hazard ratio from 1.40 (95% CI 1.00, 1.97) to 1.44 (95% CI 1.01, 2.05), which remained significant.

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Discussion

The findings of the present study support the hypothesis that a co-diagnosis of type 2 diabetes and malignancy is associated with a number of adverse outcomes, including higher number of emergency department re-presentations, higher number of hospital re-admissions, longer length of stay and greater all-cause mortality compared to malignancies without diabetes. Our analysis was adjusted for covariates that could potentially influence the above outcomes, including age, gender, ischaemic heart disease, chronic kidney disease, type of malignancy, smoking status, Charlson comorbidity score, metastatic disease and BMI. Even after adjustment for covariates, the adverse effect of a diagnosis of diabetes persisted. Furthermore, in our multivariate Cox survival analysis, a co-diagnosis of diabetes remained a statistically significant risk factor for all-cause mortality [hazard ratio 1.48 (95% CI 1.23, 1.77)]. Malignancy type was also influenced by the presence of diabetes. We found a higher prevalence of malignant neoplasms of the respiratory, intrathoracic organs, digestive organs, ill-defined, secondary and unspecified sites in people with diabetes compared with those without diabetes. In contrast, malignancies of the eye, brain and other parts of the central nervous system were less prevalent in people with malignancy and diabetes compared to those without diabetes.

The hazard ratio that we report for all-cause mortality in people with malignancies and diabetes is comparable to the increased risk reported in other studies for people with diabetes (hazard ratio range 1.26–3.87) [3,5,18,19]. Due to sample size limitations, a malignancy type-specific analysis was only possible for lymphoid and haematological malignancies. For these malignancies, we found a higher mortality rate for a co-diagnosis of diabetes of ~130% [hazard ratio 2.27 (95% CI 1.41, 3.65)]. Previous studies have reported inconsistent findings regarding the association between diabetes and mortality for people with lymphoid and haematological malignancies. One study has suggested that the adverse relationship between diabetes and blood malignancies is restricted to people with lymphoma [18]. The differences we report with regard to diabetes, cancer type and mortality may be explained by the different populations and the methods of statistical analysis used in different studies. Our chart analysis suggested that the use of steroids was unlikely to have influenced this relationship between diabetes and all-cause mortality in people with lymphoid and haematological malignancies.

The association between BMI <18.5 kg/m² and greater all-cause mortality was not unexpected given that people who are severely unwell are likely to have a lower BMI. There may also be differences in the type and intensity of malignancy treatment for people with and without diabetes that could contribute to the observed increase in mortality for people with malignancy and diabetes. It is possible that elderly people with diabetes and a high burden of other comorbidities may have received treatment with an intended palliative rather than curative outcome [20]. The results of the present study relate to people who already have cancer, and weight gain has been shown to increase the risk of developing cancer [9,21,22].

A strength of the present study was the focus on outcomes other than mortality, which have not been previously explored in this setting. We were able to demonstrate that people with malignancies and diabetes were at a significantly increased risk of inpatient re-admission, emergency department re-presentation and longer length of hospital stay. The models used to explore the above relationships were adjusted for relevant covariates that also took into account comorbidities that are more common in people with diabetes. We found that people with diabetes were at significantly increased risk of inpatient re-admission [hazard ratio 1.10 (95% CI 1.00, 1.20)] and emergency department re-presentations [hazard ratio 1.12 (95% CI 1.04, 1.20)] compared to those without diabetes. The above relationships were derived using a Prentice–Williams–Peterson total time model, which allows the adjustment of an individual's baseline risk to increase as their number of admissions or presentations increases [17]. This is achieved through stratification by number of previous failure events that an individual has experienced. Although the hazard ratios for risk of inpatient and emergency department admission were modest, given the large cost, both financial and in resources, associated with hospital attendance and admission, any increase in admission rates will most likely have a substantial negative impact on healthcare costs. We also observed that length of stay was significantly longer for people with malignancy and diabetes compared to those without diabetes [IRR 1.14 (95% CI 1.04, 1.25)], which equates to 4.98 days (95% CI 4.49, 5.46) vs 4.36 days (95% CI 4.06, 4.66) for people with and without diabetes and a malignancy. As ICD-10-AM codes were used to select admissions for malignancies, these admissions may not necessarily have been related to malignancy treatment and there were also a number of same-day admissions which resulted in an overall short length of stay.

