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SCOPING REVIEW

Leveraging Natural Language Processing and Machine Learning Methods for Adverse Drug Event Detection in Electronic Health/Medical Records: A Scoping Review

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Abstract

Background Natural language processing (NLP) and machine learning (ML) techniques may help harness unstructured free-text electronic health record (EHR) data to detect adverse drug events (ADEs) and thus improve pharmacovigilance. However, evidence of their real-world effectiveness remains unclear.

Objective To summarise the evidence on the effectiveness of NLP/ML in detecting ADEs from unstructured EHR data and ultimately improve pharmacovigilance in comparison to other data sources.

Methods A scoping review was conducted by searching six databases in July 2023. Studies leveraging NLP/ML to identify ADEs from EHR were included. Titles/abstracts were screened by two independent researchers as were full-text articles. Data extraction was conducted by one researcher and checked by another. A narrative synthesis summarises the research techniques, ADEs analysed, model performance and pharmacovigilance impacts.

Results Seven studies met the inclusion criteria covering a wide range of ADEs and medications. The utilisation of rule-based NLP, statistical models, and deep learning approaches was observed. Natural language processing/ML techniques with unstructured data improved the detection of under-reported adverse events and safety signals. However, substantial variability was noted in the techniques and evaluation methods employed across the different studies and limitations exist in integrating the findings into practice.

Conclusions Natural language processing (NLP) and machine learning (ML) have promising possibilities in extracting valuable insights with regard to pharmacovigilance from unstructured EHR data. These approaches have demonstrated proficiency in identifying specific adverse events and uncovering previously unknown safety signals that would not have been apparent through structured data alone. Nevertheless, challenges such as the absence of standardised methodologies and validation criteria obstruct the widespread adoption of NLP/ML for pharmacovigilance leveraging of unstructured EHR data.

1 Introduction

Patient data on the now ubiquitous electronic health records (EHRs) have improved the quality and safety of healthcare globally [1, 2]. Digital patient data comprise structured data points (such as demographics, vital signs, prescriptions, and lab test results) and unstructured information (such as physician notes, progress notes, clinical notes, discharge summaries, patient narratives and imaging reports) [3, 4]. These comprehensive repositories of patient information can enhance the quality of care for individual patients through data analytics techniques that take advantage of patterns and trends derived from the records as a whole [5]. Unstructured data in EHRs accounts for over 80% of patient information, offering a valuable resource for gaining knowledge [6, 7], but it is rarely used [8] as it is much harder to utilise given the ambiguity of free text expressions [6, 9]. Furthermore, utilising one-for-all methods to extract the unstructured portion of EHRs could introduce errors such as perceived data distribution, complicating the process [10].

Progress in the field of natural language processing (NLP), machine learning (ML) and artificial intelligence (AI) enables automated extraction of key information from unstructured text. These advancements prove promising in various clinical applications, such as pharmacovigilance [11]. Pharmacovigilance involves detecting, evaluating, and preventing adverse drug events (ADEs) or reactions (ADRs). With the help of NLP techniques along with ML and AI, meaningful insights can be derived from unstructured

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Key Points

The studies included in this review demonstrated not only proficiency in identifying specific adverse events but also the ability to uncover previously unknown safety signals that would not have been apparent through structured data alone.

Unstructured text from EHRs could enrich pharmacovigilance programmes that have traditionally relied on other data sources. However, research into the ease of use, usability and effectiveness of using unstructured data from EHRs in comparison to traditional data sources is limited.

This review highlights great variability in methods used and validation techniques in obtaining data from unstructured notes in EHRs for pharmacovigilance, which may limit its wide-scale implementation.

clinical text to aid in this field [12]. Automation also makes it possible to efficiently analyse large amounts of textual information related to ADEs.

Adverse drug events pose a major threat to patient safety worldwide and can have severe consequences, including hospitalisation, disability, and even death [13]. Pharmacovigilance plays a crucial role in the continuous surveillance of drug safety following regulatory approval. Traditionally, pharmacovigilance relies heavily on healthcare professionals, pharmaceutical companies, clinical research organisations and more recently patients to report ADEs through a spontaneous reporting systems [14] such as the FDA Adverse Event Reporting System (FAERS). However, approximately 6 % of all ADEs are reported through spontaneous systems [15]. This significant underreporting hampers prompt and comprehensive identification of potentially important medication safety signals [16, 17]. Apart from incomplete information, spontaneous reporting systems suffer from reporting bias [18, 19].

