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A systematic review considering risk factors for mortality of patients discharged from hospital with a diagnosis of diabetes

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ABSTRACT

Aim: To identify known risk factors for mortality for adult patients, discharged from hospital with diabetes.
Method: The systematic review was based on the PRISMA protocol. Studies were identified through EMBASE & MEDLINE databases. The inclusion criteria were papers that were published over the last 6 years, in English language, and focused on risk factors of mortality in adult patients with diabetes, after they were discharged from hospitals. This was followed by data extraction "with quality assessment and semi-quantitative synthesis according to PRISMA guidelines".
Results: There were 35 studies identified, considering risk factors relating to mortality for patients, discharged from hospital with diabetes. These studies are distributed internationally. 48 distinct statistically significant risk factors for mortality can be identified. Risk factors can be grouped into the following categories; demographic, socioeconomic, lifestyle, patient medical, inpatient stay, medication related, laboratory results, and gylcaemic status. These risk factors can be further divided into risk factors identified in generalized populations of patients with diabetes, compared to specific sub-populations of people with diabetes.
Conclusion: A relatively small number of studies have considered risk factors relating to mortality for patients, discharged from hospital with a diagnosis of diabetes. Mortality is an important outcome, when considering discharge from hospital with diabetes. However, there has only been limited consideration within the research literature.

Contents

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1. Introduction

Patients with diabetes are known to be at an increased risk of complications and mortality during their inpatient stay.[1,2] Significant research and resource has been invested into understanding how to reduce this burden of inpatient mortality for patients with diabetes.[3,4] There has been much less focus on the risk of mortality, following discharge from hospital with diabetes. Data available on post discharge outcomes, in this patient population, is not abundant and is ambiguous.[5] There is evidence of an increased risk of mortality for patients with diabetes; however, tools for predicting mortality in such patients are not easily available.[6] This study, therefore, aims to systematically identify the known risk factors for mortality in patients with diabetes, after they are discharged from hospitals.

This work builds on a previous published work, considering risk factors for readmission of patients discharged from hospital with diabetes.[7] Readmission is a commonly considered measure of care quality, when patients are discharged from hospital, and, therefore, has been more closely studied than mortality following hospital discharge, arguably due to financial incentives and costs associated with readmission rates.[8] Both readmission and mortality are, however, important outcome measures, when considering the discharge of patients with diabetes and the subsequent development of risk prediction models. The consideration of which patients are at a greatest risk of mortality, following discharge, will help allocated limited resources to supporting this population.

The identification of risk factors, in this manner, has the potential to support research that enables us to predict mortality in patients with diabetes, following hospital discharge. Once risk factors are known and understood, they can be identified in the patient's individual Electronic Health Record (EHR). Understanding risk factors, relevant to patients discharged from hospital with diabetes, is important to patients, carers, healthcare practitioners and researchers. It supports the delivery and development of individualised medicine, based on each patient's underlying risks; supports our understanding of regional variations in readmission risk; and, supports development of evidence based interventions, targeted at reducing readmission risks. Interestingly, the paucity of research in this area, for diabetes, is in direct contrast to other medical conditions, such as heart failure.[9]

2. Methods

2.1. Search strategy

The systematic review was performed according to the PRISMA protocol.[10] The PRISMA flowchart is shown in Fig. 1.

2.2. Study selection

The literature search was conducted in the MEDLINE, EMBASE & Engineering Village databases. Search terms used to identify relevant medical literature were ((“diabetes” AND “discharge”)) AND (“mortality” or “death” or “died”). Filters were applied to identify studies that were published, in English language, over the last 6 years (March 2014 to February 2020), to include the most recent clinical evidence available in this area of research. Additionally, filters were applied to set participants'