The present study has some limitations. Despite being a single-site study, it reports outcomes of people attending a large tertiary referral and university teaching hospital with a statewide

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catchment area; however, we acknowledge that our results may not be generalizable to other regions where the treatment and management of malignancies and/or diabetes may differ. The small number of deaths limited our analysis of mortality by malignancy type. The relatively short follow-up period of 3 years may also present a potential limitation. As this was an observational study, any relationship that we described for outcomes in people with malignancy and diabetes compared to those in people without diabetes should only be interpreted as describing an association, rather than establishing causation.

The ICD-10-AM-based case selection of both malignancies and diabetes could potentially represent an underestimation of the prevalence of these two diagnoses. We report a slightly lower prevalence of diabetes (17%) compared with a previous inpatient survey of hospitals including our centre, which reported a diabetes prevalence of 25% [23]. It is possible that those with milder forms of diabetes were less likely to be captured, which may have resulted in an overestimate of the relationship between diabetes and cancer outcomes.

In addition, the clinically coded hospital data used for this analysis lacked information on date of diabetes and malignancy diagnosis, a deficit which we attempted to account for through our chart reviews. We did not have information on medication use and were therefore unable to adjust our analysis for this potential confounder. We also acknowledge the limitation that mortality rates were obtained from our hospital database and not from a central registry and did not include information on cause of death. It is therefore likely that the event rates were underestimated, both in terms of hospitalization and deaths.

These limitations are counterbalanced by the strengths of this study, which include the large sample size, the availability of detailed pathology and anthropometric data, and comprehensive information on BMI and comorbidities for the whole cohort, which has been lacking in previous studies [6].

In summary, the present study shows that people with malignancies and diabetes have a significantly higher number of emergency department re-presentations and inpatient re-admissions, longer length of hospital stay and higher rates of all-cause mortality compared to people with malignancy without diabetes. Given that the number of people with diabetes is increasing throughout the world, the above findings may have implications for future

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healthcare planning. Further work is needed to explore the mechanisms that explain the adverse relationship between malignancy and a co-diagnosis of diabetes.

Funding sources

Competing interests

Commented [MD6]: AUTHOR: Please provide a statement on Competing interests or state 'None declared.'

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Table 1 Baseline characteristics

Baseline characteristics (n=7004)	No diabetes	Diabetes	Logistic regression OR (95% CI)	P
Number of individuals (%)	5809 (82.9)	1195 (17.1)		
Men, n (%)	3229 (55.6)	746 (62.5)	1.38 (1.27, 1.49)	<0.001
Median (IQR) age at first admission, years	64.0 (51.0, 74.0)	72.0 (65.0, 79.0)	1.04 (1.04, 1.05)	<0.001
CKD, n (%)				<0.001
No known CKD	5716 (98.4)	1129 (94.5)	Baseline	
CKD stage 1	0 (0.0)	1 (0.1)	N/A	
CKD stage 2	7 (0.1)	5 (0.4)	N/A	
CKD stage 3	34 (0.6)	35 (2.9)	6.09 (3.74, 9.93)	
CKD stage 4	24 (0.4)	11 (0.9)	2.54 (1.23, 5.25)	
CKD stage 5	28 (0.5)	14 (1.2)	2.23 (1.10, 4.55)	<0.001
Ischaemic heart disease, n (%)	57 (1.0)	49 (4.1)	4.32 (2.93, 6.35)	<0.001
BMI				
< 18.5 kg/m ²	161 (2.8)	20 (1.7)	Baseline	

18.5–25 kg/m ²	1277 (22.0)	206 (17.2)	1.46 (1.13, 1.91)	
> 25 kg/m ²	4371 (75.2)	969 (81.1)	1.67 (1.29, 2.15)	<0.001
Death, <i>n</i> (%)	451 (7.8)	182 (15.2)	2.14 (1.77, 2.57)	<0.001

CKD, chronic kidney disease.

