


SYSTEMATIC REVIEW

Using natural language processing in emergency medicine health service research: A systematic review and meta-analysis

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Funding information

National Institute of Health Common Fund, Grant/Award Number: 1OT2OD032581-01; National Institute on Minority Health and Health Disparities, Grant/Award Number: 5S21MD012472-05

Abstract

Objectives: Natural language processing (NLP) represents one of the adjunct technologies within artificial intelligence and machine learning, creating structure out of unstructured data. This study aims to assess the performance of employing NLP to identify and categorize unstructured data within the emergency medicine (EM) setting.

Methods: We systematically searched publications related to EM research and NLP across databases including MEDLINE, Embase, Scopus, CENTRAL, and ProQuest Dissertations & Theses Global. Independent reviewers screened, reviewed, and evaluated article quality and bias. NLP usage was categorized into syndromic surveillance, radiologic interpretation, and identification of specific diseases/events/syndromes, with respective sensitivity analysis reported. Performance metrics for NLP usage were calculated and the overall area under the summary of receiver operating characteristic curve (SROC) was determined.

Results: A total of 27 studies underwent meta-analysis. Findings indicated an overall mean sensitivity (recall) of 82%–87%, specificity of 95%, with the area under the SROC at 0.96 (95% CI 0.94–0.98). Optimal performance using NLP was observed in radiologic interpretation, demonstrating an overall mean sensitivity of 93% and specificity of 96%.

Conclusions: Our analysis revealed a generally favorable performance accuracy in using NLP within EM research, particularly in the realm of radiologic interpretation. Consequently, we advocate for the adoption of NLP-based research to augment EM health care management.

KEYWORDS

electronic health records, emergency medicine, natural language processing, performance accuracy, precision, recall

Supervising Editor: Richard Sinert

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INTRODUCTION

The utilization of artificial intelligence and machine learning (AI/ML) techniques in the medical field has become increasingly prevalent.^{1,2} At present, AI/ML is employed for various purposes, including disease diagnosis, prognosis prediction, and hospitalization determination.³⁻⁵ During the COVID-19 pandemic, studies utilized diverse clinical parameters to forecast infection severity among COVID-19-positive patients.^{6,7} Various ML algorithms have been applied to predict hospitalization, critical care conditions, and mortality rates.^{6,7} AI/ML has also found extensive use in forecasting outcomes for specific conditions such as sepsis, coronary artery diseases, and fever.^{5,8,9}

Electronic health records (EHRs) contain data that can be categorized into structured forms (e.g., age, gender, race) and unstructured forms. The latter encompasses narrative text, including histories, current medical conditions, discharge summaries, and image reports from health care providers. Structured data in EHR are formatted by health care providers through the selection of itemized boxes or options. This often requires more effort from humans to enter information but is easier for computers to process and interpret. Unstructured data include text from dictation or typing and can convey a narrative more clearly for humans reading the chart. However, it poses a challenge for computers to analyze, due to the context-sensitive nature of human language and variability across providers.^{10,11} The goal of natural language processing (NLP) is to enable computers to investigate and reason using human languages as input.^{10,11}

NLP operates by breaking sentences into words to make them comprehensible for computers, using the following methods: Tokenization breaks down a sentence into individual words, and stop words, such as "the" and "is," are often removed. Stemming and lemmatization simplify words to their base or root forms, while part-of-speech tagging labels words as nouns, verbs, adjectives, etc. Several open-source NLP programs exist that implement these steps, though some researchers develop custom NLP software. A complete NLP program, combining these various technologies, aims to understand human language accurately.

In emergency medicine (EM), timely disease recognition, appropriate treatment, and determining patient dispositions are critical. Accurate disease recognition facilitates treatment and syndromic surveillance for contagious diseases posing public threats.¹⁰ Interpreting a patient's clinical condition from narrative text can guide treatment and disposition decisions. Common NLP applications in EM focus on monitoring syndromic surveillance; interpreting imaging findings; and identifying specific diseases, events, or syndromes.¹⁰⁻¹² As the health care industry increasingly relies on technology, it becomes imperative to understand nuances of NLP in the context of EM.

Before applying NLP to unstructured EHR data, it is essential to evaluate its performance. Suboptimal performance can yield erroneous predictions and diminish credibility of the technology among users. This systematic review and meta-analysis primarily focused

on evaluating the performance of NLP to identify and categorize unstructured ED data, emphasizing three key areas: monitoring syndromic surveillance (e.g., respiratory illness, influenza, or gastrointestinal illness), determining image interpretations, and recognizing specific diseases/events/syndromes.