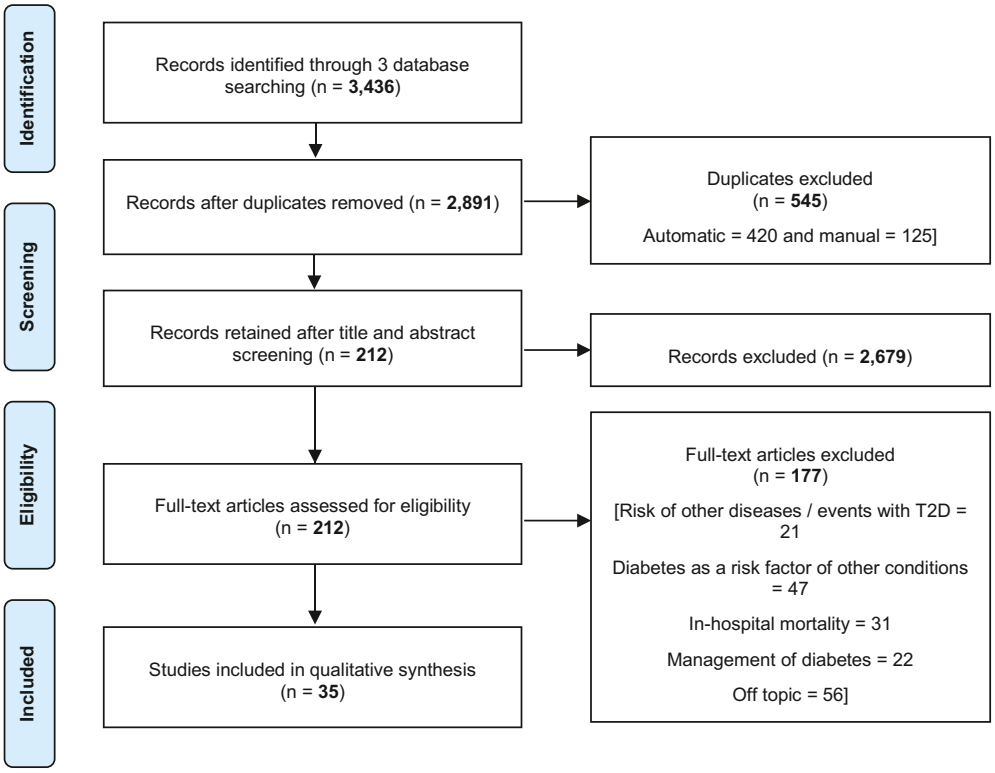

Fig. 1. PRISMA flow diagram of study selection.

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Table 1
*Comprising of: 10 retrospective cohort, 4 retrospective analysis, 2 retrospective case control, 1 retrospective observational 1 retrospective registry and 1 retrospective risk prediction modeling.

Study design	Number of papers	Percentage of papers (%)
Retrospective study*	19	54
Prospective study	10	29
Registry based	5	14
Post hoc analysis	1	3

age as 18 years and above, as this research looked at only adult patients. Any study that focused on in-hospital mortality or diabetes, as a risk factor for other clinical conditions, was excluded.

2.3. Data extraction

Data was extracted to a pre-determined, data-extraction proforma. Data was extracted based on the following variables; year of publication, type of study, location of research, sample size, sub population of people with diabetes, statistically significant risk factors and statistical tests for analysis. Additionally, risk factors not meeting significance criteria, but had impact were also extracted. Data extraction was performed independently by two authors, with any discrepancies resolved by a third author.

2.4. Quality assessment

All studies included in the review were assessed for study quality. Data was extracted using Keshav's 5Cs (category, context, correctness, contribution and clarity),[11] alongside sample size, justification of their participant selection and statistical tests applied. Papers were not excluded based on producing a negative outcome or being a low quality study.

2.5. Data synthesis

The diversity among the identified studies, in terms of their sample sizes and patient population with various co-morbidities apart from diabetes, did not allow a meta-analysis to be conducted. Instead, both a semi-quantitative and narrative summary of identified prognostic risk factors were performed. Individual risk factors have then been grouped under broader categories, as and when necessary.

Table 2
Distribution of study geographies.

Study location	# studies	Study location	# studies	Study location	# studies
United States	3	Canada	1	Spain	1
Australia	2	China	1	Middle East	1
Brazil	2	Croatia	1	Romania & Germany	1
Greece	2	Finland	1	USA & EU	1
Italy	2	Germany	1		
Taiwan	2	Israel	1		
United Kingdom	2	Latvia	1		

3. Results

3.1. Search results

3436 studies were identified from the literature search, representing 2891 studies following removal of duplicates. Title and abstract based screening resulted in 2679 articles being removed, which left 212 for full text assessment. Full text evaluation resulted in 35 articles being shortlisted for the review (Fig. 1).

3.2. Study characteristics

From the 35 articles identified, 29 were full text articles (83%) and 6 (17%) were only in abstract form, typically from conference presentations (Table 1).

The study designs noted within the review were:

The distribution of studies over time is described in Fig. 2:

(11%) studies were based on international datasets, 12studies (34%) were conducted based on national data, 9studies (26%) used regional data, 10 (29%) were single-centre studies. The distribution of study geographies is shown in Table 2:

3.3. Risk factor identification

The majority of studies analysed (24studies, 69%) identified one or more statistically significant risk factors for mortality, following discharge from hospital with a co-morbid diagnosis of diabetes. There were 11 studies (31%), which identified no statistical significant risk factors. The distribution of risk factors is demonstrated in more detail in Table 3.

