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Review

Risk Factors for Adverse Outcomes in Adult and Pediatric Patients With Hyperglycemia Presenting to the Emergency Department: A Systematic Review

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Key Messages

- Approximately 9.4% of visits to emergency departments in the United States are related to diabetes. In Canada, $830 million are spent on outpatient and emergency department visits.
- This review describes factors associated with repeated visits to emergency departments, hospitalizations or deaths in patients with hyperglycemic emergencies.
- These factors should be considered for the identification of patients at high risk for adverse outcomes to guide management.

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ABSTRACT

Hyperglycemia is a significant cause of morbidity and mortality, often resulting in adverse outcomes. This review aimed to identify predictors of adverse outcomes, such as repeated hospital visits, hospitalization or death, in patients presenting to the emergency department (ED) with hyperglycemia.

Electronic searches of Medline and EMBASE were conducted for studies in English of patients presenting to the ED with hyperglycemia. Both adult and pediatric populations were included, with and without diabetes. Two reviewers independently screened all titles and abstracts for relevance. If consensus was not reached, full-length manuscripts were reviewed. For discrepancies, a third reviewer was consulted. Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale. Study- and patient-specific data were extracted and presented descriptively.

Eight observational studies were reviewed; they included a total of 96,970 patients. Predictors of adverse outcomes included age, lowest income quintile, urban dwellers, presence of comorbidities, coexisting hyperlactatemia, having a family physician, elevated serum creatinine level, diabetes managed with insulin, sentinel visit for hyperglycemia in the past month, and high blood glucose level measured in the ED. Conflicting evidence was found for whether known history of diabetes was associated with risk. Factors associated with favourable outcomes included systolic blood pressure of 90 to 150 mmHg and tachycardia.

This systematic review found 12 factors associated with adverse outcomes, and 2 factors associated with more favourable outcomes in patients presenting to the ED with hyperglycemia. These factors should be considered for easier identification of patients at higher risk for adverse outcomes to guide management and follow up.

RÉSUMÉ

L'hyperglycémie est une cause importante de morbidité et de mortalité, qui entraîne souvent des issues défavorables. La présente revue avait pour objectif de déterminer les prédicteurs d'issues défavorables

Mots clés :
issues défavorables
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comme les visites répétitives à l'hôpital, l'hospitalisation ou la mort chez les patients qui se présentent au service des urgences (SU) en raison d'une hyperglycémie.

Nous avons mené des recherches dans les banques de données électroniques Medline et EMBASE pour trouver des études en anglais sur des patients qui s'étaient présentés au SU en raison d'une hyperglycémie. Nous avons sélectionné des populations adulte et pédiatrique, diabétiques et non diabétiques. Deux examinateurs ont passé en revue de manière indépendante tous les titres et les résumés pour évaluer leur pertinence. En absence de consensus, nous avons passé en revue les manuscrits entiers. Lors de divergences, nous avons consulté un troisième examinateur. Nous avons évalué la qualité des études à l'aide de l'échelle de Newcastle–Ottawa. Nous avons extrait et présenté de façon descriptive les données propres à chacune des études et à chacun des patients.

Nous avons passé en revue 8 études observationnelles, qui comptaient un total de 96 970 patients. Les prédicteurs d'issues défavorables étaient les suivants: l'âge, le quintile de revenu le plus bas, les résidents des villes, la présence de comorbidités, la coexistence de l'hyperlactatémie, l'accès à un médecin de famille, les concentrations sériques élevées de créatinine, le diabète traité par insuline, la visite « sentinelle » en raison d'une hyperglycémie au cours du dernier mois et les concentrations élevées de glycémie mesurées au SU. Nous avons observé que les auteurs qui s'étaient penchés sur les antécédents connus de diabète pour savoir s'ils étaient associés au risque ont publié des données contradictoires. Les facteurs associés à des issues favorables étaient les suivants: la pression artérielle systolique de 90 à 150 mmHg et la tachycardie.

La présente revue systématique a permis de trouver 12 facteurs associés à des issues défavorables et 2 facteurs associés à des issues plus favorables chez les patients qui s'étaient présentés au SU en raison d'une hyperglycémie. Ces facteurs devraient être considérés pour mieux cerner les patients exposés à un risque plus élevé d'issues défavorables et orienter la prise en charge et le suivi.

Introduction

Between 1980 and 2014, the prevalence of diabetes nearly quadrupled, from 108 million to 422 million people worldwide (1). Uncontrolled diabetes is a significant cause of morbidity, including blindness, kidney failure and stroke (2,3). The World Health Organization identifies diabetes mellitus as being among the top 10 causes of mortality globally, contributing to 1.6 million deaths in 2015, with high blood glucose levels being associated with an additional 2.2 million deaths (4). Additionally, the cost of diabetes care globally is estimated to be US$827 billion annually, making it a significant burden on both patients and the health-care system (5).

Despite a growing body of knowledge and tools available for earlier identification and control of diabetes through lifestyle modifications and pharmacologic therapies, approximately 9.4% of all emergency department (ED) visits in the United States are diabetes related (6). Approximately 1.4% of these are secondary to hyperglycemic crises, such as diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), which have mortality rates of 5% and 20%, respectively (7,8). Moreover, many patients with diabetes often have recurrent visits or hospitalizations (9). In Canada, 43.2% of the money spent on diabetes care is due to acute hospitalizations ($6.64 billion), which includes the costs of medications and beds but does not include physician costs or other inpatient services. An additional $830 million is spent on outpatient clinic and ED visits (10).

