JMIR Publications
The Leading eHealth Publisher

Identifying Patients with Hypoglycemia Using Natural Language Processing: A Systematic Literature Review

Yaguang Zheng, Victoria Vaughan Dickson, Saul B. Blecker, Jason M. Ng, Brynne Campbell Rice, Liat Shenkar, Marie Claire R. Mortejo, Stephen B. Johnson

Submitted to: JMIR Diabetes
on: November 03, 2021

Preprint
JMIR Publications

Disclaimer: © The authors. All rights reserved. This is a privileged document currently under peer-review/community review. Authors have provided JMIR Publications with an exclusive license to publish this preprint on it's website for review purposes only. While the final peer-reviewed paper may be licensed under a CC BY license on publication, at this stage authors and publisher expressively prohibit redistribution of this draft paper other than for review purposes.

Table of Contents

Original Manuscript..... 5

Preprint JMIR Publications

Identifying Patients with Hypoglycemia Using Natural Language Processing: A Systematic Literature Review

Yaguang Zheng[1] PhD; Victoria Vaughan Dickson[1] PhD, CRNP, FAHA, FHFSA, FAAN; Saul B. Blecker[2] MD, MHS; Jason M. Ng[3] MD; Brynne Campbell Rice[4] MSLIS, MA, MS; Liat Shenkar[1] BS; Marie Claire R. Mortejo[1] BSN; Stephen B. Johnson[2] PhD

[1]NYU Rory Meyers College of Nursing New York US
[2]NYU Grossman School of Medicine Department of Population Health New York US
[3]University of Pittsburgh Department of Medicine Division of Endocrinology and Metabolism Pittsburgh US
[4]NYU Libraries New York US

Corresponding Author:
Yaguang Zheng PhD
NYU Rory Meyers College of Nursing
433 1st Ave
New York
US

Preprint Not Peer-Reviewed

Abstract

Background: Approximately 34 million (~13.0%) U.S. adults have diabetes . [1] Worldwide, a total of 387-million persons have diabetes, a number that is expected to rise to 592 million by 2035. [2] In 2017, direct and indirect costs attributed to diabetes in the U.S. were estimated to $327 billion. [3] Optimal glycemic control (HbA1c < 7%) can be achieved with comprehensive antidiabetic treatment; however, the risk of hypoglycemia increases. Hypoglycemia is defined as level 1: glucose level 54-70 mg/dL; level 2: glucose level <54 mg/dL; level 3: a severe event requiring external assistance for recovery. [4] In T2D after experiencing hypoglycemia, the 3-year incidence of cardiovascular (CV) events was 35.1% and mortality 28.3%-31.9%.

Objective: Accurately identifying patients with hypoglycemia is key in preventing adverse events and mortality. Natural language processing (NLP) is a scalable, efficient, and quick method to extract hypoglycemia related information when using electronic health records resources (EHRs) from a large population. The objective of this systematic review was to synthesize the literature on the application of NLP to extract hypoglycemia from the EHR clinical notes.

Methods: Literature searches were conducted electronically from Ovid PsycINFO (Ovid), PubMed, CINAHL (EBSCO), and Web of Science Core Collection. Keywords included hypoglycemia, low blood glucose, NLP, and machine learning. Inclusion criteria included studies that applied NLP to identify hypoglycemia, reported the outcomes related to hypoglycemia, and were published in English as full papers.

Results: This review (N=7 studies) revealed heterogeneity of the reported results related to hypoglycemia. Four studies reported that the prevalence of any level of hypoglycemia was 3.4 - 46.2%. The use of NLP to analyze clinical notes improved the capture of undocumented or missed hypoglycemic events using ICD-9/10 codes or lab testing. The combination of NLP and ICD-9/10 codes significantly increased the identification of hypoglycemic events compared with individual methods, for example the prevalence of hypoglycemia was 12.4% for ICD codes, 25.1% for NLP algorithm, and 32.2% for combined algorithms. All 7 reviewed studies applied rule-based NLP algorithms to identify hypoglycemia.

Conclusions: The findings provided evidence that the application of NLP to analyze clinical notes improved the capture of hypoglycemic events, particularly when combined with

the ICD-9/10 codes and lab testing.

(JMIR Preprints 03/11/2021:34681)
DOI: https://doi.org/10.2196/preprints.34681

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

Please make my preprint PDF available to anyone at any time (recommended).

Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.

✓ **Only make the preprint title and abstract visible.**

No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v

Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Preprint JMIR Publications

Original Manuscript

Preprint
JMIR Publications

Identifying Patients with Hypoglycemia Using Natural Language Processing: A Systematic Literature Review

Yaguang Zheng, PhD[1], Victoria Vaughan Dickson, PhD, CRNP, FAHA, FHFSA, FAAN[1], Saul B. Blecker, MD, MHS[2], Jason M. Ng, MD[3], Brynne Campbell Rice, MSLIS, MA, MS[4], Liat Shenkar, BS[1], Marie Claire R. Mortejo, BSN[1], Stephen B. Johnson, PhD[2]

[1]NYU Rory Meyers College of Nursing, New York, NY 100101;
[2]NYU Grossman School of Medicine, Department of Population Health, New York, NY 100101;
[3]University of Pittsburgh Department of Medicine, Division of Endocrinology and Metabolism, Pittsburgh, PA 15206
[4]NYU Libraries, New York, NY 100101;

Corresponding author: Yaguang Zheng, PhD, RN
Assistant Professor
NYU Rory Meyers College of Nursing
433 1st Avenue,
New York, NY 10010
Email: yaguang.zheng@nyu.edu
Phone: 212-998-5170

Key words: Hypoglycemia, Natural Language Processing

Word count:2563

Preprint JMIR Publications

Abstract

Objective: Accurately identifying patients with hypoglycemia is key in preventing adverse events and mortality. Natural language processing (NLP) is a scalable, efficient, and quick method to extract hypoglycemia related information when using electronic health records resources (EHRs) from a large population. The objective of this systematic review was to synthesize the literature on the application of NLP to extract hypoglycemia from the EHR clinical notes.

Methods: Literature searches were conducted electronically from Ovid PsycINFO (Ovid), PubMed, CINAHL (EBSCO), and Web of Science Core Collection. Keywords included hypoglycemia, low blood glucose, NLP, and machine learning. Inclusion criteria included studies that applied NLP to identify hypoglycemia, reported the outcomes related to hypoglycemia, and were published in English as full papers.

Results: This review (N=7 studies) revealed heterogeneity of the reported results related to hypoglycemia. Four studies reported that the prevalence of any level of hypoglycemia was 3.4 - 46.2%. The use of NLP to analyze clinical notes improved the capture of undocumented or missed hypoglycemic events using ICD-9/10 codes or lab testing. The combination of NLP and ICD-9/10 codes significantly increased the identification of hypoglycemic events compared with individual methods, for example the prevalence of hypoglycemia was 12.4% for ICD codes, 25.1% for NLP algorithm, and 32.2% for combined algorithms. All 7 reviewed studies applied rule-based NLP algorithms to identify hypoglycemia.