The follow up period, during which mortality was looked for in the studies, was highly variable. The most common follow up period was

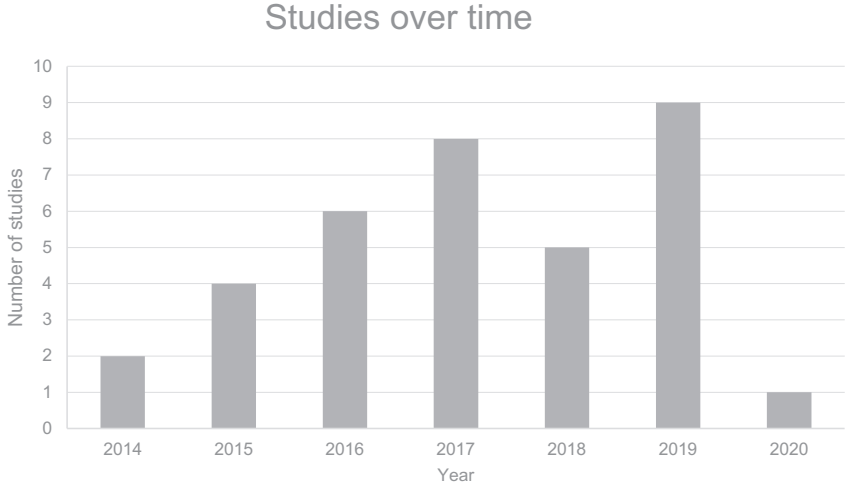

Fig. 2. Studies over time.

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Table 3
Study characteristics.

Ref	Year	Data collection	Sample size	Sub-population	Significant risk factors	No. of significant risk factors	Follow up period (years)
[12]	2017	Regional	22,473	Post Intensive Care Unit (ICU)	Hospital, age, sex, ethnicity, APACHE score, co-morbidity	6	5.1
[13]	2016	National	1613	Post Myocardial Infarction (MI)	Admission creatinine, employment, age, Haemoglobin (Hb), Left Ventricular Systolic Dysfunction (LVSD), co-morbidity, activity, in hospital revascularisation, BMI, insulin, fasting blood glucose, angina frequency	12	5
[14]	2017	Regional	59,412	All diabetes	Not specific	0	Until death
[15]	2018	Single	312	Age over 60	Gait speed, calf circumference (BMI)	2	NA
[16]	2015	Single	4607	All diabetes	Age, Gender, Cardiovascular diseases and infectious diseases (co-morbidity)	4	337 days
[17]	2014	National	1082	Heart failure	Age, co-morbidity, sodium (biochemistry), anaemia (haematology), medication, BMI, NHYA (severity scoring)	7	1
[18]	2015	National	2904	Chronic Kidney Disease (CKD) and acute MI admission	0	0	1
[19]	2015	National	4054	Admission for acute MI	Statins prior to acute MI, number of medications	2	3
[20]	2018	Single	207	Diabetic Ketoacidosis (DKA) diagnosed	Age, duration of diabetes, number of hospitalisations	3	5
[21]	2016	Single	409	Admitted with pneumonia	Hospitalization for pneumonia (admission diagnosis) Age, haemodialysis (procedure) Charlson co-morbidity index (score) renal insufficiency, pleural effusion, malnutrition (co-morbidity) pH < 7.35 (biochemistry)	8	1
[22]	2017	Single	761	Admitted with poor glucose control	Estimated Glomerular Filtration Rate (eGFR), Albuminuria (biochemistry)	2	6.6
[23]	2016	International	5005	Patients admitted with acute decompensated heart failure with diabetes	BMI (underweight, severely obese)	2	1
[24]	2018	Single	304	All diabetes	0	0	1
[25]	2019	Regional	104,525	Patients hospitalised and dispensed prescription for insulin and/or OHA within 8 days of discharge. Age > 66 years	new insulin use (medication)	1	30 days
[26]	2018	Single	130	Type 2 Diabetes Mellitus (T2DM)	0	0	30 days
[27]	2017	Single	304	T2DM patients with first ever noncardioembolic acute ischemic stroke	Age, Stroke severity (NIHSS scale), clopidogrel compared to aspirin (medication) co-morbidity	4	10
[28]	2016	National	386	DKA admitted to Intensive Treatment Unit (ITU)	Age, APACHEII score, mechanical ventilation, number of organs supported, DKA severity, creatinine, bilirubin, pCO2 (biochemistry), lowest Glasgow Coma Score (GCS)	9	5
[29]	2016	Regional	214,991	All diabetes	Age, sex, Charlson index	3	2
[30]	2018	National	17,186	Diabetes and heart failure	0	0	NA
[31]	2016	National	1743	Diabetes and Acute Coronary Syndrome (ACS)	0	0	6 months
[32]	2019	National	843,978	All diabetes	0	0	6 months
[33]	2017	National	71,640	Diabetes and cancer	0	0	3
[34]	2017	Regional	28,353	All diabetes	Median glucose during admission & glucose variability	2	6
[35]	2015	International	221	T2DM admitted with ACS	0	0	1
[36]	2014	International	1998	Patients hospitalised with worsening heart failure and an ejection fraction below 40%	0	0	9.9 months
[37]	2017	Regional	218	Haematocrit, EF, ACEi. Red blood cell distribution	0	0	1
[38]	2017	Single	202	All diabetes	hba1c, insulin resistance	2	2.5
[39]	2020	International	974	ACS	Fibrinolysis	1	1
[40]	2019	Single	306	All diabetes	Sarcopenia	1	2
[41]	2019	Regional	10,542	All diabetes	Heat wave intensity	1	NA
[42]	2019	National	13,113	Heart failure	Diabetes and heart failure	1	1
[43]	2019	National	41,776	Heart failure	0	0	1
[44]	2019	Regional	NA	All diabetes	Pharmacy follow up	1	90 days
[45]	2019	National	1221	Acute MI	Insulin prescription at discharge	1	5
[46]	2019	Regional	100,000	T2DM over 40 years	Lower limb amputation, sex	2	10