METHODS

Database search and eligibility criteria

We built a search strategy around the concepts of NLP, health services research, and ED. The strategy was drafted in Ovid Medline and translated to the following databases: Embase, CENTRAL via Cochrane, Scopus, and ProQuest Dissertations & Theses Global. We filtered the literature to encompass studies published between 1990 and August 2023. Additional manual searches were conducted to avoid missing any references cited in previously published NLP review papers. For the full strategy, see the supplemental files.

Eligible studies consisted of original prospective, retrospective, and randomized controlled studies from peer-reviewed journals, preprint, print, online ahead-of-print publications, and open-access journals. Of the included studies, the ED notes encompassed diverse document types such as triage, history of present illness, medical decision, radiology, and discharge summaries. To be included in the analysis, these notes were required to be limited to ED care. Moreover, studies were eligible for inclusion if they satisfied all the following criteria: (1) applied NLP in EM; (2) used raw clinical text as input for analysis; (3) employed a criterion standard definition to permit calculation of performance; and (4) if NLP was not open-resourced, segregated data into training and testing sets.

Exclusion criteria comprised: (1) duplicated studies; (2) studies exclusively using clinical notes unrelated to the ED (e.g., notes from solely prehospital EMS or home health care); (3) review papers, editorial comments or perspectives, notes extracted from social media platforms like Twitter or YouTube; (4) methodology studies solely addressing derivation or validation of open-resource NLP software; (5) studies not addressing NLP performance on testing data; (6) studies lacking validation or partially validating the final NLP results; (7) studies solely comparing performance between training and testing data without a defined criterion standard from NLP; and (8) studies reporting mean performance accuracies without case-specific accuracies.

Data extraction and quality assessment

Study selection and extraction

Six independent reviewers (N.A., T.S., N.H, D.P., H.K., and P.M.) conducted a comprehensive screening of search results in two distinct phases, an initial screening based on titles and abstracts (Phase 1) and then a thorough examination of full-text articles

(Phase 2). At least two independent reviewers assessed each article. Advancement from Phase 1 to Phase 2 relied on mutual agreement between both reviewers to include the individual study. In case of disagreement, a third reviewer (HW) was consulted to make a final determination regarding the study's eligibility. Instances where data were missing, incomplete, or deemed inadequate for calculating sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and positive and negative likelihood ratios (LR+ and LR-) prompted sending at least two separate emails to the study's corresponding author, requesting access to the raw study data. Studies were excluded when no response was received.

Outcome measurements

We measured three key functions of utilizing NLP including: (1) identification of cases for syndromic surveillance (e.g., respiratory illness, gastrointestinal illness); (2) extraction of specific findings from radiology interpretations (e.g., pulmonary embolism, pneumonia); and (3) recognition of diseases, events, or syndromes (e.g., sepsis, seizures, allergies).

Risk of bias and quality assessment of individual studies

We utilized the Critical Appraisal Skills Program (CASP) diagnostic checklist tool for studies' quality assessment (see detail in [Table S2](#)).^{13,14} To address potential meta-biases, including publication bias and small-study effects, several analyses were performed. Using funnel plots for assessing publication bias in diagnostic test studies may produce misleading results.^{15,16} Publication bias was evaluated in our study using a regression of diagnostic log odds ratio against 1/square root (effective sample size), weighted by effective sample size. Significant asymmetry ($p < 0.10$) indicated the presence of publication bias. Small-study effects were assessed using Harbord's and Peter's tests.^{17,18}

Data synthesis and analysis

To assess study quality, we employed kappa statistics to measure inter-rater variability. The study populations' data were aggregated to evaluate the overall performance (e.g., sensitivity, specificity, PPV, NPV, LR+, and LR-) to identify and categorize unstructured ED data. Subsequently, we determined the performance of three main NLP applications. Due to anticipated study heterogeneity, we employed a random-effects model. To assess heterogeneity, summary receiver operating characteristic analysis (SROC) was performed for a visual assessment of the threshold effect, a form of diagnostic meta-analysis heterogeneity analysis. Furthermore, our study utilized LR to calculate posttest probability using a Bayes nomogram, depicting this information via a Fagan plot.¹⁹ This plot illustrated the pretest

probability (set at 50%) through LR+ and LR- to determine posttest probability.¹⁹ We chose a pretest probability of 50% to represent a neutral uncertainty.

When studies analyzed the same data using different AI/ML algorithms, only the data exhibiting the best performance were chosen for the meta-analysis, to avoid including duplicate study patients. To mitigate potential selection biases, we conducted a sensitivity analysis using the worst-reported performance from the studies. Variation in performance might stem from different NLP algorithms, varied outcomes using the same NLP algorithms, or both.

