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Accuracy of a Composite Event Definition for Hypoglycemia

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Abstract

Purpose: To evaluate the accuracy of a composite definition for the identification of hypoglycemia events that used both administrative claims and laboratory data in a cohort of patients.

Methods: We reviewed medical records in a sample of presumed hypoglycemia events among patients who received care at the Veterans Health Administration Tennessee Valley Healthcare System in 2001–2012. A hypoglycemia event was defined as a hospitalization or emergency department visit judged by the treating clinician to be due to hypoglycemia, or an outpatient laboratory or point-of-care blood glucose measurement <60 mg/dL. Based on medical record review, each event was classified as true positive (severe, documented symptomatic, documented asymptomatic) or false positive (probable symptomatic, not hypoglycemia). The positive predictive values (PPV) of the individual event types (hospitalization, emergency department and outpatient) were estimated.

Results: Of 2250 events identified through the composite definition, 321 events (15 hospitalizations, 103 emergency department visits, and 203 outpatient events) were reviewed. The PPVs were 80% for hospitalization events, 48% for emergency department events, and 96% for outpatient events. The emergency department definition included a nonspecific diagnosis code for diabetic complications which captured many false positive events. Excluding this code from the definition improved the PPV for emergency department events to 70% and missed one true event.

Conclusions: Our composite definition for hypoglycemia performed moderately well in a cohort of Veterans. Further evaluation of the emergency department events may be needed.

Keywords

hypoglycemia; algorithm; positive predictive value; type 2 diabetes

Introduction

Hypoglycemia is an important side effect associated with use of insulin and sulfonylureas, which are common second-line antihyperglycemic medications used to treat type 2 diabetes.¹ Hypoglycemia due to antihyperglycemic therapy is associated with poor quality of life, adverse clinical outcomes such as cardiovascular disease and death, and high healthcare costs.^{2–6} Experts recommend considering the risk of hypoglycemia when evaluating diabetes treatment effectiveness.⁷ However, assessing the occurrence of hypoglycemia events accurately on a population level is challenging because many events are not captured through healthcare encounters.^{8,9} There is agreement among providers and researchers that any hypoglycemia event requiring hospitalization or emergency care is a severe event. Nonetheless, a low glucose measurement at any time can be clinically meaningful due to its potential physiologic effects, even when the patient reports no symptoms.¹⁰

Observational studies and clinical trials examining the effects of antihyperglycemic drugs have identified hypoglycemia events through various definitions. Our group recently developed a composite event definition for hypoglycemia using administrative claims and laboratory data which includes hospitalizations or emergency department visits due to hypoglycemia, and outpatient visits with an associated blood glucose measurement <60 mg/dL.^{11,12} Hospitalizations and emergency department visits are identified through an algorithm of discharge diagnosis codes. The accuracy of claims-associated definitions can vary depending on the institution, setting and time period. Specifically, the emergency department definition was adopted from a previously published algorithm which included a nonspecific code for diabetic complications.¹³ The availability of laboratory data allows identification of additional outpatient events, but it is unknown what proportion of patients with laboratory confirmed hypoglycemia have documented symptoms or receive further care. With the increasing availability of electronic healthcare data for large-scale observational studies and the complex data cleaning and transformation procedures required, a validation of the accuracy of outpatient events is also warranted. The objective of this study was to estimate the accuracy of this composite hypoglycemia event definition in a cohort of Veterans.

Methods

Study design and data sources

We performed chart reviews to validate hypoglycemia events identified through *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*¹⁴ algorithms and outpatient laboratory data. The study was nested within a retrospective cohort constructed using national Veterans Health Administration (VHA) databases including administrative, clinical and laboratory data, which included Veterans 18 years of age or older who received care at the VHA Tennessee Valley Healthcare System between October 1, 2001 and September 31, 2012. The institutional review boards of VHA Tennessee Valley Healthcare System approved the study.

Selection criteria

From the parent cohort population, presumed hypoglycemia events eligible for inclusion in the validation study were identified in the database using the following definitions: 1) hospitalization with a primary ICD-9-CM discharge diagnosis code for hypoglycemia (adapted from Shorr et al¹⁵); 2) emergency department visit with an ICD-9-CM discharge diagnosis code for hypoglycemia in any position (adapted from Ginde et al¹³); or 3) outpatient laboratory or point-of-care blood glucose measurement <60 mg/dL (Table 1). For hospitalizations and emergency department visits we were interested in capturing events where hypoglycemia was the primary reason for the encounter, indicated by a discharge diagnosis code for hypoglycemia in the primary position for hospitalizations and any position for emergency department visits. For outpatient events, we were interested in evaluating whether the outpatient blood glucose information in the cohort database accurately reflected what was recorded in the chart, and how often symptoms were documented.