However, there is a limited number of studies that predispose individuals to hyperglycemic emergencies and adverse outcomes related to those events. Identifying such factors may help physicians recognize patients at higher risk and guide management to prevent adverse outcomes, which may relieve some burden on the health-care system. The objective of this systematic review was to comprehensively describe the predictors of adverse outcomes in patients who present to the ED with hyperglycemia, including repeat visits, hospitalization or death.

Methods

Literature search strategy

A systematic literature search of the MEDLINE (1946 to June 2017) and EMBASE (1947 to June 2017) electronic databases, using the OvidSP search interface, was conducted by a research librarian (AI) with formal training in performing literature searches to inform systematic reviews. A sensitive search strategy (Supplementary Material) was utilized to include studies that identified the outcomes of patients who were found to have high blood glucose levels on initial assessment in the ED. The search comprised the following search terms: emergency medical services, emergency health services, emergency treatment, hyperglycemia, diabetes mellitus, dm2, patient readmission, hospital readmission and re-hospitalization. The search was limited to human studies and English-language publications.

The search strategies were modified for each database to include database-specific thesaurus terms and field names. Additionally, searches were supplemented by manually screening reference lists of relevant studies to identify additional published data that met our inclusion criteria. Grey literature, including conference abstracts and conference publications presented at major national and international emergency medicine meetings, were also reviewed for relevance. These are included in the discussion to ensure comprehensiveness, but are not included in the summary of results because they had not been peer reviewed.

Study setting and population

Studies including adult or pediatric patients presenting to the ED with high blood glucose levels ($\geq$11.1 mmol/L) were eligible for inclusion, regardless of whether the patients had had pre-existing diagnoses of diabetes. The studies included randomized controlled trials and observational studies. Any study that explored and quantified potential risk factors linked to the outcomes of interest were included.

Outcome measures

The primary outcome of interest was a recurrent ED visit related to hyperglycemia within 30 days of an index visit for hyperglycemia. Secondary outcomes included other adverse outcomes, such as repeated hospitalizations or death within 30 days of the index ED visit. This included all-cause mortality, both in hospital and at home. The aim of this systematic review was to comprehensively describe the risk factors associated with these outcomes.

Review process

Two reviewers (LS and KVA) initially screened all titles and abstracts for relevance to the research question. Assessment involved determining whether abstracts met the following criteria: 1) setting of the ED for the index visit; 2) patients presenting with hyperglycemia at the index visit; 3) the assessment of risk factors; and 4) the desired outcomes (i.e. recurrent ED visits for hyperglycemia, recurrent hospitalizations or death within 30 days). If consensus could not be reached from the abstract alone, then, if available, the full-length manuscript was reviewed in its entirety. If a discrepancy was still present after full review of the manuscripts, a third reviewer (JY) was consulted, and disagreement was resolved through discussion. The Cohen kappa statistic was calculated to obtain a measurement of inter-rater agreement for final study selection.

For papers included in the final systematic review, one reviewer (LS) extracted and synthesized data such as study characteristics as well as demographics and any potential risk factors for adverse outcomes of patients in the studies. Only peer--reviewed studies were included in the final results, but any relevant abstracts were incorporated into the discussion of this systematic review.

Each study's risk of bias was assessed using the Newcastle-Ottawa Scale for nonrandomized studies and the Cochrane tool for risk of bias for randomized control trials (11,12). The following domains were assessed: selection (representativeness of cohort, selection of nonexposed cohort, ascertainment of exposure), comparability of cohorts and outcome (assessment, and adequate follow up).

Results

Search results and study characteristics

The literature search yielded a total of 305 potentially relevant citations. After excluding duplicates and studies not meeting eligibility criteria based on screening of the abstracts, 22 full-length articles were retrieved for full-text review (Figure 1). Of these, 8 peer-reviewed observational studies were ultimately included, which had a combined total of 96,970 patients. A flowchart to show study selection was completed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Figure 1 [13]). No randomized controlled trials met the eligibility criteria to be included in this systematic review. The percentage of agreement for the final selection of included studies was 97.3%, with good inter-rater agreement (kappa=0.72; 95% CI 0.50 to 0.93).

Table 1 summarizes the characteristics of the studies, all of which included adult populations (≥18 years of age) and 1 including patients ≥15 years (14). Of the studies, 3 included only patients with diabetes (14–16). The study by Green et al specifically explored the outcomes of patients without diabetes who presented with infection and hyperglycemia (17). We attempted to contact the authors of 4 of the studies with questions regarding patient demographics, specific values for patient characteristics and outcomes in the case of abstracts, and clarification regarding study methodology or data analysis (14,15,18,19). We received responses from 2 of the authors (14,19).

Of the studies included, 5 were conducted with patient populations in North America (15,17,19–21), while the other 3 were conducted in Ireland (18), Taiwan (16) or Ethiopia (14).

Patient demographics for each of the studies are outlined in Table 2. Male patients comprised 36.5% to 62.6% of the patient population across the studies. Patient ages ranged from 15 to 88 years (mean age, 36 to 65 years).