This systematic review and meta-analysis were managed using Covidence software, a tool for systematic review screening and data extraction. STATA statistical software version 14.2 was utilized for meta-analysis. This study was registered with PROSPERO (International Prospective Register of Systematic Reviews, CRD42023477884).

Reporting guidelines

This study report followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).²⁰

RESULTS

Through a comprehensive literature search ([Table S1](#)), 596 studies were initially screened. After titles and abstracts were reviewed, 207 studies were excluded. An additional 190 studies were excluded with the review of full-text articles, leaving 33 studies for quality assessment. Among these, four studies were excluded by the quality assessment due to lacking reference standards,²¹⁻²⁴ and an additional two studies were omitted due to not being able to calculate NLP performance.^{25,26} Consequently, a total of 27 studies were included in the final analysis ([Table 1](#); [Figure 1](#)).²⁷⁻⁵³

Risk of bias

High agreement was observed in the quality assessment among raters (inter-rater variability test, $\kappa = 0.8630$, $p > 0.05$), indicating no statistically significant differences in inter-rater variability. The quality assessment for all 33 included studies was summarized ([Table S2](#)).

To mitigate potential biases in assessed studies, such as publication and small-study effects, publication bias analysis was utilized. The bias coefficient was -14.06 with a [95% CI of -51.00 to 22.87], and a p -value of 0.440 was obtained, indicating no evidence of publication bias ([Table S3](#)). Harbord and Peters tests were employed for small-study bias analysis. The Harbord test yielded an estimated intercept of 2.72 with a standard error of 3.29 and a p -value of 0.261 , indicating no statistically significant evidence of small-study effects. The Peters test produced a bias coefficient of -263.24 with a p -value of 0.311 , aligning with the findings from the Harbord test ([Table S3](#)).

TABLE 1 General information of included articles in this study.

Year of publication	First author	Type of study	Total number of patients or images	Purpose of NLP	NLP Applications	Unstructured data used for NLP	Criterion standard comparisons
2007	Travers ²⁷	Retrospective	3699	Surveillance study	Acute respiratory illness	ED chief complaint	Manual review
2012	Raja ²⁸	Retrospective	179	Radiology interpretation	Pulmonary embolism	ED radiology report	Manual review
2013	Travers ²⁹	Retrospective	500	Surveillance study	Gastrointestinal syndromes	ED notes	Manual review
2013	Yadav ³⁰	Retrospective	1855	Radiology interpretation	Orbital fractures	ED radiology report	Manual review
2013	Dutta ³¹	Retrospective	1635	Radiology interpretation	Incidental image findings	ED radiology report	Manual review
2013	Wagholikar ³²	Retrospective	99	Radiology interpretation	Limb fractures	ED radiology report	Manual review
2014	Haas ³³	Retrospective	485	Surveillance study	Respiratory illness	ED chief complaint, triage notes	Manual review
2015	Koopman ³⁴	Retrospective	2378	Radiology interpretation	Fracture, dislocation, foreign body abnormal findings	ED radiology report	Manual review
2016	Yadav ³⁵	Retrospective ^a	1042	Radiology interpretation	Pediatric traumatic brain injury	ED radiological report	Manual review
2016	Pestian ³⁶	Prospective	60	Identify diseases/events/syndromes	Suicidal adolescents	Response to the Questionnaires	CSSRS screening (Columbia Suicidal Severity Rating Scale)
2018	Jones ³⁷	Retrospective	100	Identify diseases/events/syndromes	Pneumonia	ED notes	Manual review
2019	Patterson ³⁸	Retrospective	500	Identify diseases/events/syndromes	Falls in older adults	ED notes	Manual review
2020	Fernandes ³⁹	Retrospective	70,750	Identify diseases/events/syndromes	Hospital mortality and cardiopulmonary arrest	ED triage notes	Hospital mortality and cardiopulmonary arrest
2020	Osborne ⁴⁰	Retrospective	264	Identify diseases/events/syndromes	Gout flare	ED chief complaint	Manual review
2021	Bouchouar ⁴¹	Retrospective	19,023	Surveillance study	Influenza like illness	ED chief complaint, clinical triage notes, and discharge diagnosis text	ICD-10 code with manual review
2021	Chartash ⁴²	Retrospective	600	Identify diseases/events/syndromes	Shared decision making and general practice decision	ED notes	Manual review
2021	Shung ⁴³	Retrospective	2988	Identify diseases/events/syndromes	Gastrointestinal bleeding	ED triage notes	Manual review

(Continues)

TABLE 1 (Continued)