12 months in 8 studies (23%). The shortest follow up period was 1 month and the longest follow up period was 10 years.

The extracted studies varied according to whether they considered risk in all patients with diabetes (6 studies, 17%) or a specific sub population. Those sub populations were defined either by the type of diabetes, or the characteristics relevant to the inpatient stay, and are demonstrated in more detail in Table 3.

In total, there were 48 distinct risk factors identified. These can be grouped into risk factor categories, alongside grouping according to whether they were identified for all patients with diabetes. The results of this grouping is shown in Table 4, which represents a complete list of all statistically significant risk factors identified within the published research literature, alongside the number (and references) of studies, which identified these risk factors as significant.

3.4. Study quality

The sample size of extracted studies varied between 130 participants and 843,978 participants. The mean average number of participants per study was 44,484, with a median of 1743 participants.

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Table 4
Risk factors.

Risk factors for specific diabetes subpopulations		Risk factors in general diabetes populations	
Risk factor	Number of studies & Ref	Risk Factor	No.& Ref
Demographic			
Age	7[12,13,17,20,21,24,27,28]	Age	2[16,29]
Gender	1[12,46]	Gender	2[16,29]
Race	1[12]		
Socioeconomic status			
Employment status	1[13]		
Lifestyle			
Leisure time activity	1[13]		
External factors			
		Weather conditions	1[41]
Patient medical factors			
Co-morbidity	6[12,13,17,25,27,42]	Co-morbidity	2[16,29,40]
Malnutrition	1[21]		
Duration of diabetes	1[20]		
Severity score	4[12,17,27,28]		
DKA Severity	1[47]		
Body mass index	3[13,17,23]		
Gait speed	1[15]		
Calf circumference	1[15]		
Angina frequency	1[13]		
Inpatient stay factors			
Procedure	2[13,21,46]		
Admission diagnosis	1[21]		
Length of stay	1[24]		
Glasgow coma score (GCS)	1[28]		
Mechanical ventilation	1[28]		
Number of organs supported	1[28]		
No. of hospitalisations	1[20]		
Which hospital admitted to	1[12]		
Medication related			
Beta blocker	1[17]	Pharmacy follow up	1[44]
ACEi/ARB blocker	1[17]		
Statins prior to AMI	1[19]		
No. of medications at discharge	1[19]		
Insulin use	1[25,45]		
Clopidogrel	1[27]		
Laboratory results			
Admission creatinine	2[13,28]	Hba1c	1[38]
Fasting glucose	1[13]		
Sodium level	1[17]		
pH below 7.35	1[21]		
eGFR	1[22]		
Albuminura	1[22]		
Bilirubin	1[28]		
PCO2 (on blood gas)	1[28]		
Admission haemoglobin	1[13]		
Anaemia	1[27]		
Fibrinolysis	1[39]		
Glycaemic Status (not including Hba1c above)			
		Glycaemic variability	1[34]
		Mean capillary blood glucose	1[38]
		Insulin resistance	1[38]

All the papers used statistical tests to assess the impact of potential risk factors and evaluate their significance. Statistical significance was set at a standard of p-value less than 0.05. The majority of the papers, which was 14 in number (40%), used Cox proportional hazards model. 7 papers (20%) had not defined their statistical test, 5 papers (14%) used univariate and multivariate Cox regression analysis, 3 studies (8%) utilised univariate and multivariate analysis, 2 papers (6%) used multivariate analysis, 1 study (3%) used multivariate binary logistic regression, 1 study used Kaplan Meir curves (3%), 1 study used sensitivity analysis (3%) and finally 1 additional study (3%) used parametric and non-parametric tests. No studies considered the application of standardized effect size measures; there was very limited calculation of power sizes, in advance, to identify and appropriate population size for the study.