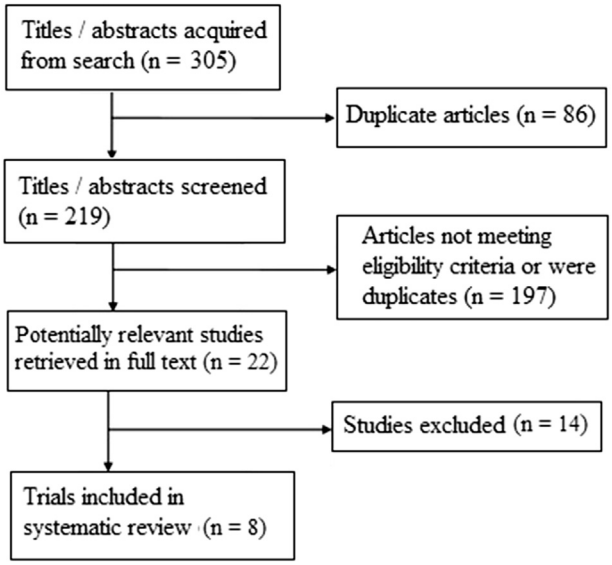

Figure 1. Flow diagram of the selection of eligible studies for systematic review.

Risk of bias

The assessment of the included studies was completed using a modified Newcastle-Ottawa scoring system in which each observational study could receive a maximum score of 8 (Supplementary Table 1). Overall, 5 of the studies received a total score of 8 (15,17,19–21); 1 received a score of 7 (14); and 2 received a score of 6 (16,18).

All the observational studies met the criteria for selecting representative cohorts (hyperglycemic patients in the ED), and all studies extracted data through secure records to maintain patient confidentiality. However, with regard to comparability, only the 5 studies receiving a score of 8 matched the control and study groups for age (1 point) as well as other factors (an additional point), with an adjusted odds ratio being available (15,17,19–21). The study that received a score of 7 adjusted only for age or other factors, but not both (14). The 2 studies that received a score of 6 did not meet the "comparability" criteria for any factors (16,18).

With regard to evaluating the risk of bias present in outcomes, all studies met the criteria for assessing outcomes through record linkage (1 point) and having adequate follow up for at least 7 days (1 point).

Data synthesis

Tables 1 and 3 summarize the potential risk factors identified in the studies. Predictors of adverse outcomes included older age (≥65 years), lowest income quintile, urban dweller, presence of comorbidities, presence of sepsis, coexisting hyperlactatemia, sentinel visit for hyperglycemia in the past month, access to a family physician, patients who required insulin for diabetes management, elevated serum creatinine level (>106 μmol/L) and high blood glucose level (>20 mmol/L) as measured in the ED.

Factors associated with potentially favourable outcomes included a systolic blood pressure of 90 to 150 mmHg and tachycardia (heart rate over 110 bpm). Conflicting results were present between some studies as to whether younger age (<25 years) or a previous history of diabetes were related to adverse outcomes. Factors that were not predictive of adverse outcomes included sex and discharge glucose levels on the index visit.

Table 1
Qualitative analysis of included studies describing the geographic location, type of study, inclusion and exclusion criteria, and risk factors identified

Study	Country	Type of study	Inclusion criteria	Exclusion criteria	Outcomes of interest	Risk factors identified*
Booth (2003)	Canada	Retrospective cohort	• Patients with diabetes	• No census data available	• Repeat hospitalization or ED visit	• Age <18 years (2.6 vs. 1.6 ED visits, p < 0.001) • Urban dwellers (2.0 vs. 1.8, p <0.001) • Lowest income quintile (1.9 vs. 1.6, p < 0.001)
Chou (2014)	Taiwan	Prospective cohort	• Age >18 years • DKA, HHS or mixed syndrome	• Insufficient data	• 30-day mortality	• History of diabetes (12.9% vs. 3.7%, p = 0.021)
Desse (2015)	Ethiopia	Retrospective cohort	• Diagnoses of diabetes, with HEs • Age ≥15 years	• Pregnant • Incomplete data	• In-hospital mortality	• Comorbidity [AOR: 15.26 (95% CI: 3.67-63.41), p <0.001] • Sepsis [AOR: 9.38 (95% CI: 1.59-60.79), p = 0.014] • Age: highest rate ≥ 65 years (37.5%); lowest in 15-24 age group (2.5%) • High serum Creatinine (>106 umol/L) [AOR: 5.86 (95% CI: 1.36-25.28), p < 0.02] • Not predictive: sex, history of DM
Driver (2016)	USA	Retrospective cohort	• Age ≥18 years • Glucose ≥22.2mmol/L at any point in ED	• Admitted from ED • T1DM • CC = hypoglycemia	• Repeat ED visit for HE • Hospitalization within 7 days of index ED encounter	• Not predictive: discharge glucose level for repeat ED visit [AOR: 0.997 (95% CI: 0.993-1.001)] or hospitalization [AOR: 0.998 (95% CI: 0.995-1.002)]
Glynn (2013)	Ireland	Retrospective†	• Acutely ill		• In-hospital mortality by day 30	• Protective: Known history of diabetes [OR: 0.74 (95% CI: 0.56-0.98), p = 0.04]
Green (2012)	USA	Post-hoc nested analysis of retrospective cohort	• Patients without diabetes • Age ≥ 21 years • Hospitalized with admitting diagnosis of infection • 2+ SIRS criteria • Serum lactate and glucose tests in ED	• Repeat ED encounters (i.e. only initial visit included)	• 28-day mortality	• Coexisting hyperlactatemia (OR: 3.96, 95% CI = 2.01 to 7.79)
Schuetz (2011)	USA	Prospective cohort	• Age ≥18 years • Clinically suspected infection • Hospital admission from ED		• In-hospital mortality for any reason	• Patients without diabetes [AOR 2.1 (95% CI 1.4-3.0)] • Not predictive: diagnosis of diabetes [AOR: 1.0 (95% CI 0.2-4.7)], age, sex, disease severity or sepsis.
Yan (2017)	Canada	Retrospective cohort	• Age ≥18 years • Discharge diagnosis of HE, DKA, HHS.	• ACD: refusal of treatment • Transferred from peripheral / community hospital	• Recurrent ED visits / hospitalization for hyperglycemia	• Previous hyperglycemia visit in past month [AOR: 3.5 (95% CI: 2.1-5.8), p <0.01] • Age < 25 [AOR: 2.6 (95% CI: 1.5-4.7), p <0.01] • Glucose > 20 mmol/L [AOR: 2.2 (95% CI: 1.3-3.7), p <0.01] • Having a family physician [AOR: 2.2 (95% CI: 1.0-4.6), p = 0.04] • Taking insulin [AOR: 1.9 (95% CI: 1.1-3.1), p = 0.02] • Protective: SBP: 90-150 mmHg [AOR: 0.53 (95% CI: 0.30-0.93), p = 0.03] • Protective: HR > 110 bpm [AOR: 0.41 (95% CI: 0.23-0.72), p <0.01]