The need to enhance pharmacovigilance capabilities at scale has led to a growing research focus on incorporating unstructured clinical text alongside structured EHR data [20]. Unstructured text offers valuable contextual details and may uncover suspected ADEs not specifically identified through coding processes, such as ICD-9 (International Classification of Diseases, 9th revision) [12, 21–25]. While the potential of using EHR data for pharmacovigilance has been acknowledged, there are still uncertainties regarding the value obtained from extracting information from unstructured clinical text compared to relying solely on structured data [9, 26–29]. There is currently no comprehensive synthesis of the effectiveness of utilising unstructured EHR data for pharmacovigilance purposes and patient safety outcomes in comparison to other data sources [30]. We aim to address this gap through a scoping review of the literature that assesses the performance and utility of using unstructured data in EHR data to identify adverse events as compared to other data sources.

2 Methods

This scoping review was conducted and reported according to PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist [31] (see checklist in Supplementary material). A predefined protocol was initially written to guide the process with any deviations or changes documented. The research question was developed using the PICO framework (Population, Intervention, Comparison, and Outcomes); the inclusion and exclusion criteria are presented in Table 1. Studies after 1990 were filtered for this review as there were key developments in AI methods for extracting and analysing EHRs after this date [32]. Due to resource constraints, only English-language studies were included.

2.1 Search Strategy

The following electronic databases were searched: Medline, Embase, PsycINFO, IEEE Xplore (Institute of Electrical and Electronics Engineers) and ACM Digital Library (Association of Computing Machinery) as well as Google Scholar (of which only the first 300 records were sifted) [33]. Additionally, the reference lists of selected studies were manually reviewed. The final search was completed on 18 July 2023. The full search strategy for all the databases is detailed in Supplementary material.

2.2 Screening

Title and abstract screening were conducted in Covidence [34], a web-based workflow platform for systematic reviews, by two reviewers independently. Full texts were retrieved for those that could not be excluded based on title and abstract review alone. Rigorous exclusion criteria were applied to eliminate papers that did not have a clear focus on NLP/ML or AI for pharmacovigilance, lacked relevant adverse event outcomes, or provided insufficient evidence, or did not have a comparator. Reasons for excluding selected full-text articles were noted.

Table 1 Inclusion and exclusion criteria for studies on utilising ADEs/ADRs from unstructured EHR data

	Inclusion	Exclusion
Participants	Patients of all age and demographic characteristics categories with reported adverse/side effects documented in unstructured text in EHRs/EMRs	Patients with no adverse/side effects documented in EHRs/EMRs
Intervention	Extraction and utilisation of unstructured data from EHRs/EMRs on pharmacovigilance practices (typically using NLP/ML methods)	Studies that primarily focused on structured data and studies not providing sufficient details on the impact of utilising unstructured data in pharmacovigilance practices
Comparator	Studies that include a comparison group using one or more of the following as a comparator: Structured data from EHR/EMR: Studies that utilise structured data (well-defined, coded data) from EHR/EMR Spontaneous reporting systems (e.g., FDA Adverse Event Reporting System, MHRA Yellow Card Scheme) Clinical trials data SmPC Traditional pharmacovigilance methods	Studies that do not have a comparison group or one of the comparators outlined in the inclusion criteria
Outcomes	Impact on identification of ADRs, including the completeness and accuracy of such reports. Secondary outcomes included the identification of safety signals, the timeliness of detecting safety signals, and any improvements in patient safety outcomes resulting from the utilisation of unstructured data in pharmacovigilance practices	Pure technological methods
Setting	Any healthcare setting from any geographical location	Non-healthcare settings
Study Design	Any type of research design. RCTs, non-randomised controlled studies, before-and-after studies, time series evaluations, cohort studies, case-control studies, and observational studies	Non-empirical research, opinion pieces, commentaries, letters to the editors, or editorials
Restrictions	Published in or after 1990 In English language (or translation available)	Published before 1990 In non-English language