Conclusion: The findings provided evidence that the application of NLP to analyze clinical notes improved the capture of hypoglycemic events, particularly when combined with the ICD-9/10 codes and lab testing.

Background

Approximately 34 million (~13.0%) U.S. adults have diabetes .[1] Worldwide, a total of 387-million persons have diabetes, a number that is expected to rise to 592 million by 2035.[2] In 2017,

direct and indirect costs attributed to diabetes in the U.S. were estimated to $327 billion.[3] Optimal glycemic control (HbA1c < 7%) can be achieved with comprehensive antidiabetic treatment; however, the risk of hypoglycemia increases. Hypoglycemia is defined as level 1: glucose level 54-70 mg/dL; level 2: glucose level <54 mg/dL; level 3: a severe event requiring external assistance for recovery.[4] In T2D after experiencing hypoglycemia, the 3-year incidence of cardiovascular (CV) events was 35.1% and mortality 28.3%-31.9%.[5, 6]

The incidence of hypoglycemia has been reported to vary widely for patients with diabetes. An earlier systematic review and meta-analysis of 46 studies found that 45% of patients with type 2 diabetes (T2D) had mild/moderate (levels 1 and 2) hypoglycemia and 6% had severe (level 3); the prevalence was even higher among those treated with insulin with 50% having mild/moderate hypoglycemia events and 21% having severe events.[7] A subsequent review study showed that the rates of severe hypoglycemia in T2D were between 0.7 to 12 per 100 person-years in randomized controlled trials and 0.2 (without the treatment of insulin or sulfonylurea) to 2.0 per 100 person-years (with the treatment of insulin- or sulfonylurea).[8] The most recent systematic review and meta-analysis of 72 studies indicated that the incidence rate of hypoglycemia was 14.5 to 42,890 episodes per 1,000 person-years in type 1 diabetes (T1D) and 0.072 to 16,360 episodes per 1,000-person years in T2D.[9]

The reported rates of hypoglycemia vary largely due to the marked heterogeneity in the way that hypoglycemia is defined, measured, and reported. Accurately identifying patients with hypoglycemia is key to prevent adverse events and mortality. There are several methods to identify hypoglycemia events and severity in large populations including questionnaire surveys and International Classification of Diseases (ICD)-9/10 codes. Studies found that using questionnaire surveys[10] or ICD codes[11] is often insensitive, underestimated, and non-specific in detecting hypoglycemia events.

Electronic health records (EHRs) have been widely adopted by health care systems, resulting in large amounts of data including unstructured texts from clinical notes.[12, 13] The body of such unstructured text is already vast and continues to grow at a breakneck pace. The application of such data not only enables health care providers to identify patients at risk of hypoglycemia, but also to obtain details on hypoglycemia, e.g., symptomatic or asymptomatic.[14] Once the at-risk patients are identified, the treatment for such patients can be personalized, which helps to prevent future hypoglycemia and the resulting serious adverse effects. Traditional methods such as manual chart review can extract information related to hypoglycemia from EHR clinical notes;[15] however, such methods are time consuming, labor intensive, and not scalable, which makes them impractical for use in large populations.[16]

By contrast, novel data science approaches, including natural language processing (NLP), have been applied to overcome the above difficulties. The application of NLP algorithms is scalable, efficient, and quick to extract unstructured data from a large population.[17, 18] Applications of NLP in the health domain can be categorized into two different groups: rule-based methods and machine-learning methods.[19] Deep learning approaches (neural networks) are a form of machine learning used in recent years.[20, 21] Study has reported the higher hypoglycemia events that were identified from clinical notes using NLP than from ICD codes (65% vs. 20%, respectively).[22]However, little is known about what types of NLP algorithms were applied to identify hypoglycemia and how differences in hypoglycemia incidence identified from unstructured data using NLP compared with from structured data (e.g., ICD codes) across studies. Thus, in this systematic review, we synthesized the literature on the application of NLP to extract hypoglycemia from EHR clinical notes.

Methods

Search Strategies

Literature searches for a comprehensive review were conducted in four electronic databases,

including PubMed, PsycINFO (Ovid), CINAHL (EBSCO), and Web of Science Core Collection. The search strategies were developed in consultation with a health sciences librarian. Searching took place until March 2, 2021. Database-specific subject headings (e.g., Medical Subject Headings (MeSH)) and relevant keywords were identified to describe hypoglycemia and these terms were searched in combination with terms related to natural language processing. Because few articles related to hypoglycemia and NLP were located, the searches were widened to include broader terms like “blood sugar” or “blood glucose”, and “machine learning” or “artificial intelligence”. No date, language or publication filters were applied within the databases. Appropriate Boolean operators were used to structure the search queries and both unqualified free text searching and field tags were employed; the detailed search queries for each database are presented in Table 1.

Inclusion and Exclusion Criteria

Inclusion criteria included studies that: (1) were restricted to participants who are not pediatrics; (2) reported a sample with a diagnosis of diabetes; (3) applied NLP to identify hypoglycemia; (4) reported the number or percent of participants who had experienced at least one hypoglycemic episode, the incidence of hypoglycemic episodes experienced, or data to allow the calculation of one of these measures; (5) published as full papers; (6) published in the English language. No restrictions were applied regarding the definition or measurement of hypoglycemia. Studies were excluded if: (1) they were pharmacological trials or the intervention focused on treatment or care; (2) the participants were all pregnant or children.

Data Extraction

We firstly developed and tested a data extraction form, with adaptations made accordingly. Two reviewers independently screened the title, abstracts, and full text articles, respectively. Once conflicts were identified, agreement was reached after discussion with the third expert. The results related to the identification of eligible studies were summarized in PRISMA (Figure 1). Searches yielded 896 citations, leaving 683 titles and abstracts to be screened for eligibility after removing

duplications. Following full text retrieval of 313 potentially relevant papers, 239 were subsequently excluded, leaving 46 studies related to hypoglycemia, and 7 papers applied NLP that were eligible for inclusion in the analyses. The reference sections of the relevant articles were searched manually, but no further relevant articles were found. Studies were summarized based on the following categories: authors/country, sample size/characteristics, medical conditions, anti-hyperglycemic medication, study design, data source, definition of hypoglycemia, method used to identify hypoglycemia, NLP Algorithm (e.g., rule-based or machine learning), and outcomes (Table 2).