ACD, Advance care directive; *AOR*, adjusted odds ratio; *bpm*, beats per minute; *CC*, chief complaint; *CI*, confidence interval; *DKA*, diabetic ketoacidosis; *ED*, emergency department; *HE*, hyperglycemic emergency; *HHS*, hyperosmolar hyperglycemic state; *HR*, heart rate; *OR*, odds ratio; *SBP*, systolic blood pressure; *SIRS*, systemic inflammatory response syndrome; *T1DM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

* OR provided for studies which made these available in manuscripts.

† Retrospective analysis of prospective group.

Table 2
Patient characteristics in each of the studies

Study	Total study participants	Sex	Age (years ± SD)	Type of diabetes
Booth (2003)	605,825 DM, with 87,425 (14%) seen for hypo- or hyperglycemia 94% hospitalizations due to hyperglycemia	52.0% M	Mean 58.8	100.0% DM patients
Chou (2014)	330 emergency admissions 295 unique patients	40.1% M	Mean 60.5±21.3	24.5% with no history of DM
Desse (2015)	163 hyperglycemic patients	62.6% M	Mean: 36.57±15.91 (Range, 15–84 years)	63.8% T1DM 45.4% newly diagnosed
Driver (2016)	422 patients with 566 ED encounters	58.0% M	Mean 46.9±12	100.0% T2DM
Glynn (2013)	45,068 ED admissions • 3,288 (7.3%) with presentation glucose of >7, ≤10.0 mmol/L • 2,109 (4.7%) with presentation glucose >10 mmol/L	52.1% M*	Mean 64.9	11.4% previously diagnosed or impaired glucose tolerance
Green (2012)	1,234 patients • 115 (9.3%) hyperglycemic	36.5% M in HE cohort	Median 80 (IQR: 72–88) in HE cohort	0.0% with diabetes
Schuetz (2011)	7,754 patients	48.8% M	Mean: 54–60	23.7% with diabetes
Voulgaris (2011)	106 cases of DKA in 713 insulin-treated T2DM patients	Not available	Mean: 58±5.0	100.0% T2DM
Yan (2017)	833 emergency admissions • 645 unique patients • 156 (18.7%) with repeat visits	54.6% M	Mean: 48.8±22.4 (Range: 18–88)	39.0% T1DM 47.6% T2DM 13.4% new DM

DKA, Diabetic ketoacidosis; *DM*, diabetes mellitus; *ED*, emergency department; *HE*, hyperglycemic emergency; *M*, male; *T1DM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

* Includes patients with both hypo- and hyperglycemia.

Discussion

Factors of interest

Age

Research by Desse et al indicated that patients who were older had higher mortality rates following ED visits (14). Similarly, Chou et al (who found that hyperglycemic patients with diabetes had greater rates of mortality than those without diabetes) noted a difference in the subgroup characteristics in which patients with diabetes tended to be of older age ($p<0.05$) (16). This is consistent with previous findings that older patients are more likely to have additional risk factors or comorbidities, and are at higher risk for death (22).