Year of publication	First author	Type of study	Total number of patients or images	Purpose of NLP	NLP Applications	Unstructured data used for NLP	Criterion standard comparisons
2021	Sax ⁴⁴	Retrospective	150	Identify diseases/events/syndromes	Acute heart failure	ED triage notes, chief complaints	Manual review
2022	Cohen ⁴⁵	Retrospective	70	Identify diseases/events/syndromes	Suicidal ideation	ED interviews' note	CSSRS screening
2022	Irvin ⁴⁶	Retrospective	461	Radiology interpretation	Unilobar vs. multilobar pneumonia, pleural effusion, pneumonia	ED radiology report	Manual review
2022	Yaeger ⁴⁷	Retrospective	1190	Identify diseases/events/syndromes	Infants with fever	ED notes including triage, nursing, physician, resident notes	Manual review
2022	Rozova ⁴⁸	Retrospective	78,045	Identify diseases/events/syndromes	Self-harm	ED triage notes	Manual review
2022	Kooragayala ⁴⁹	Retrospective	398	Radiology interpretation	Worrisome pancreatic lesions	ED radiology report	Manual review
2022	Gordon ⁵⁰	Retrospective	355	Radiology interpretation	Intracranial mass effect	ED radiology report	Manual review
2023	Evans ⁵¹	Retrospective	282	Radiology interpretation	Incidental findings from trauma CT	ED radiology report	Manual review
2023	Dotson ⁵²	Retrospective	341	Radiology interpretation	Incidental pulmonary nodules	ED radiology report	Manual review
2023	MacPhaul ⁵³	Retrospective	685	Identify diseases/events/syndromes	Assault	ED notes	Manual review

Abbreviation: NLP, natural language processing.

^aSecondary data analysis from prospectively collected data.