Results

Description of Included Studies

All 7 studies were conducted in the United States.[22-28] The sample sizes were large, ranging from 6,024 to 844,683. Five studies included only T2D,[22-25, 27] 1 included both T1D and T2D,[28] and 1 did not specify the type of diabetes.[26] The participants varied in age from 57- 68 years and 48.7%-56% were females. Of the 6 studies that reported on ethnicity, the percentage of non-white participants ranged from 18.8% to 62.0%. Mean body mass index (BMI) ranged from 31.8 to 35.7 kg/m^2 and mean HbA1c was from 6.6 to 9.64%. Varied comorbidities were reported, e.g., hypertension, hyperlipidemia, ischemic heart disease, and heart failure. Four studies provided diabetes related complications, including retinopathy, neuropathy, and nephropathy.[22, 23, 25, 26] Five studies reported 1.6-100% participants injected insulin[24-28] and 5 studies reported 4.4-100% sulfonylureas use.[22, 25-28]

All 7 studies were retrospective cohort study designs, the observational length of the cohort ranging from 2 to 12 years. Population samples were obtained from varied electronic health records (EHR) database, such as Humedica Optum,[22-25] Regenstrief,[26] Cleveland Clinic Health System patient records,[27] and Amplity Insights.[28]

Methods of Identifying Hypoglycemia

All 7 studies used a combination of ICD codes NLP to identify hypoglycemia; other methods

were applied, including laboratory tests for plasma glucose measures ≤70 or <54 mg/dL[25, 26] and glucagon administration.[25] ICD-9/10 codes used to identify hypoglycemia were described in detail by Misra-Hebert, et al., 2020.[27] Three studies reported both serious (level 3) and mild/moderate hypoglycemia (level 1 and 2),[22, 23, 27] 1 study reported both overall unspecified and severe hypoglycemia,[25] 3 studies reported data on unspecified hypoglycemia.[24, 26, 28] Two studies also reported symptom-based and non-symptom-based hypoglycemia.[24, 28]

NLP Algorithms Applied to Identify hypoglycemia

All 7 studies applied rule-based algorithms (Table 3). The study by Misra-Hebert, et al., 2020[27] described detail steps of NLP, including: splitting clinical notes to sentences/phrases, filtering sentences/phrases to those containing reference to a hypoglycemia-related Unified Medical Language System (UMLS)[29] concept, identifying temporal phrases (identify when the event took place), and clarifying polarity (assertion or negation) into no, non-severe, and severe event using both rule-based algorithms. Li and his colleagues [26] identified hypoglycemia using a formally defined pattern (*regular expression*),[30] such as a “blood sugar word” followed within five words by what could be a low blood-sugar value represented by a number in the range 10 to 69. Uzoigwe, et al., 2020[28] identified keywords or concepts of interest related to both symptom-based and non-symptom-based hypoglycemic events. The remaining four studies applied the same NLP algorithms to identify:[22-25] 1) terms or concepts (e.g., hypoglycemia) including alternative/incorrect spellings and abbreviations, 2) descriptive attributes of the hypoglycemia mention (e.g., seriousness, duration, and frequency); 3) sentiment of the mention (e.g., denial, affirmation, discussion); and 4) other contextual information (e.g., note section headers and neighboring text).

Manual review of clinical notes was used as the gold standard to validate the NLP algorithms in five studies. Two studies did not report validation of the algorithm. In the five reporting studies, the precision (positive predictive value) for the hypoglycemia algorithm was 0.77-93%.[22-25, 27] Four studies reported that the recall (sensitivity) was 0.67. [21-24]

Prevalence or Incidence of Hypoglycemia

The prevalence or the incidence of hypoglycemia largely varied across studies. The outcomes related to hypoglycemia also varied across studies. All studies used a combination of NLP and other approaches (e.g., ICD codes) to identify hypoglycemia. Overall, the prevalence of any condition of hypoglycemia was 3.4 - 46.2% that reported by 4 studies,[23, 25, 26, 28] incidence rate was 6.28 - 65.7% that reported by 2 studies.[22-24] The prevalence of non-severe hypoglycemia was 0.1-3.4%[22, 23, 27] and severe hypoglycemia was 5.1- 18.7%.[22, 23, 25] Four of seven studies compared the prevalence or incidence of hypoglycemia identified by NLP and ICD codes. In the study by Nunes, et al (2016), the prevalence of any hypoglycemia within the study period was 12.4%, 25.1%, and 32.2% for the ICD-9, NLP algorithm, and combined algorithm, respectively.[23] Similarly, Misra-Hebert, et al. found NLP identified higher non-serious hypoglycemia events compared with ICD codes (14,763 vs. 10,205 events) during the study period from 2005 to 2017; among 204,517 patients with no ICD codes for non-severe hypoglycemia, evidence of non-severe hypoglycemia was found in 7,035 (3.4%) using NLP.[27] Li, et al. also showed that hypoglycemia was identified in 21% of the participants, with 9.67% identified only by NLP algorithms. [26] Additionally, Uzoigwe and his colleagues found that the prevalence of hypoglycemia was 11.4% and <0.1% using NLP algorithms and ICD codes in T2D; such prevalence was 20.4% and 0.1% in T1D. [28]

Using the combination of NLP and other approaches (e.g., ICD codes) identified the highest prevalence or incidence of hypoglycemia compared with either method alone. Nunes, et al (2016) found the prevalence of hypoglycemia was 12.4% for ICD codes, 25.1% for NLP algorithm, and 32.2% for combined algorithms; the incidence rate per 100 person-years was 2.3%, 4.8%, and 6.3% using ICD codes, NLP, and combined algorithms, respectively.[23] Similarly, Misra-Hebert, et al. identified the incidence proportion of patients in 2005 to 2017 was 0.4% and 1.3% for non-severe hypoglycemia, while when NLP was added, the incidence increased to 0.8% and 2.6%.[27]

Discussion

This systematic review aimed to synthesize the literature on the application of NLP to extract hypoglycemia from the EHR clinical notes. Four studies reported that the prevalence of any level of hypoglycemia was 3.4 - 46.2%. Overall, the use of NLP to analyze the clinical notes improved the capture of hypoglycemic events that may have been undocumented or missed using lab testing or ICD-9/10 codes. The combination of NLP and other approaches significantly increased the identification of hypoglycemic events compared with individual methods. All reviewed studies applied rule-based NLP methods to identify hypoglycemia.

Previous reviews about the prevalence and incidence of hypoglycemia using NLP are limited. Our study found that the prevalence of any condition of hypoglycemia was 3.4 - 46.2%, while a previous review study reported that the prevalence of any condition of hypoglycemia ranged from 1.0% to 19.0% for studies using EHR as a data resource.[9] Also, one of the studies in our review reported symptom-based hypoglycemia, the estimated prevalence of hypoglycemia using combined symptom-based and non-symptom-based definitions was 20.4% (T1D) and 11.4% (T2D),[28] which is more prevalent than previous analyses without applying NLP for data extraction.[31, 32]

All 7 studies applied rule-based NLP to identify hypoglycemia. Rule-based NLP techniques are based on pre-defined clinical vocabulary, which identifies a set of core concepts for target extraction (e.g., hypoglycemia), and may also employ pattern matching (such as regular expressions) and filters.[33, 34] Rule systems are time consuming to set up, but they are easy to understand and modify, and often require less data than machine learning approaches.[33, 35, 36] Machine-learning systems leverage the same feature sets as used in rule-based systems, but do the work to discover the rules needed for a solution; however this comes at a price: the resulting systems often function as a “black box”, which is difficult for humans to understand and trust.[19] In addition, machine-learning systems typically require very large sample sizes for development.[35] When considering scalability to large EHR databases, the flexibility of machine-learned algorithms may be more preferable to the

rigidity of rules-based models.[35] Chen et al. incorporated 3 machine learning algorithms to detect hypoglycemia, including logistic regression, linear support vector machines and random forest.[37] The result showed that single cross-validation, logistic regression with cost-sensitive learning achieved the best performance with sensitivity of 0.693 and specificity of 0.974.[37] However, Chen et al. did not report the incidence of hypoglycemia. Thus, we did not include the article by Chen et al. in our review. Additionally, studies have found that deep learning models (e.g., recurrent neural networks and wor2vec embedding) outperformed rule-based and traditional machine-learned models (e.g., support vector machine, random forest) for detecting medical adverse event,[38] child physical abuse,[39] and pulmonary embolisms and fractures by leveraging radiology reports.[40] However, no study in our review applied deep learning models in the detection of hypoglycemia.