Medical records were reviewed for all events that met the hypoglycemia definition for hospitalizations, and a random sample of events that met the emergency department definition. For outpatient events, we randomly sampled 100 of 1160 laboratory measurements where blood glucose was between 51–60 mg/dL; 60 of 567 measurements where glucose was between 41–50 mg/dL; and 50 of 285 measurements where glucose was between 0–40 mg/dL. This was done to ensure that we reviewed sufficient charts for those with very low blood glucose measurements. Some patients had more than one hypoglycemia event during the study period, and thus, more than one presumed event per patient were allowed.

Outcome validation

Two trained chart abstractors, who were blinded to administrative data such as diagnoses and medications, reviewed the medical records to verify each of the presumed hypoglycemia events using a structured chart abstraction tool (Appendix A). In addition to hospitalization and emergency department events, outpatient laboratory events were also reviewed to check the consistency and accuracy of the information in the analytic database compared to the electronic health record, as data errors can occur during data cleaning and transformation into common data models. Information on hypoglycemia-related symptoms, treatment, history of present illness, potential contributors to the event, documented glucose measurements, and antihyperglycemic medications at time of event were collected from provider notes, medication and laboratory records in the chart.

Based on medical record review, each presumed hypoglycemia event was classified as a true event if there was a documented blood glucose measurement <60 mg/dL, and then was further classified into subcategories (severe, documented symptomatic, or asymptomatic/atypical) following a modification of the American Diabetes Association (ADA) workgroup definitions (Appendix A).¹⁶ Severe events were those that led to a hospitalization or emergency department visit, where the primary reason for the encounter was noted as hypoglycemia in the chart. Documented symptomatic events had documentation of typical symptoms, whereas asymptomatic/atypical events had no symptoms or atypical symptoms

only. Typical hypoglycemia symptoms included mental status changes, seizure, sweatiness, hunger, palpitations, blurred vision, restlessness, syncope, and faintness or lightheadedness. Atypical symptoms included transient ischemic attack, cerebrovascular accident, myocardial infarction, injury to self or others, and death.

False positive events had no documented blood glucose measurement <60 mg/dL. If there were typical symptoms noted without a documented blood glucose <60 mg/dL, it was further classified as a probable symptomatic event but was counted as a false event because we could not verify that the patient had hypoglycemia.

Data analysis

Using the medical chart reviews as reference the positive predictive values (PPV) and corresponding 95% confidence intervals (CI) were calculated for the individual definitions (hospitalization, emergency department, or outpatient) and each ICD-9-CM code using the Wilson method¹⁷. For a 20% random sample of all abstracted events, both abstractors independently performed chart reviews to assess the reliability of the review process and to estimate the interrater agreement using the kappa statistic.¹⁸ If there was disagreement, a third abstractor reviewed the chart to determine the appropriate classification for the event.

Sensitivity analysis

Our study protocol was developed prior to the publication of the recent ADA and European Association for the Study of Diabetes (EASD) guidelines, which recommends that clinical studies define serious clinically important hypoglycemia as glucose levels of <54 mg/dL regardless of symptoms.¹⁹ We performed sensitivity analyses using 54 mg/dL as the threshold for a true hypoglycemia event.

We also conducted two sensitivity analyses to assess the performance of the emergency department event type under alternative criteria. The first analysis considered only the primary position of the discharge diagnosis codes. The second analysis evaluated a broader definition of true hypoglycemia which considered any low blood glucose in the emergency department to be a true event even if it was not the primary reason for the visit.

Results

Of 2250 potential hypoglycemia events identified among 886 unique patients during the defined study time period, 335 events were selected for chart review (Figure 1). We further excluded 13 events because the charts were not accessible for review. One additional emergency department event was excluded due to missing diagnosis code data. Chart abstractions were completed for 321 events (214 unique patients), including 15 hospitalizations, 103 emergency department visits, and 203 outpatient glucose measurements. The number of events reviewed per patient ranged from 1 to 10. The median age at the time of event was 65 years (interquartile range [IQR] 58,77), and the median documented blood glucose measurement was 53 (IQR 42, 59) mg/dL. At the time of event, 86% had an active prescription for a sulfonylurea or insulin (Table 2). All selected presumed events had a measurement of glucose on the event date, except for one event that was identified through the outpatient blood glucose definition. This event was noted to have a

glucose measurement <60 mg/dL in the cohort database but no laboratory record was found upon reviewing the chart.