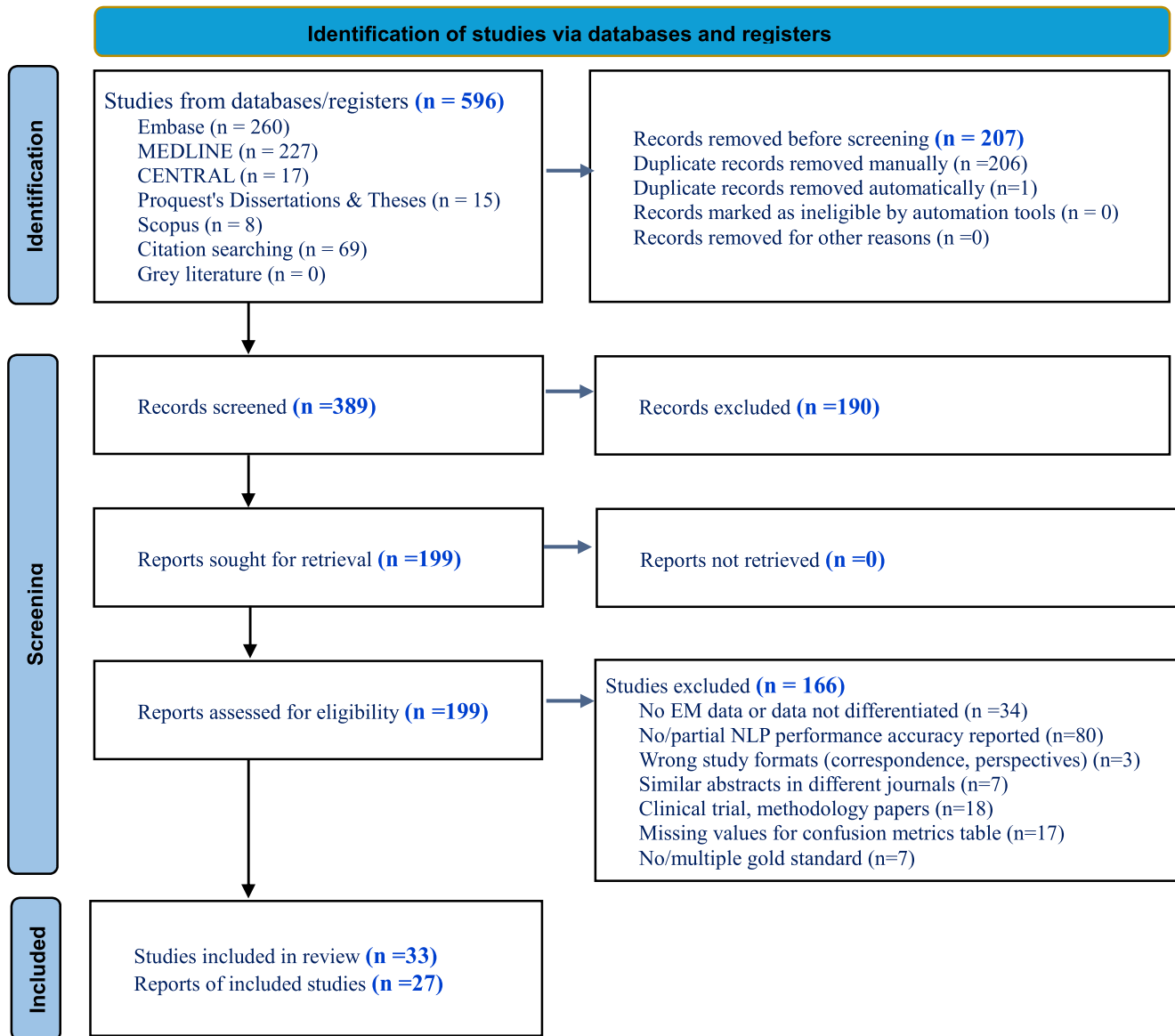


FIGURE 1 PRISMA flow diagram: using NLP in EM research. NLP, natural language processing.

Main results

Overall, this meta-analysis included 27 studies with 179,109 patients and 9025 images. It consisted of four studies involving 23,707 patients focused on syndromic surveillance,^{27,29,33,41} 12 studies covering 155,402 patients targeting diseases/events/syndromes recognition,^{36-40,42-45,47,48,53} and 11 studies involving 9025 images concentrating on radiology interpretations.^{28,30-32,34,35,46,49-52} Detailed descriptions of each study are provided in [Table 2](#). The mean sensitivity across studies was 0.87 (95% CI 0.82-0.91), specificity was 0.95 (95% CI 0.92-0.97), PPV was 0.18 (95% CI 0.18-0.18), NPV was 1.00 (95% CI 1.00-1.00), LR+ was 17.4 (95% CI 10.3-29.5), and LR- was 0.13 (95% CI 0.09-0.19). [Figure 2](#) illustrates a forest plot displaying mean recall (sensitivity) and specificity. Upon subgroup analysis, it was noted that NLP's optimal performance lay in

interpreting image reports (mean sensitivity of 0.93 and specificity of 0.96, [Table 2](#)).

Sensitivity analysis

Among the 27 studies, variations arose due to different NLP algorithms used for outcome prediction and the measurement of diverse outcomes. To address this variability, a sensitivity analysis was conducted to ascertain the worst performance among these studies. Confusion matrices were unsuccessfully derived from two studies,^{39,46} and the other 10 reported varying performance.^{31,33,36,39-41,43,45-48,53}

The sensitivity analysis revealed that the mean sensitivity was 0.82 (95% CI 0.73-0.88), specificity was 0.95 (95% CI 0.92-0.97), PPV was 0.14 (95% CI 0.14-0.14), NPV was 1.00 (95% CI 1.00-1.00),

LR+ was 15.8 (95% CI 10.1–24.6), and LR– was 0.19 (95% CI 0.13–0.29). These metrics represented a less optimal performance, when compared to the best-reported performance observed across the studies (Table 3).

DISCUSSION

The manual conversion of unstructured data into structured data has historically posed significant challenges within research, including extensive time investment in data collection and training, different inter-rater variabilities, and a propensity for errors during manual processing.^{54–56} Leveraging NLP to identify and classify unstructured data has notable advantages in the realm of AI/ML, by mitigating these issues.^{57,58} In our investigation, we observed a generally favorable performance of NLP usage in EM research. Additionally, upon categorizing NLP applications into three key areas, we discovered that the highest performance was achieved in interpreting radiological reports. These findings encourage further exploration and research into the application of NLP for managing unstructured data.

NLP can extract various medical concepts from clinical documentation, facilitating analysis or reasoning based on human language.^{31,59} Substantial potential exists for leveraging EHR data for health care advancements through NLP-based decision support

systems.^{60,61} These systems, derived from NLP-based research, may reduce health care costs while enhancing clinical decision making.

Upon review of the literature, we noted a dearth of performance reports employing meta-analysis to gauge the performance of NLP in identifying and categorizing unstructured data. Currently, there exists only one such meta-analysis, which evaluated postoperative complications within the surgical domain.⁶² The authors reported an overall sensitivity of 92% and specificity of 99%. Our study, although focused on EM research, yielded similar results. Such consistent findings support the potential of NLP to bolster health care efficiency and precision across various medical domains.

Our analysis indicated an overall lower PPV in the range of 0.13–0.14. This outcome was predominantly influenced by a single study with a substantial sample size, which contributed to over 80% of the weighting in the meta-analysis.³⁹ This study utilized triage notes to predict instances of mortality and cardiopulmonary arrest, employing NLP techniques for managing and analyzing these notes to predict said events.³⁹ A low PPV can be anticipated when the prevalence of the event, such as mortality and cardiopulmonary arrest, is exceedingly low (i.e., 0.48% in this study).³⁹ Upon the removal of this influential study from the meta-analysis, the overall mean PPV became 0.82. This revised finding aligns more closely with the PPV we observed when utilizing NLP for syndromic surveillance or interpreting radiology reports.