ADE adverse drug event, *ADRs* adverse drug reaction, *EHRs* electronic health records, *EMR* electronic medical record, *MHRA* Medicines & Healthcare products Regulatory Agency, *NLP/ML* natural language processing/machine learning, *RCTs* randomised control trials, *SmPC* Summary of Product Characteristics

2.3 Data Extraction

A customised data extraction form was created in Covidence. Details summarized in the extraction form included: study ID, paper title, authors, publication year, objectives, study design, methods, data source, population, interventions/exposures, outcomes, results/ conclusions, and how it was relevant to the review topic.

Quality parameters of the studies were extracted and discussed in lieu of formal methodological quality assessment (or risk of bias assessment)—as this is a scoping review. The quality parameters included research design, sample size, appropriateness of data sources, use of suitable NLP/ML techniques, evaluation metrics, comprehensive interpretation of results, reliability measures, and alignment with the review objective.

We also provided an overview of the NLP and ML techniques utilised in existing pharmacovigilance research for ADE and safety signal detection, as well as the specific adverse events analysed, outcome metrics used and overall findings. This scoping review aims to offer a comprehensive summary of the existing literature while underscoring its limitations and key gaps that should be addressed in future research on utilising NLP/ML for pharmacovigilance with EHR/EMR data.

3 Results

3.1 Selection of Studies

A total of 1191 references from the six databases were imported into Covidence after eliminating 152 duplicates. Of the 1039 remaining records screened based on titles and abstracts, 857 were excluded for being irrelevant to the review topic. Of the 184 articles reviewed for full-text screening, 174 were excluded based on the predetermined

inclusion criteria (see Supplementary material). Ultimately, 7 studies from 10 publications (Table 2) spanning the publication years from 2013 to 2023 met all our inclusion criteria [35–44] (Fig. 1). For each study thereafter we cite all the related publications.

3.2 Study Sample Size

The sample sizes of the reviewed studies varied greatly, whilst some reported the number of patients (from 286 to 1.8 million) others reported the quantity of clinical notes (up to 11 million EHR notes). One study [41] focused specifically on ICU notes, four studies [35, 37, 38, 40, 43, 44] on emergency departments, inpatient departments or outpatient departments, whilst the remaining two studies [36, 39, 42] did not specify any particular note types. The outcomes examined revolved around the identification and documentation of specific adverse events including arthralgias, opioid overdoses, diarrhoea, hypoglycaemia, acute pancreatitis and acute kidney injury, among others. Comparisons of the data retrieved from unstructured notes to other data sources were mostly confined to comparisons with structured data [35, 38–41], with some comparisons to FAERS [36, 37, 42], claims data [35, 38, 40], and known signals [36, 37, 42–44].

3.3 NLP/ML Approaches

The studies listed in Table 2 cover a range of applications and methodologies of how NLP and ML are utilised for pharmacovigilance purposes and for evaluating patient safety outcomes. The NLP tasks covered in these reviewed studies include information extraction [36–39, 42–44], classification methods [35, 40] and information retrieval [41]. Two studies used information extraction to identify ADEs directly [37, 38], while the remaining three studies [36, 39, 42–44] used information extraction as a preliminary step for further analysis. An example showed that one study used extracted information to build logistic regression to assess the association between arthralgia and vedolizumab [35, 39, 40], another study used a temporally ordered patient feature matrix to investigate ADEs in EHR [43, 44], and another study used a case-crossover design to screen potential ADEs [36, 42]. For the classifier task, a rule-based classifier was used to identify opioid overdose [35, 40]. For the information retrieval task, one study [41] utilised keyword search to find documentation of drug-associated acute kidney injury (DAKI) in clinical notes. Clinical applications in these studies include detecting association between medications and their ADRs [36, 39, 42–44], identifying or classifying ADEs [35, 37, 38, 40], and investigating drug-related acute kidney injury [41]. Figure 2 provides an overview of the NLP/ML methods used and synthesizes the reported results of the best performing system for each study.