Hospitalization events

For hospitalization events, the PPV was 80% (95% CI 55, 93) (Table 3). For individual ICD-9-CM diagnosis codes (primary position only), 251.1 had a PPV of 100%, 251.2 had a PPV of 100%, and 962.3 had a PPV of 67%. Of the 3 false positive events, 2 had no evidence of hypoglycemia but were admitted to the hospital due to intentional metformin overdose. One event was a hospitalization due to hypokalemia.

Emergency department events

For emergency department events, the PPV was 48% (95% CI 38, 57). Of 103 events reviewed, 49 were true hypoglycemia events (5 were asymptomatic) (Table 3). Of the 54 false positive events, 11 were possible hypoglycemia events with no documented glucose measurement <60 mg/dL, and 3 occurred during an emergency department visit for another primary indication and did not meet our event definition which required hypoglycemia as the primary reason for the visit. Of the 40 remaining false positives, 24 were hyperglycemia events, and 7 were related to other diabetes complications such as foot ulcer or cellulitis that were coded incorrectly. For individual ICD-9-CM codes (any position), 251.2 had a PPV of 69%; 962.3 had a PPV of 100%, and 250.8 had a PPV of 8.3%. When the code 250.8 was excluded from the definition, the PPV for emergency department events improved to 70% and only 1 of 49 true events was missed in the study sample. The other 2 true events with 250.8 were captured through another code.

Outpatient events

For outpatient events, the PPV was 96% (95% CI 92, 98) (Table 3). Presumed events that were not true hypoglycemia events included: 3 that occurred during a hospitalization and 1 that occurred during an emergency department visit due to another primary indication, and 4 with no record of blood glucose <60mg/dL. In the latter 4 events, we found that the blood glucose measurement values were inconsistent between the electronic health record and the analytic database.

Of 195 true hypoglycemia events with a confirmed blood glucose <60 mg/dL, 165 (81%) had no documented symptoms; 30 (15%) had typical symptoms, and 7 (23%) of these were severe events that led to an emergency department visit or hospitalization.

The median blood glucose measurements were 39 mg/dL (IQR 28, 44) for severe events; 46 mg/dL (IQR 39, 56) for documented symptomatic events; and 52 mg/dL (IQR 47, 57) for asymptomatic events. Symptoms were noted in 9.9% of 111 events with glucose between 50–60 mg/dL, 16.7% of 60 events with glucose between 40–50 mg/dL, and 31.3% of 32 events with glucose <40 mg/dL. Of the 203 presumed outpatient events, 89 (44%) had no associated clinic visit; 15 had a laboratory appointment only and 74 were in a skilled nursing or long-term care facility with daily point-of-care glucose measurements and nursing evaluations.

Interrater agreement

The two abstractors each independently reviewed 65 presumed events. They disagreed on the validity of the hypoglycemia event for 6 events, and on the specific type of hypoglycemia event (e.g. asymptomatic vs. documented symptomatic) for 7 events. The resulting kappa statistic for interrater agreement was 0.79 for the overall identification of true hypoglycemia events, and 0.61 for assignment of specific hypoglycemia classification. The reasons for disagreement included differential consideration of notes from transferring hospital, misinterpreting inpatient units as the outpatient setting, and missing point-of-care glucose measurements recorded as free text in nursing notes.

Sensitivity analyses

When <54 mg/dL was chosen as the cutoff for a true hypoglycemia event, one hospitalization event and 6 emergency department (ED) events that were originally verified as true hypoglycemia events were re-categorized as false events. The PPV of the hospitalization and emergency department definitions were 73% (95% CI 48, 89) and 42% (95% CI 33, 51), respectively. For outpatient events, we examined the change in total number of outpatient events captured by the alternative cutoff for defining hypoglycemia. The total number of eligible outpatient events for review under this alternative cutoff would have been 1,164. This means we would capture 36.3% fewer events when applying this outpatient definition in a study.