TABLE 2 Performance of NLP in EM.

	Sensitivity (recall)	Specificity	PPV (precision)	NPV	LR+	LR–
Overall						
Pooled	0.87	0.95	0.18	1.00	17.4	0.13
95% CI	0.82–0.91	0.92–0.97	0.18–0.18	1.00–1.00	10.3–29.5	0.09–0.19
Range	0.33–1.00	0.55–1.00	0.02–0.95	0.72–1.00	1.78–286.46	0.01–0.67
Subgroup, pooled (95% CI)						
Syndromic surveillance	0.73 (0.51–0.87)	0.96 (0.82–0.99)	0.85 (0.84–0.85)	0.99 (0.99–0.99)	16.3 (3.7–72.6)	0.29 (0.14–0.57)
Radiology interpretation	0.93 (0.90–0.94)	0.96 (0.92–0.98)	0.82 (0.81–0.83)	0.99 (0.99–1.00)	20.8 (11.3–38.2)	0.08 (0.06–0.10)
Identifying diseases/events/syndromes	0.86 (0.79–0.91)	0.94 (0.86–0.98)	0.13 (0.13–0.13)	1.00 (1.00–1.00)	14.5 (5.9–35.6)	0.15 (0.09–0.23)

Abbreviations: LR, likelihood ratio; NLP, natural language processing; NPV, negative predictive value; PPV, positive predictive value.

TABLE 3 Sensitivity analysis of performance using NLP in EM.

	Sensitivity (recall)	Specificity	PPV (precision)	NPV	LR+	LR–
Overall	0.82 (0.73–0.88)	0.95 (0.92–0.97)	0.14 (0.14–0.14)	1.00 (1.00–1.00)	15.8 (10.1–24.6)	0.19 (0.13–0.29)
Subgroup						
Syndromic surveillance	0.58 (0.38–0.75)	0.92 (0.86–0.95)	0.46 (0.46–0.47)	0.94 (0.93–0.94)	7.0 (5.7–8.5)	0.46 (0.30–0.70)
Radiology interpretation	0.88 (0.75–0.95)	0.96 (0.92–0.98)	0.87 (0.86–0.87)	0.98 (0.98–0.99)	22.1 (11.5–42.3)	0.12 (0.06–0.27)
Identifying diseases/events/syndromes	0.81 (0.73–0.87)	0.94 (0.88–0.97)	0.12 (0.11–0.12)	1.00 (1.00–1.00)	14.4 (6.8–30.8)	0.20 (0.14–0.30)

Note: Data are reported as pooled performance metrics with 95% CI.

Abbreviations: LR, likelihood ratio; NLP, natural language processing; NPV, negative predictive value; PPV, positive predictive value.