Table 2 Malignancy type at death or final admission by diabetes status

	No diabetes <i>n</i> (%)	Diabetes <i>n</i> (%)	<i>P</i>
Number of individuals	5809 (82.9)	1195 (17.1)	
Malignant neoplasms of breast	253 (4.4)	45 (3.8)	0.36
Malignant neoplasms of eye, brain and other parts of CNS	380 (6.5)	49 (4.1)	0.001
Malignant neoplasms of ill-defined, secondary and unspecified sites	1280 (22.0)	316 (26.4)	<0.001
Malignant neoplasms of lymphoid, haematopoietic and related tissues	391 (6.7)	78 (6.5)	0.80
Malignant neoplasms of skin, lip and oral cavity and <i>in situ</i> and benign neoplasms	1447 (24.9)	279 (23.3)	0.25
Malignant neoplasms of respiratory, intrathoracic	1045 (18.0)	339 (28.4)	<0.001

organs or digestive organs			
Malignant neoplasms of bone, articular cartilage, mesothelial or soft tissue	254 (4.4)	48 (4.0)	0.58
Malignant neoplasms of genitourinary tract	395 (6.8)	94 (7.9)	0.19

CNS, central nervous system

Table 3 Hospital presentations and length of stay, stratified by presentation

	No diabetes	Diabetes	Univariate hazard ratio	<i>P</i> *
Total	12776	3398		
Number of emergency department presentations	2.0 (1.0, 3.0)	3.0 (2.0, 5.0)	1.19 (1.11, 1.27)	<0.001
Number of inpatient admissions	1.0 (1.0, 2.0)	2.0 (1.0, 3.0)	1.10 (1.01, 1.20)	<0.001
Length of stay, days	4.0 (1.0, 9.0)	5.0 (2.0, 11.0)	1.38 (1.31, 1.46)	<0.001

* Using Wilcoxon's rank-sum test.

Data are median (interquartile range).

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Inpatient admissions (Prentice–Williams–Peterson total time model)

Table S2. Emergency department visits (Prentice–Williams–Peterson total time model).

Table S3. Length of stay (truncated negative binomial regression).

Table S4. Survival (multivariate Cox regression model).

Table S5. Multivariate Cox-regression model for lymphoid and hematological cancers.

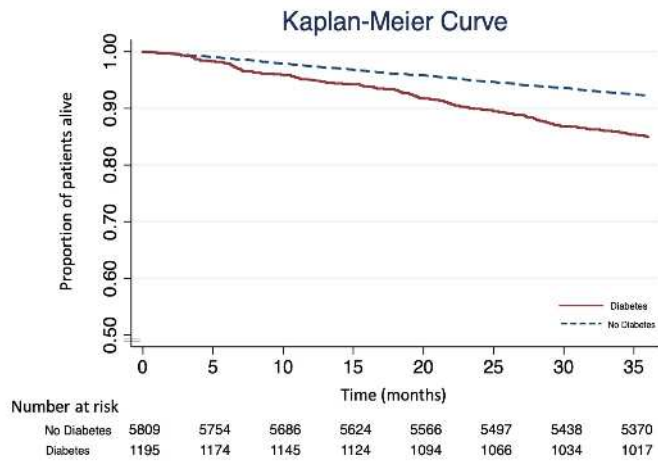
Table S6. balance of baseline covariates between patients with and without diabetes in weighted sample.

Table S7. Distribution of average treatment effect in treated weights.

Table S8. Outcomes using average treatment effect on the treated (95% CIs) sensitivity to large weights.

Figure S1. Distribution of propensity scores by diabetes status.

Figure 1: Univariate Kaplan Meier curve of patients with and without diabetes, all-cause mortality



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