Using an alternative definition for emergency department events where the ICD-9 discharge diagnosis code for hypoglycemia was limited to the primary position only, we found that 64 presumed emergency department events met this definition, 41 of which were confirmed as true cases by chart review. While this alternative definition improved the emergency department event PPV to 64% (95% CI 52, 75), it resulted in missing 8 true events, and the PPV of the nonspecific code 250.8 remained low at 13% (95% CI 4, 38). If the 3 hypoglycemia events that occurred during an emergency department due to another primary cause were reclassified as true cases, the PPV remained similar at 50% (95% CI 41, 60).

Discussion

In this study, the positive predictive value of the composite hypoglycemia definition was 80% for hospitalization events, 48% for emergency department events, and 96% for outpatient events in a sample of Veterans receiving care within VHA. Modifying the emergency department event definition to exclude ICD-9 code 250.8 resulted in higher positive predictive values for that specific event type (70%). Excluding 250.8 from the algorithm led to missing only one of 48 true events, which further justified excluding this code in future studies of our cohort population. Alternatively, limiting the emergency department diagnosis codes to the primary position only improved the PPV but missed several true events.

Our definitions used a threshold of 60 mg/dL to define hypoglycemia events compared to the newer ADA/EASD guidelines of <54 mg/dL to define serious clinically significant hypoglycemia.¹⁹ When we applied this alternative cutoff, the accuracy of the hospitalization

and emergency department event definitions became slightly lower. In addition, we found that we would capture 36.3% fewer presumed outpatient events overall.

In a previous validation study, Ginde et al found that their emergency department algorithm performed well with a positive predictive value of 89%.¹³ We adapted their algorithm for our composite definition, but found that our positive predictive value was much lower. There are many possible explanations for these results, including differences in administrative coding at institutions, study period, and validation methods. Ginde et al validated their algorithm at 3 institutions during the time period 2005–2006, while we validated events at a single institution for a longer study period, 2001–2012. Importantly, the diagnosis code with the lowest performance in our study (ICD-9-CM 250.8) is a nonspecific code, so it is possible that different institutions used this code differently.

Our study adds valuable information to previous validation studies of hypoglycemia in that it evaluated a composite definition which includes hospitalizations, emergency department visits, and outpatient events based on blood glucose measurements. The identification of serious events that result from medications used in the outpatient setting is paramount to evaluating the comparative effectiveness of diabetes regimens. Because medications are often administered during the course of a visit to an emergency department or after hospital admission, we excluded events in which hypoglycemia occurred after presentation or was not the primary reason for admission. However, including hypoglycemia events which occurred during the course of an emergency department visit as true events did not change the main results. For outpatient events, we considered records for point-of-care or laboratory blood glucose measurements to identify true events. Upon conducting chart reviews, we found that only 15% had documentation of hypoglycemia-related symptoms or were transferred to the ED or hospital setting for further treatment of hypoglycemia. These patients had a lower median blood glucose measurement compared to those who had no record of symptoms or further treatment.

One limitation of this study is that we only reviewed presumed events that met the composite definition, and thus could only estimate the positive predictive values but not the sensitivity, specificity, or negative predictive values. To estimate these other parameters, we would have had to perform chart reviews on a sample of patients who were not identified as having a hypoglycemic event. This would have greatly increased the data collection burden and created additional challenges with regards to control sampling. Even with the selection of controls, it would have been difficult to estimate the sensitivity of the definition with accuracy, since many hypoglycemia events that occur in the community setting are not captured in medical records, though we included an outpatient definition to capture more events..^{6,8,9} For the outpatient events that are based on laboratory glucose measurements, spuriously low glucose values may occur due to glycolysis if the blood samples are untreated and there is any delay in testing. However, 53% of all outpatient events we reviewed were based on point-of-care glucose values, where this particular issue would not have been a concern. Finally, ICD-10 codes identifying hypoglycemia events need to be validated separately.

In summary, we found that our composite definition for hypoglycemia performed moderately well in identifying true hypoglycemia cases in a cohort of Veterans with type 2 diabetes. However, the nonspecific ICD-9-CM code 250.8 from the emergency department event definition captured many false positive events. Excluding this code from the definition improved the positive predictive value of the algorithm in our study population. Further validation of the emergency department algorithm may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Key Points:

1. We developed a composite event definition for the identification of hospitalizations and emergency department visits due to hypoglycemia and outpatient hypoglycemia episodes using administrative claims and laboratory data.
2. We completed chart reviews for a sample of 321 presumed hypoglycemia events identified by the definitions, and found that the positive predictive values (PPV) were 80% for the hospitalization events and 96% for the outpatient laboratory events.
3. The PPV of the emergency department event definitions, which was adopted from a previous study, was low (48%) in our study population, warranting further evaluation.