One limitation of this review is the heterogeneity of the reported results. This heterogeneity prevents the estimation of the pooled incidence and prevalence of hypoglycemia in diabetes using NLP algorithms. However, to the best of our knowledge, this is the first systematic review to synthesize the prevalence and incidence of hypoglycemia using NLP in individuals with diabetes. All the studies applied the combination of NLP with ICD codes and/or lab testing and identified higher incidence of hypoglycemia when using the EHR data sources. This has significant clinical implications for the prevention and management of hypoglycemia; with the widespread use of EHR, leveraging clinical notes significantly improves the identification of individuals with hypoglycemia. The preferred strategy is to use structured data (ICD codes) followed by NLP to synthesize the unstructured data to pinpoint those at highest risk for hypoglycemia.

In conclusion, our study indicated that the application of NLP improves the identification of hypoglycemia. Identifying such patients with diabetes is important and necessary for characterizing treatment and unmet needs, thus preventing the adverse events and mortality associated with hypoglycemia. Future research directions should explore comparison of the rule-based and machine-learned approaches to improve NLP efficiency.

Acknowledgement: Not available.

Conflict of Interest: The author and coauthors have no relevant relationships with commercial interests to disclose.

Funding statement: Not available

Preprint JMIR Publications

References

1. Centers for Disease Control and Prevention, *National Diabetes Statistics Report, 2020*. 2020, Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services: Atlanta, GA.
2. Ogurtsova, K., et al., *IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040.* Diabetes Res Clin Pract, 2017. **128**: p. 40-50.
3. American Diabetes Association, *Economic Costs of Diabetes in the U.S. in 2017.* Diabetes Care, 2018. **41**(5): p. 917-928.
4. American Diabetes Association, *6. Glycemic Targets: Standards of Medical Care in Diabetes-2020.* Diabetes Care, 2020. **43**(Suppl 1): p. S66-s76.
5. Lee, A.K., et al., *The Association of Severe Hypoglycemia With Incident Cardiovascular Events and Mortality in Adults With Type 2 Diabetes.* Diabetes Care, 2018. **41**(1): p. 104-111.
6. Akirov, A., et al., *Mortality Among Hospitalized Patients With Hypoglycemia: Insulin Related and Noninsulin Related.* J Clin Endocrinol Metab, 2017. **102**(2): p. 416-424.
7. Edridge, C.L., et al., *Prevalence and Incidence of Hypoglycaemia in 532,542 People with Type 2 Diabetes on Oral Therapies and Insulin: A Systematic Review and Meta-Analysis of Population Based Studies.* PLoS One, 2015. **10**(6): p. e0126427.
8. Silbert, R., et al., *Hypoglycemia Among Patients with Type 2 Diabetes: Epidemiology, Risk Factors, and Prevention Strategies.* Curr Diab Rep, 2018. **18**(8): p. 53.
9. Alwafi, H., et al., *Incidence and prevalence of hypoglycaemia in type 1 and type 2 diabetes individuals: A systematic review and meta-analysis.* Diabetes Res Clin Pract, 2020. **170**: p. 108522.
10. Han, K., et al., *Development and validation of a risk prediction model for severe hypoglycemia in adult patients with type 2 diabetes: a nationwide population-based cohort study.* Clin Epidemiol, 2018. **10**: p. 1545-1559.

11. Karter, A.J., et al., *Surveillance of Hypoglycemia-Limitations of Emergency Department and Hospital Utilization Data.* JAMA Intern Med, 2018. **178**(7): p. 987-988.
12. Yu, K.H., A.L. Beam, and I.S. Kohane, *Artificial intelligence in healthcare.* Nat Biomed Eng, 2018. **2**(10): p. 719-731.
13. MIT Critical Data, *Secondary Analysis of Electronic Health Records*. 2016, Cambridge, MA: Springer.
14. Zhou, L., et al., *Text preprocessing for improving hypoglycemia detection from clinical notes - A case study of patients with diabetes.* Int J Med Inform, 2019. **129**: p. 374-380.
15. Murdoch, T.B. and A.S. Detsky, *The inevitable application of big data to health care.* JAMA, 2013. **309**(13): p. 1351-2.
16. Zheng, Y., et al., *905-P: Is Continuous Glucose Monitoring Effective? Evidence from Real-World Data*. Diabetes, 2020. **69**.
17. Pivovarov, R. and N. Elhadad, *Automated methods for the summarization of electronic health records.* J Am Med Inform Assoc, 2015. **22**(5): p. 938-47.
18. Chen, L., et al., *Racing Against the Clock: Internal Medicine Residents' Time Spent On Electronic Health Records.* J Grad Med Educ, 2016. **8**(1): p. 39-44.
19. Olthof, A.W., et al., *Machine learning based natural language processing of radiology reports in orthopaedic trauma.* Comput Methods Programs Biomed, 2021. **208**: p. 106304.
20. Sulieman, L., et al., *Classifying patient portal messages using Convolutional Neural Networks.* J Biomed Inform, 2017. **74**: p. 59-70.
21. Wu, S., et al., *Deep learning in clinical natural language processing: a methodical review.* J Am Med Inform Assoc, 2020. **27**(3): p. 457-470.
22. Nunes, A.P., et al., *Hypoglycaemia seriousness and weight gain as determinants of cardiovascular disease outcomes among sulfonylurea users.* Diabetes Obes Metab, 2017. **19**(10): p. 1425-1435.

Preprint JMIR Publications

23. Nunes, A.P., et al., *Assessing occurrence of hypoglycemia and its severity from electronic health records of patients with type 2 diabetes mellitus.* Diabetes Res Clin Pract, 2016. **121**: p. 192-203.

24. Loughlin, A.M., et al., *Effectiveness and Tolerability of Therapy With Once-Weekly Exenatide Versus Basal Insulin Among Injectable-Naive Patients With Type 2 Diabetes in a Real-World Setting in the United States.* Diabetes Spectr, 2018. **31**(2): p. 129-137.

25. Pettus, J., et al., *Rates of Hypoglycemia Predicted in Patients with Type 2 Diabetes on Insulin Glargine 300 U/ml Versus First- and Second-Generation Basal Insulin Analogs: The Real-World LIGHTNING Study.* Diabetes Ther, 2019. **10**(2): p. 617-633.

26. Li, X., et al., *Predictive modeling of hypoglycemia for clinical decision support in evaluating outpatients with diabetes mellitus.* Curr Med Res Opin, 2019. **35**(11): p. 1885-1891.