Additionally, younger age (defined as age <25 years in the study by Yan et al, and age <18 years in the study by Booth et al) was associated with increased frequency of recurrent hospital (or ED) visits (15,21). Among youth, type 1 diabetes mellitus, or insulin-dependent diabetes, is more prevalent than type 2 diabetes (23–25). It is often associated with a lower threshold for hyperglycemic emergencies and higher rates of complications if adequate glycemic control is not achieved, because patients with type 1 diabetes do not have endogenous insulin production (26). It was hypothesized by both Booth et al and Yan et al that younger patients may be less adherent or have less experience with their condition, resulting in recurrent visits and adverse outcomes (15,21). Previous research has indicated that youth transitioning to adulthood have high rates of nonadherence (61.3%) or suboptimal medication control (21.3%), precipitating hyperglycemia (27). Often, these patients will be or have been discharged from the care of pediatricians, and studies have shown high rates of loss to follow up (28). These are key factors that could warrant greater emphasis in diabetes management of youth.

Socioeconomic factors

The illness burden on patients with lower incomes has been studied extensively and indicates that these individuals face higher rates of illness or complications and have slower recovery periods for various diseases (29–31). The prevalence of diabetes may be 2 times greater in low-income populations than in their higher-income counterparts (32,33). This was exemplified in the study by Booth et al, which indicated that the population in the lowest income quintile was not only 44% more likely to have a diabetes emergency but was also at greater risk for recurrent ED visits ($p<0.001$) (15). The authors suggest this may be due to increased difficulty with transportation costs, affordability of medications and being unable to take time off from work to attend appointments. This may result in less preventive care and poorer management of health, thereby increasing the susceptibility of this population to additional episodes of hyperglycemia.

Booth et al also suggested that patients who live in urban areas are at increased risk for recurrent hyperglycemic emergencies ($p<0.001$) (15). There have been conflicting results concerning this topic; some studies have associated rural regions with having a higher prevalence of diabetes and complications, while others state that patient populations in urban areas have higher risks (34–37). It would be beneficial to study this variable in greater depth, with subgroup analyses, to determine whether sex, income level and accessibility are major contributors to an increased risk for episodes of hyperglycemia.

Known history of diabetes

There was no consensus among studies on the association between known diabetes history and adverse outcomes. The study by Chou et al suggested that a known history of diabetes may be related to a higher risk of mortality ($p = 0.021$) (16). Yan et al also found a univariate association between a known history of diabetes and recurrent ED visits ($p = 0.004$). They also indicated a statistical significance for a higher risk of recurrent ED visits among patients who have family physicians (AOR 2.2; 95% CI 1.0-4.6; $p = 0.04$) (21). In their discussion, the research team identified this as being an unexpected finding, and as such, reviewed the original patient records to ensure accurate coding in their database, as well as statistical accuracy. The calculated lower limit of the 95% CI for the risk factor was 1.01, confirming that there is an association between having a family physician and recurrent ED visits. The authors hypothesized that patients with more diabetes-related symptoms and

Table 3
Summary of factors identified as being associated with risk or protective for recurrent visits or mortality*

	Associated with risk	Associated as protective	Not predictive
Age Younger age (< 25)	• Booth (2003): age < 18 years (p < 0.001) • Yan (2017): age < 25 years [AOR: 2.6 (95% CI: 1.5-4.7), p <0.01]	• Desse (2015): 15-24 age group (2.5% vs. 37.5% if age ≥ 65 years)	• Schuetz (2011): for in-hospital mortality
Older age (> 65)	• Desse (2015): age ≥ 65 years (37.5% vs. 2.5% in the 15-24 age group)		
Known history of diabetes	• Chou (2014): 30-day mortality (p = 0.021) • Yan (2017): 30-day return ED visit (p = 0.004)	• Glynn (2013): for in-hospital mortality [OR: 0.74 (95% CI: 0.56-0.98), p = 0.04]	• Desse (2015): for in-hospital mortality [AOR: 4.88 (95% CI: 0.95-24.97), p = 0.06] • Schuetz (2011): for in-hospital mortality [AOR: 1.0 (95% CI 0.2-4.7)]
No diabetes history		• Schuetz (2011): for in-hospital mortality [AOR: 2.1 (95% CI 1.4-3.0)]	
Requiring insulin	• Yan (2017): for repeat visit or 30-day in-hospital mortality [AOR: 1.9 (95% CI: 1.1-3.1), p = 0.02]		
Comorbidity	• Desse (2015): for in-hospital mortality [AOR: 15.26 (95% CI: 3.67-63.41), p <0.001]		
Sepsis	• Desse (2015): for in hospital-mortality [AOR: 9.38 (95% CI: 1.59-60.79), p = 0.014]		• Schuetz (2011): for in-hospital mortality
Previous visit for hyperglycemia	• Yan (2017): previous visit in the past month [AOR: 3.5 (95% CI: 2.1-5.8), p <0.01]		
Glucose levels during visit	• Yan (2017): initial glucose > 20 mmol/L in the ED [AOR: 2.2 (95% CI: 1.3-3.7), p <0.01]		• Driver (2016): discharge glucose level for repeat ED visit [AOR: 0.997 (95% CI: 0.993-1.001)] or hospitalization [AOR: 0.998 (95% CI: 0.995-1.002)]
Bloodwork (other than glucose levels)	• Green (2012): co-existing hyperlactatemia (OR: 3.96, 95% CI = 2.01 to 7.79) • Desse (2015): high serum creatinine (>106 umol/L) [AOR: 5.86 (95% CI: 1.36-25.28), p < 0.02]		
Vital signs		• Yan (2017): SBP: 90-150 mmHg [AOR: 0.53 (95% CI: 0.30-0.93), p = 0.03] • Yan (2017): HR > 110 bpm [AOR: 0.41 (95% CI: 0.23-0.72), p <0.01]	
Living in an urban setting	• Booth (2003): for recurrent ED visits (2.0 vs. 1.8, p <0.001)		
Lowest income quintile	• Booth (2003): for recurrent ED visits (1.9 vs. 1.6, p < 0.001)		
Having a family physician	• Yan (2017): for repeat visit or 30-day in-hospital mortality [AOR: 2.2 (95% CI: 1.0-4.6), p = 0.04]		