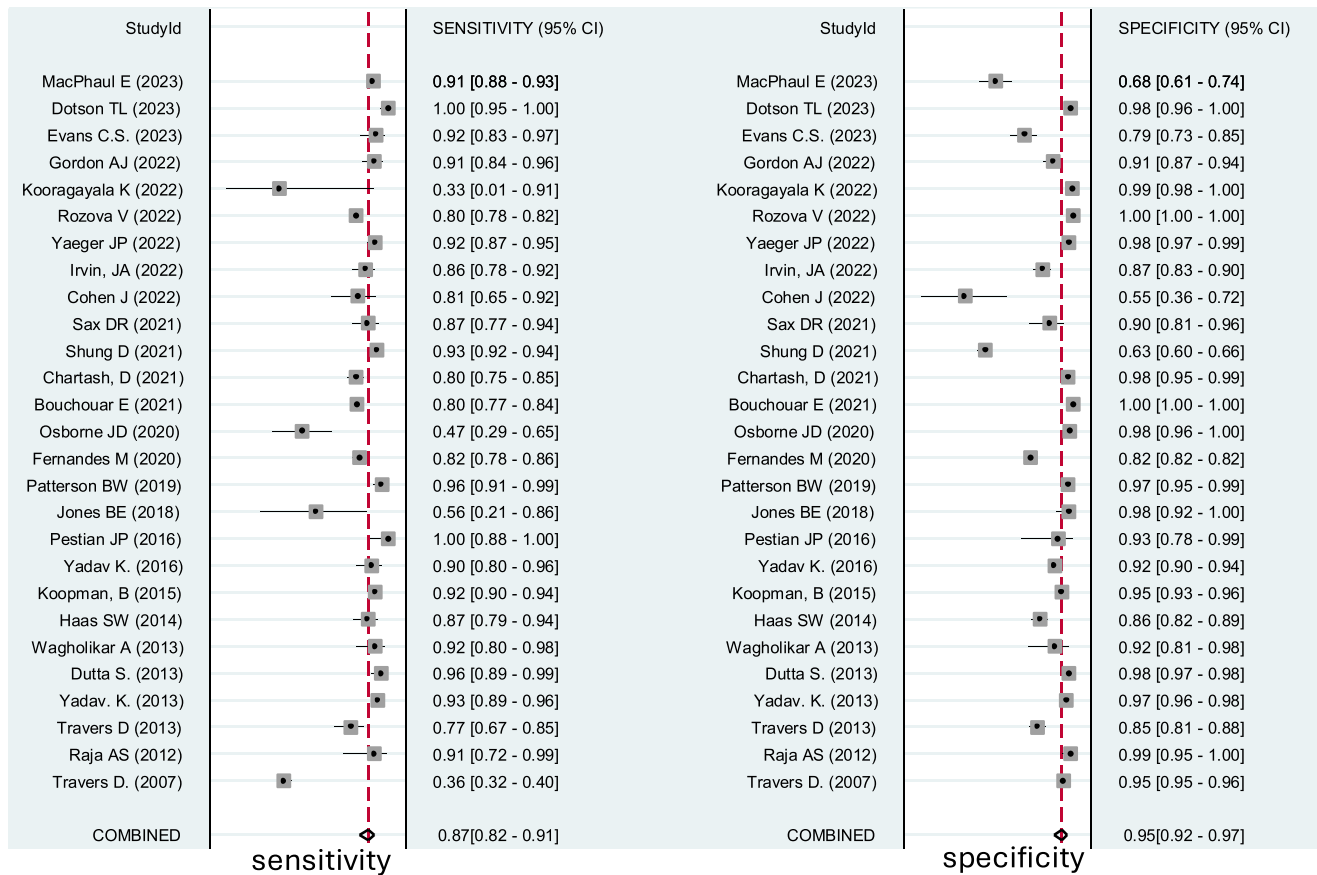


FIGURE 2 Performance (sensitivity and specificity) of using NLP in EM research. The SROC curve depicts mean operating sensitivity and specificity points (Figure 3). The area under the SROC was calculated as 0.96 (95% CI 0.94–0.98). Setting the pretest probability at 50%, following the use of NLP to identify unstructured ED data, the probability of correct prediction reached 95% (Figure 4). Utilizing NLP to exclude cases/disease/events at the same pretest probability (50%) resulted in a posttest probability of 12%, indicating fairly accurate classifications of unstructured data through NLP. NLP, natural language processing; SROC, summary receiver operating characteristic.

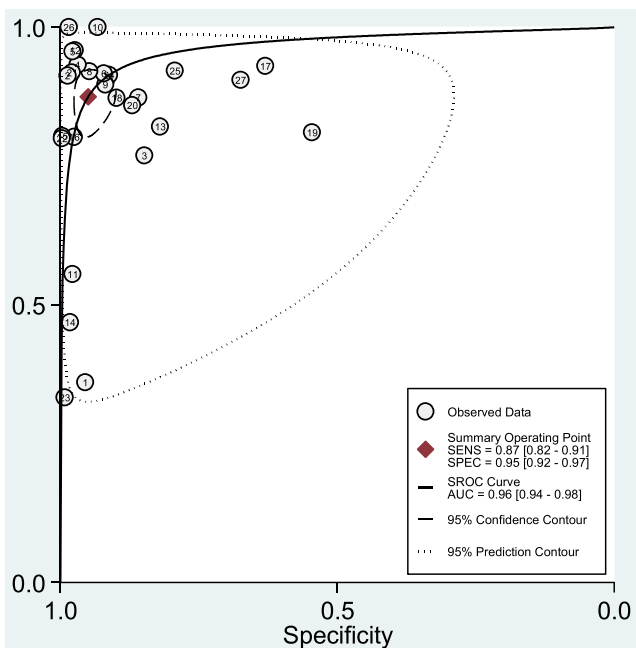


FIGURE 3 An SROC curve. SROC, summary receiver operating characteristic.

Considerable variations in performance among studies underscored the heterogeneity observed in our analysis, plausible mechanisms behind these variations may stem from the inherent challenge of interpreting human language and the utilization of diverse ML models.^{45,63} Our sensitivity analysis highlighted the potential influence of language variance across different times, geographic regions, or events, contributing to this observed heterogeneity. It is imperative to exercise caution when applying open-source NLP programs to individual studies, emphasizing the necessity of validation before formal application.