27. Misra-Hebert, A.D., et al., *Natural Language Processing Improves Detection of Nonsevere Hypoglycemia in Medical Records Versus Coding Alone in Patients With Type 2 Diabetes but Does Not Improve Prediction of Severe Hypoglycemia Events: An Analysis Using the Electronic Medical Record in a Large Health System.* Diabetes Care, 2020. **43**(8): p. 1937-1940.

28. Uzoigwe, C., et al., *Assessing Prevalence of Hypoglycemia in a Medical Transcription Database.* Diabetes Metab Syndr Obes, 2020. **13**: p. 2209-2216.

29. Humphreys, B.L., D.A. Lindberg, and W.T. Hole, *Assessing and enhancing the value of the UMLS Knowledge Sources.* Proc Annu Symp Comput Appl Med Care, 1991: p. 78-82.

30. Ye, X., et al., *Sketch-Driven Regular Expression Generation from Natural Language and Examples.* Transactions of the Association for Computational Linguistics, 2020. **8**: p. 679-694.

31. Liu, J., et al., *The burden of severe hypoglycemia in type 1 diabetes.* Curr Med Res Opin, 2018. **34**(1): p. 171-177.

32. Liu, J., et al., *The burden of severe hypoglycemia in type 2 diabetes.* Curr Med Res Opin, 2018. **34**(1): p. 179-186.

33. Johnson, S.B., et al., *From Sour Grapes to Low-Hanging Fruit: A Case Study Demonstrating a Practical Strategy for Natural Language Processing Portability.* AMIA Jt Summits Transl Sci Proc, 2018. **2017**: p. 104-112.

34. Sholle, E.T., et al., *Underserved populations with missing race ethnicity data differ significantly from those with structured race/ethnicity documentation.* J Am Med Inform Assoc, 2019. **26**(8-9): p. 722-729.

35. Tan, W.K., et al., *Comparison of Natural Language Processing Rules-based and Machine-learning Systems to Identify Lumbar Spine Imaging Findings Related to Low Back Pain.* Acad Radiol, 2018. **25**(11): p. 1422-1432.

36. Chen, L., et al., *Clinical trial cohort selection based on multi-level rule-based natural language processing system.* J Am Med Inform Assoc, 2019. **26**(11): p. 1218-1226.

37. Chen, J., et al., *Detecting Hypoglycemia Incidents Reported in Patients' Secure Messages: Using Cost-Sensitive Learning and Oversampling to Reduce Data Imbalance.* J Med Internet Res, 2019. **21**(3): p. e11990.

38. Borjali, A., et al., *Natural language processing with deep learning for medical adverse event detection from free-text medical narratives: A case study of detecting total hip replacement dislocation.* Comput Biol Med, 2021. **129**: p. 104140.

39. Shahi, N., et al., *Using deep learning and natural language processing models to detect child physical abuse.* J Pediatr Surg, 2021.

40. Sorin, V., et al., *Deep Learning for Natural Language Processing in Radiology-Fundamentals and a Systematic Review.* J Am Coll Radiol, 2020. **17**(5): p. 639-648.

Preprint JMIR Publications

Table 1. Search Strategies for Hypoglycemia and Natural Language Processing

PubMed ("hypoglycemia"[Text Word] OR "blood sugar"[Text Word] OR "blood glucose"[Text Word]) AND ("Natural Language Processing"[Text Word] OR "Machine Learning"[Text Word] OR "Artificial Intelligence"[Text Word] OR (electronic health records[TW] AND diagnos*[TW]))
Web of Science (hypoglycemia OR “blood sugar” OR “blood glucose”) AND ("Natural Language Processing" OR "Machine Learning" OR "Artificial Intelligence"OR (electronic health records AND diagnos*))
CINAHL: ((MH "Natural Language Processing") OR "natural language processing" OR (MH "Artificial Intelligence+") OR (MH "Machine Learning+") OR (electronic health records AND diagnos*)) AND ((MH "Hypoglycemia") OR "hypoglycemia" OR (MH "Blood Glucose") OR "blood sugar" OR "blood glucose")
PsycINFO via Ovid: **(**hypoglycemia.mp. or exp Hypoglycemia/ or blood sugar.mp. or exp Blood Sugar/ or blood glucose.mp.**) AND (**natural language processing.mp. or exp Natural Language Processing/ or machine learning.mp. or exp Machine Learning/ or artificial intelligence.mp. or exp Artificial Intelligence/ or ((exp Electronic Health Records/ or electronic health record.mp.) and (exp Diagnosis/ or diagnos*.mp.))**)**

Preprint JMIR Publications

Table 2. Studies on Natural Language Processing and Hypoglycemia

Author/ country	Sample characteristics	Medical conditions n(%):	Anti-hyperglycemic medication n(%)	Study design	Data source	Definition of hypoglycemia	Method used to identify hypoglycemia	NLP Algorithm: Rule-based or machine learning?	NLP Algorithm validation	Outcomes
Nunes, et al, 2016[23] US	N = 844,683 Age (years): (n(%)) <30: 10,138(1.2) 30-39: 38,491(4.5) 40-49: 105.476(12.5) 50-59: 196,494(23.2) 60-69: 232,885(27.5) >69: 261,199(30.8) Female (%): 51.3 White (%): 77.6 T2D (%): 100 **Baseline measures** BMI (kg/m^2): 31.8 ± 10.2 HbA1c (%): 7.0 ± 1.9 Blood glucose: 139.0 ± 82	Atrial fibrillation: 60,773 (7.2) Hypertension: 555,482 (65.6) Hyperlipidemia: 510,944 (60.3) Cerebrovascular disease: 54,336 (6.4) CKD: Retinopathy: 10,356 (1.2) Neuropathy: 44,352 (5.2) Nephropathy: 26,498 (3.1) Ischemic heart disease: 154,049 (18.2) Congestive heart failure: 59,438 (7.0)	Not specified	Retrospective cohort study	Optum Humedica EHR database, incorporates EHRs from 35 large medical provider organizations (including over 195 hospitals), over 25,000 physicians, and over 25 million patients, making up the largest EHR database within the United States. January 2009-March 2014	Serious ICD-9-identified events were characterized as serious or nonserious if the diagnosis was identified within a problem list. NLP-identified categories included serious (e.g., serious, acute, severe, profound) Mild-to-moderate NLP-identified categories included mild-to-moderate (e.g., mild, moderate, slight, minor).	ICD-9 Algorithm (Structured diagnostic codes only) NLP Algorithm (NLP of clinical notes) Combined algorithm (either ICD-9 diagnostic codes or NLP of clinical notes)	Rule-based	The final algorithm was validated by manual review: Precision (positive predictive values) (PPV)= 0.77 Recall (sensitivity) =0.67.	**Period prevalence**: Any conditions: ICD-9: 12.37 NLP:25.11 Combined: 32.19 Serious ICD-9: 11.93 NLP:10.71 Combined:18.72 Mild-to-moderate ICD-9: 0.00 NLP:0.76 Combined: 0.78 **Incidence rate (per 100 person-years)** Any conditions: ICD-9: 2.25 NLP: 4.78 Combined: 6.28 Serious ICD-9: 2.12 NLP:1.72 Combined:3.19 Mild-to-moderate ICD-9: 0.00 NLP:0.09 Combined: 0.08 **Event rate (per 100 person-years)** Any conditions: ICD-9: 6.92 NLP:

Author/ country	Sample characteristics	Medical conditions n(%):	Anti-hyperglycemic medication n(%)	Study design	Data source	Definition of hypoglycemia	Method used to identify hypoglycemia	NLP Algorithm: Rule-based or machine learning?	NLP Algorithm validation	Outcomes
										10.03 Combined: 16.12 Serious ICD-9: 6.63 NLP: 3.06 Combined: 8.90 Mild-to-moderate ICD-9: 0.00 NLP:0.20 Combined: 0.19
Nunes, et al., 2017[22] US	N = 143,635 Age (years) (n(%)): <30: 1333 (0.9) 30-39: 5420 (3.8) 40-49: 15,645 (10.9) 50-59: 32,796 (22.8) 60-69: 39,852 (27.7) >69: 48,491 (33.8) Female (n(%)): 69,879 (48.7) White (n(%)): 116,701 (81.2) T2D (%): 100 **Baseline measures** median (IQR): BMI (kg/m^2): 32.3 (28.1,37.6) HbA1c (%): 7.1 (6.5,8.1) Blood glucose:	Cerebrovascular disease: 11,903 (8.3) Retinopathy: 3091 (2.2) Neuropathy: 12,961 (9.0) Nephropathy: 8338 (5.8) Ischemic heart disease: 33,570 (23.4)	Sulfonylureas 143,635 (100)	Retrospective cohort study	January 2009-December 2014 Optum EHR database	Serious: ICD/CPT evidence of medical intervention and/or abstracted descriptors suggestive of serious event Non-serious, mild-moderate: No ICD/CPT evidence of medical intervention but with abstracted descriptors suggestive of mild-moderate event Non-serious, unspecified No ICD/CPT evidence of medical intervention and no descriptors of event	ICD code: 20% NLP: 65% ICD & NLP: 15%	Rule-based	The final algorithm was validated by manual review: Precision (positive predictive values) (PPV)= 0.77 Recall (sensitivity) =0.67.	**Incidence rate (per 100 person-years):** Any conditions: Overall: 11.76 (11.49-12.04) SU use: 12.77 (12.40-13.15) SU none-use: 10.39 (10.00-10.79) Serious**:** Overall: 5.06 (4.88-5.24) SU use: 5.77 (5.52-6.03) SU none-use: 4.09 (3.84-4.34) Non-serious, mild-moderate: Overall: 0.14 (0.11-0.17) SU use: 0.17 (0.13-0.22) SU none-use: 0.09

Author/ country	Sample characteristics	Medical conditions n(%):	Anti-hyperglycemic medication n(%)	Study design	Data source	Definition of hypoglycemia	Method used to identify hypoglycemia	NLP Algorithm: Rule-based or machine learning?	NLP Algorithm validation	Outcomes
	146.0 (116.0, 191.0)					seriousness				(0.06-0.13) Non-serious, unspecified Overall: 6.57 (6.37-6.78) SU use: 6.83 (6.56-7.11) SU none-use: 6.21 (5.91-6.52)
Loughlin, et al., 2018[24] US	N=6,024 Exenatide once weekly (EQW) Cohort N = 2,008 Age (years): NA Female (%): 50.0 White (%): 81.2 T2D (%): 100 **Baseline measures** NA BI Cohort N = 4,016 Age (years): NA Female (%): 50.7 White (%): 81.6 T2D (%): 100 **Baseline measures** NA	NA	Insulin: 100	Retrospective cohort study	Optum's electronic health records (EHR) database, January 2012 to January 2015	Documented blood glucose less than 3.9 mmol/L or emergency physician charted diagnosis of hypoglycemia (Ginde et al.)	Hypoglycemia and gastrointestinal symptoms (vomiting, nausea, diarrhea, or constipation) were identified by using both ICD-9-CM diagnostic codes within structured fields and NLP clinical note Hypoglycemia was identified using an algorithm developed by Optum, incorporated diagnostic codes and NLP from clinical notes	Rule-based	The final algorithm was validated by manual review: Precision (positive predictive values) (PPV)= 0.77 Recall (sensitivity) =0.67.	**Incidence per 1,000 Person-Years*** (95% CI) EQW Cohort 52.5 (44.4-61.6) BI Cohort 65.7 (59.1-72.7) Any GI symptoms EQW Cohort 225.5 (206.8–245.5) BI Cohort 191.0 (179.1–203.6) **Number With at Least One Event (%)** EQW Cohort 149 (7.4%) BI Cohort 368 (9.2%) Any GI symptoms EQW Cohort 534 (26.6) BI Cohort 946 (23.6)

Author/ country	Sample characteristics	Medical conditions n(%):	Anti-hyperglycemic medication n(%)	Study design	Data source	Definition of hypoglycemia	Method used to identify hypoglycemia	NLP Algorithm: Rule-based or machine learning?	NLP Algorithm validation	Outcomes
Pettus, et al., 2019[25] US	N = 831,456 BI switchers (n=3,920 - 19,256) Age (years): 58.2-60.1 Female (%): 49.8-52.0 White (%): NA T2D (%): 100 **Baseline measures** BMI (kg/m^2): 33.8-35.0 HbA1c (%):8.91-9.02 Blood glucose: NA Smoking (%): NA Insulin-naïve (n=2,279 - 47,085) Age (years): 58.8-60.4 Female (%):48.6-52.1 White (%): NA T2D (%): 100 **Baseline measures** BMI (kg/m^2): 34.0-34.6 HbA1c (%):9.39-9.64 Blood glucose:	BI switchers Hypertension: 63.4-73.4 Hyperlipidemia: 68.1-77.8 Microvascular complication: 44.7-55.7 Macrovascular complication: 44.2 - 63.5 Insulin-naïve Hypertension: 56.8-74.2 Hyperlipidemia: 61.5-77.8 Microvascular complication: 25.3-34.6 Macrovascular complication:32.7-63.5	BI switchers Sulfonylureas: 24.5-28.3 Any OAD: 63.6-75.2 Insulin-naïve: Sulfonylureas: 47.6-56.6 Any OAD: 100.0	Retrospective cohort study	Optum Humedica EHR database. The data were retrieved from 1 January 2007 to 31 March 2017	Hypoglycemia: ICD-9/10 codes for hypoglycemia; Plasma glucose Measures ≤70 mg/dL; IM glucagon administration; NLP: Mention of hypoglycemia Severe hypoglycemia: ICD-9/10 code for hypoglycemia that is severe by default OR ICD-9/10 code for hypoglycemia AND Hypoglycemia is reason for care on discharge or admission OR hypoglycemia index date on same day as ED visit/inpatient diagnosis on admission (all related to hypoglycemic coma); Plasma glucose Measures <54 mg/dL; IM	ICD-9/10 codes Plasma glucose Measures ≤70 IM glucagon administration NLP	Rule-based	The final algorithm was validated by manual review: Precision (positive predictive values) (PPV)= 0.77 Recall (sensitivity) =0.67.	**Any hypoglycemia (%)** Basal insulin - switcher: 42.2 -46.2 insulin-naïve: 22.8 - 28.8 Severe hypoglycemia Basal insulin - switcher: 8.2-17.4 insulin-naïve: 2.7-8.6