ED, Emergency department; *HE*, hyperglycemic emergency; *SBP*, systolic blood pressure; *HR*, heart rate; *bpm*, beats per minute.
* Odds ratio provided for studies that made these available in manuscripts.

comorbidities may require closer follow up or may be more proactive about having a physician with whom to follow up, and generally have a worse prognosis. Meanwhile, patients with milder disease or those with better glycemic control may not be registered with a family physician.

Yan et al discussed that the retrospective nature of their study was an inherent limitation; as such, they were also unable to confirm accessibility to follow up for patients who were rostered with a family physician. A prospective study is in progress to account for questions and limitations of the retrospective study. The abstract for this prospective study indicated that 36% of patients with even 1 ED visit for hyperglycemia saw their family physician after the initial ED visit. However, a statistical significance to indicate if this has any impact on recurrent ED visits was unavailable at the time of submission of this systematic review (38). Finally, they stated that the retrospective nature of the study prevented them from assessing patient perception of the urgency of their illness process, as previous research has suggested this could be a factor in patients waiting to see a family physician or presenting immediately to the ED (39,40).

On the other hand, research by Desse et al suggested a history of diabetes has no statistically significant predictive value on mortality (AOR 4.88; 95% CI 0.95-24.97; p = 0.06), while Glynn et al and an abstract by Lucas et al indicated that a known history of diabetes may instead be protective for in-hospital mortality (OR 0.74; 95% CI 0.56-0.98; p = 0.04 and AOR 0.3; 95% CI 0.1-0.6; p <0.001, respectively) (14,18,41). The study by Glynn et al defined hyperglycemia as a blood glucose level of over 7.0 mmol/L, and did not differentiate the findings for patients who presented with blood glucose levels over 11.0 mmol/L; however, this study was included to make this systematic review comprehensive. Schuetz et al similarly found that having no previous diagnosis of diabetes placed patients presenting with hyperglycemia at greater risk of in-hospital mortality (AOR 2.1; 95% CI 1.4-3.0) (19). This may be because patients who are undiagnosed or do not have diabetes are likely to have less follow up and longer periods of untreated blood glucose levels, resulting in poorer outcomes (4). Unfortunately, due to the retrospective nature of these studies, it was difficult to assess why this was the case, and it would be beneficial to investigate this factor further through prospective studies.

Diabetes medications

Although diabetes can be controlled through diet, patients often require oral hypoglycemic medications or insulin to ensure optimal glucose control. Good adherence to diet and medication limits diabetes complications (42). It also slows disease progression and end-organ damage, thus conferring a survivability benefit (42). Yan et al found that patients taking insulin had higher risks for adverse outcomes (AOR 1.9; 95% CI 1.1 to 3.1; p=0.02), while an abstract by Lucas et al determined that oral hypoglycemic use is a protective factor (AOR 0.2; 95% CI 0.07 to 0.6; p<0.01) (21,41). The need for various types of medication can often be used as a surrogate marker for disease severity because the need for exogenous insulin is associated with a greater risk for type 2 diabetes complications and mortality (43). Patients with type 2 diabetes are commonly prescribed oral hypoglycemic medications initially if blood glucose levels are not sufficiently controlled by lifestyle modifications. Treatment progresses to insulin therapy if there is a high level of ongoing glucose intolerance and poor control despite maximal oral hypoglycemic medication therapy (44). Thus, findings that insulin use is correlated with worse outcomes may result from patients already experiencing more substantial effects of the disease, and they may already be at higher risk for hyperglycemic events. Further research may be needed to elucidate the characteristics of patients that predispose them to recurrent ED visits or higher mortality rates.

Severity of disease and issues with adherence

An abstract by Manjunatha et al determined that there was a lower mortality rate in patients with no previous admission in the past 12 months (p<0.001) (45). Similarly, Yan et al found factors independently associated with recurrent ED visits, including having a sentinel hyperglycemia visit in the past month (AOR 3.5; 95% CI 2.1 to 5.8; p<0.01) or a higher triage glucose level >20 mmol/L (AOR 2.2; 95% CI 1.3 to 3.7; p<0.01) (21). These factors potentially predispose patients to hyperglycemic episodes due to poorer adherence, the impact of polypharmacy (such as steroid use) or the presence of comorbidities. Such patients would be expected to have greater rates of ED visits with regard to poor glycemic control, because medication issues (nonadherence, underdosing and insulin-pump problems) have been shown to account for 67.1% of hyperglycemic emergencies (9). Desse et al reported that patients of older age and those who had more comorbidities (including serum creatinine levels greater than 106 μmol/L) had higher mortality rates (14). The elevated serum creatinine may be a marker of diabetic nephropathy, suggestive of more severe diabetes progression and worse prognosis (46). This is consistent with previous findings that medication nonadherence is linked to faster disease progression and end-organ damage, resulting in poorer outcomes (47). Driver et al suggested that for these patients, glucose levels at the time of discharge from the ED are not associated with recurrent ED visits (AOR 0.997; 95% CI 0.993 to 1.001) or hospitalization (AOR 0.998; 95% CI 0.995 to 1.002) (20). Thus, it is likely that patient adherence and education may be greater predictors of recurrent visits, suggesting that more efforts should be aimed toward those factors.