Figure 1.
Identification of potential hypoglycemia cases that were selected for chart review and validation

Table 1.

Description of composite event definition for hypoglycemia

A. Event types and definitions	
<i>Hypoglycemia Event</i>	<i>Definition</i>
1. Hospitalization	ICD-9 CM discharge diagnosis codes 251.0, 251.1, 251.2, 962.3, or 270.3 in <u>primary</u> position
2. Emergency Department	ICD-9 CM discharge diagnosis codes 251.0, 251.1, 251.2, 962.3, 270.3, or 250.8 without co-existence of 259.8, 272.7, 681.X, 682.X, 686.9, 707.1–707.9, 730.0–730.2, or 731.8 in <u>any</u> position *
3. Outpatient	Outpatient laboratory or point-of-care blood glucose measurement <60 mg/dL
B. Description of ICD-9-CM codes used in definitions	
<i>ICD-9-CM code</i>	<i>Description</i>
251.0	Hypoglycemic coma
251.1	Other specified hypoglycemia
251.2	Hypoglycemia, unspecified
962.3	Poisoning by insulins and antidiabetic agents
270.3	Disturbances of branched-chain amino-acid metabolism
250.8 *	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
*Without coexistence of:	
259.8	Other specified endocrine disorders
272.7	Lipidoses
681.X	Cellulitis and abscess of finger and toe
682.X	Other cellulitis and abscess
686.9	Unspecified local infection of skin and subcutaneous tissue
707.1–707.9	Chronic ulcer of skin
730.0–730.2	Osteomyelitis
731.8	Other bone involvement in diseases classified elsewhere

* Concurrent CPT codes were required to identify correct encounter type (emergency department) in the database: 99281, 99282, 99283, 99284, 99285, or 99288

Table 2.

Characteristics of presumed hypoglycemia events reviewed

<i>Characteristic</i>	<i>Study sample N=321 events*</i>
Age, median (IQR) *	65 (58, 77)
Male (%)	307 (96%)
Race, (%)	194 (60%)
White	
Black	108 (34%)
Hispanic/Other	3 (1%)
Missing	16 (5%)
Diagnosed with diabetes, %	311 (97%)
Event type	
Hospitalization	15
Emergency department visit	103
Outpatient glucose measurement <60 mg/dL	203
Typical symptoms (%)	102 (32%)
Atypical symptoms (%)	21 (7%)
Blood glucose (mg/dL) at time of event, median (IQR)	53 (42, 59)
On antidiabetic drug at time of event	290 (90%)
On sulfonylurea or insulin, %	276 (86%)
Aspirin use, %	174 (54%)
Smoking, %	112 (35%)

* Each event was considered independent

Table 3.

Accuracy of hypoglycemia definition based on classification of reviewed events

A. Positive predictive value (PPV) of hypoglycemia definitions and diagnosis codes			
<i>Definitions and ICD-9-CM codes</i>	<i>Presumed events</i>	<i>Confirmed events</i>	<i>PPV (%) (95% CI)</i>
All	321	256	80 (75, 84)
1. Hospitalizations	15	12	80 (55, 93)
251.0	0	0	-
251.1	2	2	100 (34, 100)
251.2	4	4	100 (51, 100)
962.3	9	6	67 (35, 88)
270.3	0	0	-
2. Emergency department visits	103	49	48 (38, 57)
251.0	0	0	-
251.1	0	0	-
251.2	68	47	69 (57, 79)
962.3	1	1	100 (21, 100)
270.3	0	0	-
250.8*	36	3	8 (3, 22)
3. Outpatient glucose	203	195	96 (92, 98)
B. Classifications of all presumed hypoglycemia events reviewed			
<i>Event classification</i>	<i>Hospitalization N=15</i>	<i>Emergency department visit N=103</i>	<i>Outpatient blood glucose measurement N=203</i>
Severe	12 (80%)	44 (43%)	7 (3%)
Documented symptomatic	0 (0%)	0 (0%)	23 (22%)
Asymptomatic/atypical	0 (0%)	5 (5%)	165 (81%)
Probable symptomatic	0 (0%)	11 (11%)	0 (0%)
Not an event	3 (20%)	43 (42%)	8 (4%)

* without co-existence of 259.8, 272.7, 681.X, 682.X, 686.9, 707.1–707.9, 730.0–730.2, or 731.8 in any position