Author/ country	Sample characteristics	Medical conditions n(%):	Anti-hyperglycemic medication n(%)	Study design	Data source	Definition of hypoglycemia	Method used to identify hypoglycemia	NLP Algorithm: Rule-based or machine learning?	NLP Algorithm validation	Outcomes
	NA Smoking (%): NA					glucagon administration; NLP: Mention of hypoglycemia with either – Descriptor of hypoglycemia severity – including severity terms (e.g.,. 'severe') and attributes (e.g., 'emergency') – ED visit/inpatient admission on same day as medical record was written				
Li, et al, 2019[26] US	N = 38,780 Age (years) Mean: 57.0 Female (%): 56.0 White (%): 47.0 T2D (%): not reported **Baseline measures** BMI (kg/m^2): 35.7±9.8 HbA1c (n(%)): ≤6.5%: 5321(13.7) >6.5%,<7%: 1840(4.7)	Coronary artery disease: 2,021(5.2) Chronic heart failure: 1582(4.1) Diabetic neuropathy: 1414 (3.6)	Long-acting insulin (LAI): 615 (1.6) SU: 8727 (22.5)	Retrospective cohort study	Regenstrief Medical Record System, which is an urban safety-net medical institution in Indianapolis, Indiana, USA. In 2012, Eskenazi had 1081 physicians on staff and serviced 950,592	Plasma or point-of-care glucose value of at least 5 mg/dL, and less than 70 mg/dL, documented in the medical record. ICD-9 code: 251.1 or 251.2. ICD code 250.8 without any of the following codes44: 259.8, 272.7, 681.xx, 682.x, 686.9,	Laboratory tests Diagnostic codes NLP	Rule-based	Not reported	A one-year window for prior episodes of hypoglycemia <u>Overall prevalence</u> (n (%)): 8182 (21.10) Non-LAI insulin and SU within 90 days: 42.92 SU without insulin: 23.82 No insulin, no SU: 17.85 Glucose value <5

Author/ country	Sample characteristics	Medical conditions n(%):	Anti-hyperglycemic medication n(%)	Study design	Data source	Definition of hypoglycemia	Method used to identify hypoglycemia	NLP Algorithm: Rule-based or machine learning?	NLP Algorithm validation	Outcomes
	≥7%, <8%: 3155(8.1) ≥8%, <9%: 1773(4.6) ≥9%: 3977(10.3) Missing: 22,714(58.6)				outpatient visits, including 234,637 community health center visits. The data were retrieved from 1 January 2004 to 31 December 2013	707.1x, 707.2x, 707.8, 707.9, 709.3, 730.0x, 730.1x, 730.2x, 731.8. Text note indicating hypoglycemia, including a glucose value.				mg/dL and <70 mg/dL: 7070 (18.23) Glucose value <54 mg/dL: 4784 (12.34) NLP: 3751 (9.67), with 539 identified only by NLP
Misra-Hebert, et al., 2020[27] US	N = 204,517 Age (years): 61.48 Female (%): 48.9 White (%): 73.4 T2D (%): 100 **Baseline measures** BMI (kg/m^2) 32.2 HbA1c (%) 6.6 Blood glucose: NA	Cardiovascular disease: 13,372 (28.9) Congestive heart failure: 2,195 (4.7) Chronic Kidney Disease: 2,460 (5.3) Alcohol or substance abuse: 1,218 (2.6)	Insulin: 8,050 (17.4) Glucagon-like-peptide-1 receptor agonist (GLP-1RA): 1,781 (3.8) DPP4: 4,437 (9.6) Sodium-glucose cotransporter-2 inhibitor (SGLT-2i): 791 (1.7) Metformin: 28,851 (62.3) Sulfonylurea: 10,098 (21.8) Alpha-glucosidase inhibitor (AGI): 107 (0.2)	Retrospective cohort study	Cleveland Clinic Health System patient records (2005 – 2017)	Hypoglycemia: glucose <70 mg/dL Severe hypoglycemia (SH): requires hospitalization or emergency department visit in patients with T2D Non-severe hypoglycemia (NSH): doesn't require assistance for recovery	**NLP;** **ICD-9 codes:** 251.0, 251.1, 251.2 **ICD-10 codes:** E08.641**,** E11.641, E11.649, E13.64, E13.641, E13.649, E16.0**,** E16.1, E15, E16.2 **(See detail from Appendix)**	Rule-based	Compared with clinician chart review manually, positive predictive value: 93%	**Prevalence**: Among 204,517 patients with no codes for NSH, evidence of NSH was found in 7,035 (3.4%) using NLP # of NSH events ICD: 10,205 NLP: 14,763 with overlap of only 5 events. **The incidence proportion of patients** from 2005 to 2017 ICD codes: SH: 0.3 to 1.7% NSH: 0.4 to 1.3%

Author/ country	Sample characteristics	Medical conditions n(%):	Anti-hyperglycemic medication n(%)	Study design	Data source	Definition of hypoglycemia	Method used to identify hypoglycemia	NLP Algorithm: Rule-based or machine learning?	NLP Algorithm validation	Outcomes
										NLP+ICD: NSH: 0.8% to 2.6%
Uzoigwe, et al., 2020[28] US	N=359,087 T2D N = 317,399 Age (years) median: 68.0 Female (%): 49.0 White (%): 38.0 **Baseline measures** BMI (kg/m^2):NA HbA1c (%):NA Blood glucose: NA Smoking (%): 34.0 T1D N = 41,688 Age (years): median 55.0 Female (%): 51.0 White (%): 39 **Baseline measures** BMI (kg/m^2) NA HbA1c (%):NA Blood glucose: NA Smoking (%): 22.0	Hypertension: 257,093 (81.0) Hyperlipidemia: 193,616 (61.0) cardiovascular disease: 158,699 (50.0) High blood sugar/diabetic ketoacidosis: 14,067 (33.7) Cancer: 6,752 (16.2) Stroke: 7,377 (17.7) Substance use/abuse: 4,917 (11.8)	T2D Insulin: 174,569 (55.0) Sulfonylureas:55,710 (18.0) Metformin: 114,263(36.0) T1D Insulin: 37,279 (89.4) Sulfonylureas: 1,846 (4.4) Metformin: 5,059 (12.1)	Retrospective cohort study	Amplity Insights database, unstructured health records, generated from provider notes as transcribed from verbal to written form (January 1, 2016 to April 30, 2018)	Non-symptom-based: mention of hypoglycemia, low glucose, or blood glucose value ≤70 mg/dL Symptom-based: keywords identified by endocrinologists, used by patients to describe hypoglycemia	ICD NLP	Rule-based	Not reported	Prevalence during 2 years: T2D ICD: 52 (<0.1) Combined symptom and non-symptom based: 11.4 Non-symptom-based: 24,082 (7.6) Symptom-based: Irritable/ anxious 3493 (14.5) Cognitive issues 2923 (12.1) Elevated/ irregular heart rate 2459 (10.2) T1DM ICD: 30 (0.1) Combined symptom and non-symptom based: 20.4 Non-symptom-based hypoglycemia: 7,555 (18.1) Symptom-based: Irritable/