Our study focused solely on assessing the performance of using NLP independently, while other studies in the literature adopt a fusion of NLP and additional AI/ML algorithms to handle both structured and unstructured data.^{64,65} To offer a broader understanding of NLP usage, future studies could compare performance between both approaches.

LIMITATIONS

Our study, despite a robust search strategy utilizing various databases and manually searching relevant NLP studies, may have missed

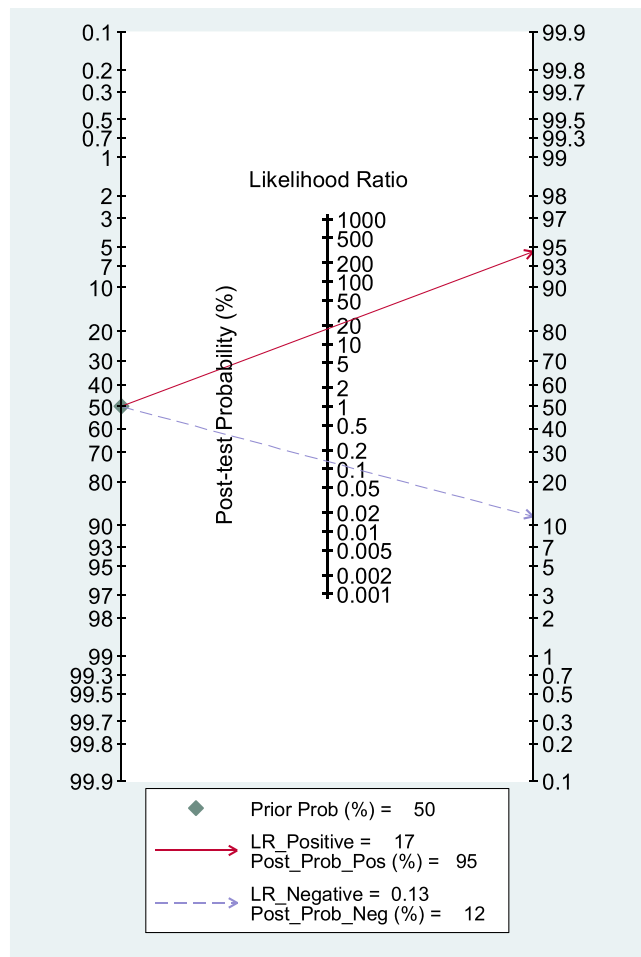


FIGURE 4 Fagan plot.

other NLP studies related to EM, which might affect the overall findings of performance. Another major limitation of this meta-analysis was the potential high heterogeneity found between studies due to threshold effect, which may compromise the accuracy of the meta-analysis results in this study.^{66,67} Moreover, several studies employed a blend of NLP and other AI/ML algorithms to handle both structured and unstructured data.^{68,69} As our inclusion criteria were focused primarily on NLP accuracy, studies employing such combinations were excluded, potentially limiting the scope of NLP investigation. Many studies used sample sizes for NLP validation compared to their designated “criterion standard.”^{28,38,44} Typically, the criterion standard in most studies involved the consensus of manual review, due to the unstructured nature of data. Following validation, these studies applied NLP to larger data sets without additional validation against the criterion standard. Our meta-analysis only incorporated validated data, which might lead to an inaccurate performance assessment of NLP. Some studies have indicated degraded performance when prospectively applying models that were trained retrospectively, underscoring the potential bias in our analysis.^{31,45,63} Lastly, although NLP is commonly used to handle unstructured data, our investigation focused solely on NLP studies within the field of EM. Because our meta-analysis was limited to EM, our results on NLP performance may not generalize to other specialties.

Future studies concentrating on different outcomes, purposes, or diverse medical domains are necessary to validate and expand upon our findings.

CONCLUSIONS

Our study identified generally favorable performance when employing natural language processing in emergency medicine research, with higher performance for radiologic interpretation when compared with syndromic surveillance and disease/event/syndrome recognition. We advocate for further natural language processing research to augment health care efficiency and precision.

ACKNOWLEDGMENTS

We express our gratitude to Dr. James P. d'Etienne and Ms. Alejandra Powers for their review and valuable editorial comments on the manuscript.

FUNDING INFORMATION

Usha Sambamoorthi received funds from the National Institute on Minority Health and Health Disparities through the Texas Center for Health Disparities (NIMHD) 5S21MD012472-05 and the NIH Common Fund Grant 1OT2OD032581-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang H, Alanis N, Haygood L, et al. Using natural language processing in emergency medicine health service research: A systematic review and meta-analysis. *Acad Emerg Med*. 2024;31:696-706. doi:[10.1111/acem.14937](https://doi.org/10.1111/acem.14937)