Infection

Sepsis was found to be a significant risk factor in the study by Desse et al (AOR 9.83; 95% CI 1.59 to 60.79; p=0.014] (14). Similarly, Chou et al found that sepsis was the precipitating component of all deaths in patients without diabetes and in 84.4% of patients with diabetes (16). However, Schuetz et al suggested that among patients with sepsis and with hyperglycemia, only patients without diabetes were associated with higher levels of mortality compared to patients with diabetes (19). Green et al performed a subgroup analysis of patients with hyperglycemia who did not have diabetes, but did have sepsis; the analysis demonstrated that only those with hyperlactatemia had a greater risk for mortality (17). Normal lactate levels were not associated with a statistically significant risk. High serum lactate levels have been well described as a poor prognostic factor for any patient with sepsis because it is indicative of poor tissue perfusion and, thus, end-organ damage (48). Further research should be conducted to assess whether this difference between populations with and without diabetes is truly significant with regard to sepsis. However, these findings do suggest that interventions to reduce infection rates and ensure good volume status and oxygenation could result in decreased mortality in patients with hyperglycemia.

Access to a diabetes team during ED visit or hospitalization

Although this study was not included in the final results of this systematic review, an abstract by Manjunatha et al stated that patients who received care from a diabetes team in hospital were less likely to die during an unspecified time period (p=0.01) (45). This is likely because proper follow up or diabetes-specific care could reinforce the importance of diabetes management. Since only 1 study with a small sample size studied this factor, further research in this field could allow for cost-benefit analysis of access to a diabetes care team during admissions for diabetes-related health issues.

Role of culture and language barriers

Although it did not meet the inclusion criteria for this review, a study by Okrainec et al explored the role of language barriers among immigrant populations with diabetes, as one might expect this factor to be associated with higher rates of complications and mortality (49). However, they reported no statistical difference when a hazard ratio was calculated. This study did not take into account repeat admissions, and the outcome of death was not independently measured (that is, it was combined with cardiovascular events).

An abstract by Voulgaris et al found that readmission rates differ among ethnic minorities in Greece, with readmission for DKA being more common in the Romanian cohort compared to Albanians (p<0.001) (50). Deaths among study participants (2%) also occurred only with these 2 ethnic minorities, but they did compose 75% of the sample size, making it unclear if this was of statistical significance (50). It may be useful to investigate discrepancies between ethnic minorities to determine the impact of socioeconomic status, literacy and cultural beliefs and how these translate into health outcomes. This could be useful in determining whether additional resources should be put in place to enable better health care for immigrant populations.

Tachycardia as a protective factor

The study by Yan et al identified that patients who presented with both hyperglycemia and tachycardia had more favourable outcomes with respect to return ED visits for hyperglycemia. After performing a sensitivity analysis and adjusting for hospital admissions from the index visit, tachycardia was still found to be protective (unadjusted OR 0.42, 95% CI 0.24-0.74 vs. adjusted OR 0.41, 95% CI 0.23-0.72). The authors hypothesized that individuals presenting with tachycardia may have had comorbid conditions not related to diabetes; therefore, this patient population may have been less likely to return to the ED for hyperglycemia within 30 days (23).

Limitations

Several limitations were identified in this review. Some of the studies had small sample sizes and may not have had adequate power to draw conclusions that would be applicable to larger

populations. Multiple risk factors were only studied in a single research paper, so their findings can only be used to drive further research to determine whether there was a true association between the risk factors identified and the outcomes of interest. A few studies also did not provide multivariate regression analyses. These limitations meant we were limited in assessing the impacts of findings with respect to statistical significance or subgroup analysis.

Additionally, although we attempted to contact authors of 4 of the publications, we received only 2 responses. This made it difficult to accurately interpret some of the results and their relevance to the question of this review. However, to avoid excluding potential results, we decided to include these studies in our systematic review.

The search strategy was done through only MEDLINE and EMBASE, and our search excluded studies not published in the English language, so some research papers may have been missed. Finally, most of these studies were retrospective in nature, making it difficult to evaluate additional factors that may not be routinely documented, such as medication adherence or follow up. The retrospective nature of the studies also limited the explanation for unexpected findings in some studies.

Conclusions

Overall, the 8 studies included in this systematic review identified potentially modifiable and nonmodifiable risk factors in patients with hyperglycemia that could predict adverse outcomes, such as recurrent visits to EDs because of hyperglycemia and hospitalizations or death within 30 days. These included patient age, income, urban dwelling, previous hospital or ED visit, known history of diabetes, presence of comorbidities, blood glucose level in the ED, presence of sepsis, serum creatinine level, coexisting hyperlactatemia, diabetes managed with insulin and access to family physicians. Patient and physician awareness of these factors may benefit patients because it could result in closer follow up that would minimize adverse outcomes. These factors reinforce the importance of using an individualized care approach to optimize diabetes management based on patient- and disease-specific factors. Further research is needed to evaluate each of these potential predictors and the impact of integrating this knowledge in current health-care practices to reduce adverse outcomes in hyperglycemic patients.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at www.canadianjournalofdiabetes.com.