4. Discussion

The identification of risk factors, following discharge from hospital is an important consideration for patients, clinicians, managers and policy makers. This review represents the first systematic collection and identification of risk factors for mortality in the published research literature. We identify a total of 48 distinct, statistically significant risk factors across 9 categories reported in 35 studies. The most commonly reported risk factor was age, followed by co-morbidity burden. Thirty-seven of the risk factors were only identified as statistically significant in a single research paper. We would argue that this represents a research literature that is at a relatively early stage of maturity, in considering this important topic area.

The quality of studies identified was relatively high, with acceptable sample sizes, albeit frequently lacking a power-calculation for the results reported. The statistical tests used were acceptable, with the majority using Cox proportional hazard models. The small number of papers not defining the statistical test used was however concerning. A large proportion of the extracted articles represented conference abstracts rather than full research papers. These conference abstracts are typically shorter, lack full methodological detail and often do not undergo such rigorous peer review. This again supports the argument that the research literature in this area is at an early stage of maturity.

The results presented in this paper can be compared to a similar review that considered risk factors, specifically for *readmission*, when patients with diabetes are discharged from hospital.[7] In the review, considering *readmission*, a significantly larger number of studies were reported (82 studies compared to 35) and 72 distinct risk factors were identified, in comparison to the 48 statistically significant risk factors identified here. There is a higher proportion of conference abstracts within the mortality articles, as compared to the readmission articles, and the mortality articles included fewer reports of prospective studies, compared to the readmission papers. These comparisons, therefore, contrast the early state of the research literature for mortality risk factors with a more complete picture seen relating to risk factors, for readmission. Readmission and post-discharge mortality are both important negative outcomes, in the context of discharge from hospitals. Clinicians, managers and policy makers are motivated to reduce both outcomes. However, it is more typically avoiding readmission that is associated with financial incentivisation for clinical providers. This incentivisation, alongside readmission typically happening sooner than mortality events, may have led researchers more towards conducting readmission rather than mortality studies. However, mortality is undoubtedly a vitally important consideration for all those involved with the discharge process and it is important that adequate research resource is directed towards this outcome.

The strengths of this research include the PRISMA approach to reporting, the use of Keshav's 5Cs approach to quality assessment and the level of detail in data collection. There are however a number of limitations that should be considered. The research only considers papers published in the English Language; there may be other risk factors identified in other studies that are published in different languages. Furthermore, the study only considers papers published over the last 6 years.

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This ensures that all risk factors identified are relevant to current medical practice, although it is possible that previously identified risk factors may be also identified. Finally, the search term used to identify discharge from hospital was only "discharge," this is a relatively universally accepted term for when a patient leaves hospital following an inpatient admission, however it is possible that a very small number of articles used an alternative descriptor and therefore the results should be interpreted with awareness of this.

There is a lot of scope and future work that can be recommended, based on this systematic review. The identified significant risk factors can be stratified according to their effectiveness in predicting mortality in type 2 diabetes patients, following their discharge from hospitals. These will highlight patients who are most vulnerable and need special attention. Additionally, available EHR based predictive tools, such as "deep learning" models that use machine learning techniques and could potentially be used for risk prediction of mortality in such patients, could be found out. Following this step, the feasibility of the chosen predictive tools can be examined and validated. Such evaluated tools for risk prediction can be integrated within the EHR system, to predict the risk of mortality post hospital discharge tailored for each patient who has type 2 diabetes.

5. Conclusions

Mortality, following hospital discharge, is necessarily an important outcome of relevance to patients, carers, clinicians and policymakers. This review is the first systematic collection of risk factors identified for mortality for patients being discharged from hospital with diabetes. The review demonstrates that the literature is at an early stage of maturity, particularly in comparison to the literature considering risks factors for readmission following discharge. This research is particularly important for the future development of risk prediction models that can support the better identification of patients at most risk, and the tailoring of support strategies to individual patient needs in an evidence-based manner.

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Declaration of competing interest

This is to declare that all authors have no conflicts of interest to declare and all funding has been noted in the manuscript.

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