Author/ country	Sample characteristics	Medical conditions n(%):	Anti-hyperglycemic medication n(%)	Study design	Data source	Definition of hypoglycemia	Method used to identify hypoglycemia	NLP Algorithm: Rule-based or machine learning?	NLP Algorithm validation	Outcomes
										anxious 1209 (16.0) Cognitive issues 617 (8.2) Elevated/ irregular heart rate 617 (8.2)

Note: NLP= natural language processing; SU= sulfonylurea; ICD= International Classification of Diseases; CPT=Current Procedures Terminology

Preprint JMIR Publications

Table 3 Natural Language Processing Algorithms Applied in the Reviewed Studies

Author	NLP Algorithms	
Nunes, et al, 2016[23] Nunes, et al., 2017[22] Loughlin, et al., 2018[24] Pettus, et al., 2019[25]	Rule-based	Identify **terms** consistent with hypoglycemia, (including alternative/incorrect spellings and abbreviations) Identify **descriptive attributes** of the hypoglycemia mention (e.g., seriousness, duration, and frequency) Identify **sentiment** of the mention (e.g., denial, affirmation, including "has," "diagnosed," "present," etc.) Identify **contextual information** (e.g., note section headers and neighboring text). Sections such as ''history of present illness", ''assessment", ''hospital course", ''reason", ''review of symptoms" and ''chief complaint" generally reflected occurrence of hypoglycemia.
Li, et al, 2019[26]	Rule-based	A formally defined pattern (regular expression), which identified clinical reports mentioning a "blood sugar word" followed within five words by what could be a low blood-sugar value represented by a number in the range 10 to 69.
Misra-Hebert, et al., 2020[27]	Rule-based	• Split clinical notes to sentences/phrases • Filter sentences/phrases to those containing a hypoglycemia-related Unified Medical Language System (UMLS) concept, • Identifying temporal phrases (when the event took place • Classify polarity (assertion or negation) into no, non-severe, and severe event.
Uzoigwe, et al., 2020[28]	Rule-based	Identify keywords or concepts of interest: symptom-based and non-symptom-based hypoglycemic events. Symptom-based terms: neuroglycopenic and adrenergic symptomology associated with hypoglycemia. • Adrenergic symptomology: elevated/irregular heart rate, sweating, tremor/trembling/tingling/shaking, vision impairment • Neuroglycopenic symptomology : cognitive issues, irritable/anxious, mood/behavior change + NOT substance abuse/alcohol, Slurred speech + NOT stroke +NOT substance abuse/alcohol Non-symptom-based definition: • Mention of "hypoglycemia" • Relevant medical ontology such as "low glucose" • A blood glucose laboratory value ≤70 mg/dL documented

Preprint JMIR Publications

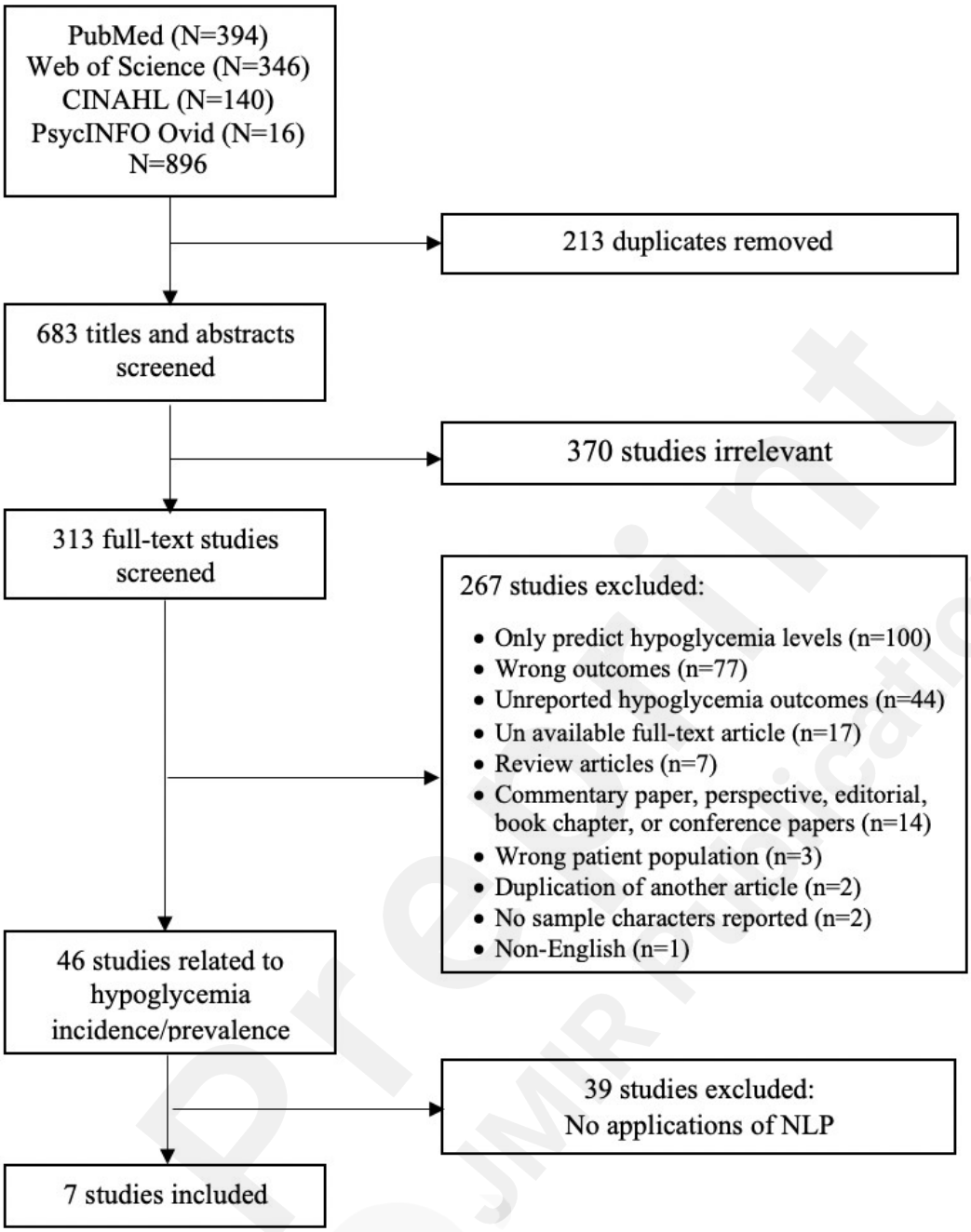

Figure 1. PRISMA Flowchart