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Author Contributions

JY designed the initial research question, with revisions provided by LS, KVA and JY to finalize outcomes of interest. AI defined the parameters of the search, designed the literature search strategy and modification across databases, and reported the search methodology for manuscript. LS and KVA performed the initial screen of all titles and abstracts for relevance to the research question, and reviewed full-length manuscripts for final inclusion. JY performed a manual screen of reference lists of relevant studies to identify additional potential literature, and reviewed articles for which a consensus could not be reached for final study selection. KVA calculated the Cohen's Kappa statistic for inter-rater agreement of final study selection. LS synthesized data, completed a risk of bias assessment for included studies, and drafted the first version of the manuscript. All authors critically revised and approved the final manuscript for submission.

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Supplementary Material.
Search strategy: Ovid MEDLINE 1946 to September 2014

Database: Ovid MEDLINE, Epub ahead of print, in-process and other nonindexed citations, Ovid MEDLINE Daily and Ovid MEDLINE <1946 to June 9, 2017.

Search Strategy:

1. exp Emergency Medical Services/or emergency.af. (343,516)
2. exp diabetes mellitus/or diabetes$.mp. (558,829)
3. (diabetic$ adj3 (acidosis$ or acidosis$ or ketoacidoses$ or ketoacidosis$ or ketoses$ or ketosis$)).mp. (7,591)
4. (diab$ and DM).tw. (15,917)
5. (dm2 or t2dm or MODY or niddm or iidm or non insulin depend$ or noninsulin depend$ or noninsulindepend$ or non insulin?depend$ or type 2 diab$ or type ii diab$ or type 2 DM).tw. (126,351)
6. or/2-5 (561,226)
7. exp hyperglycemia/(32,001)
8. (hyperglyc?em$ or hyperglucem$).mp. (61,599)
9. or/7–8 (68,158)
10. 1 and 6 and 9 (629)
11. Patient Readmission/or (recurr$ or re-curr$ or readmit$ or re-admit$ or readmission$ or re-admission$ or rehospitali$ or re-hospitali$ or recidiv$ or re-cidiv$ or return$ or (rate$ adj2 admission$) or relaps$ or re-laps$ or recrudescence$ or re-crudescence$).tw. (863,561)
12. (multiple or multi or multi- or repeat$) adj3 (hospitalization$ or visit$ or attendance$ or use$ or using$ or utilizat$ or admission$ or return$).tw. (92,037)
13. (visit or visits).tw. (146,709)
14. or/11-13 (1,079,109)
15. 10 and 14 (95)
16. limit 15 to English language (91)
17. (mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or sheep$1 or swine$1 or pig$1 or canine$1 or feline$1 or porcine$ or calf).ti. (1,658,653)
18. 16 not 17 (91)

Supplementary Table 1
Risk of bias assessment of the 8 studies included in this systematic review

Newcastle-Ottawa Quality Assessment Scale for Cohort Studies									
Study	Selection				Comparability	Outcome			Total score (max 8)
	Representativeness of the exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome	Length of follow up	Adequacy of follow up	
Booth (2003)	*	*	a*	N/A	**	b*	*	*	8
Chou (2014)	*	*	a*	N/A		b*	*	*	6
Desse (2015)	*	*	a*	N/A	*	b*	*	*	7
Driver (2016)	*	*	a*	N/A	**	b*	*	*	8
Glynn (2013)	*	*	a*	N/A		b*	*	*	6
Green (2012)	*	*	a*	N/A	**	b*	*	*	8
Schuetz (2011)	*	*	a*	N/A	**	b*	*	*	8
Yan (2017)	*	*	a*	N/A	**	b*	*	*	8

Notes: The Newcastle-Ottawa Quality Assessment Scale for Cohort Studies was used. The total number of stars possible was 8. Quality assessment was done by 1 investigator (LS), and any uncertainties were discussed with other investigators (JY and KVA).
Selection: A maximum of 3 stars: 1 star was allocated for whether the cohort was truly (A) or somewhat (B) representative of the average patient with hyperglycemia (with or without certain traits, such as infection, depending on study inclusion criteria) in the community; 1 star was allotted if the comparison group was drawn from the same community as the exposed cohort; 1 star could be obtained if ascertainment of exposure was done through access to a secure record (A) or through a structured interview (B). The outcomes of interest could not have been present at the start of the study, so the fourth category was not applicable in any of these papers.
Comparability: A maximum of 2 stars was assigned if the control and study groups were matched for comparability, for age (1 star) or other factors (1 star) (i.e. an adjusted odds ratio was calculated).
Outcome: A maximum of 3 stars: 1 star was allotted for each of the following: if assessment of outcome was done through independent blind assessment (A) or record linkage (B); if follow up was long enough for outcomes to occur; if (A) complete follow up was present, or (B) if subjects lost to follow up were unlikely to introduce bias (75% follow up).