3.4 Overview of ADE Identification/Classification Performance

For identifying ADEs from clinical notes, three studies employed rule-based methods for ADE identification/classification tasks. Green et al (2019) [35, 40] leveraged NLP to build rule-based systems for identifying and classifying opioid-related overdoses using EHR data. By extracting information related to overdose indicators and types from clinical narratives, they demonstrated that NLP-enhanced algorithms for suicides/suicide attempts and abuse-related overdoses perform significantly better than code-based algorithms and are appropriate for use in the setting that have data and capacity. Geva et al (2020) [38] used a NLP tool—Apache clinical Text Analysis Knowledge Extraction System (cTAKES)—to extract textual mentions of medication and signs/symptoms that may represent ADE mentions from clinical notes. In their experiments, using cTAKES to analyse clinical notes generally identified more potential ADEs than diagnostic codes in either EHR or insurance claims datasets. Similarly, Harpaz et al (2013) [37] used an NLP tool—MedLEE—to extract and normalise medications, diseases, and signs and symptoms from EHR notes. After combining this extracted information with the signal from adverse event reporting system (AERS), they found that this strategy enhanced signal detection under certain operating scenarios and objectives for potentially novel ADRs.

3.5 Overview of ADE-Drug Association Detection Model Performance

For detecting association between medications and their ADEs, these studies [36, 39, 41–44] first utilised NLP techniques to extract ADEs, and such ADE information was applied in different models for association analysis. For instance, Cai et al (2016) [39] employed NLP to extract mentions of arthralgias from clinical notes and subsequently used logistic regression models to assess the association between arthralgia and vedolizumab. Their NLP approach demonstrated higher accuracy compared to traditional ICD-9 coding methods, enabling more precise identification of adverse events. Lependu et al (2013) [43, 44] used NLP pipelines to extract and normalise biomedical concepts such as the drug, disease, device, and procedure, and used such information and the time stamps of the clinical notes to produce a deidentified, temporally ordered patient feature matrix, which was then used for detecting drug safety signals at scale. The overall performances of detecting associations

Table 2 Studies included in this scoping review

Author, year	Aim	Methods	Data source	Drug-ADE	Evaluation metrics used	Results	Conclusion
Cai 2016 [39]	Assess association between arthralgia and vedolizumab	Used NLP to extract mentions of arthralgias, then a logistic regression models to test the association between arthralgia and vedolizumab. The NLP approach was compared against ICD-9 coding information. Used unspecified NLP method for extraction	367 IBD patients on vedolizumab and 1218 IBD patients on TNFi (control) in two US hospitals compared to ICD-9 codes	Vedolizumab—arthralgia	Sensitivity, specificity, PPV, NPV PPV = 0.9, NPV = 0.88, Sensitivity = 0.83, Specificity = 0.93	The NLP approach had a higher accuracy for identifying arthralgias V/S ICD-9 codes: PPV 0.90 vs 0.78, NPV 0.88 vs 0.71. Using NLP, the prevalence of arthralgia was higher among IBD patients who received vedolizumab (77.1 %) compared to those who did not (49.1 %)	Confirmed increased arthralgia with vedolizumab. NLP was able to uncover AE-drug associations not visible through traditional coding
Geva 2020 [38]	Compare ADE rates determined from EHRs and administrative claims data among children treated with drugs for PH	Used NLP (Apache [cTAKES]) to extract textual mentions of medication and signs/symptoms that may represent ADE mentions from clinical notes, compared the results to EHR diagnostic codes and payor claims data. Used rule-based NLP tool for extraction	Two retrospective data sources including the EHR dataset from the Boston Children's Hospital and the claims dataset from a national, private health plan in the USA. After data analysis and filtering, 286 patients that have used PH-targeted medication from EHR dataset and 253 patients that claimed for at least 1 PH-targeted drug from claims dataset. EHR dataset contains plain-text admission, discharge, consultation, progress, emergency department, procedure, and clinic notes	Drugs for pulmonary hypertension in children (sildenafil, tadalafil, bosentan, ambrisentan)—ADEs (anaemia, diarrhoea, oedema, headache, hearing loss, dizziness/hypotension, intracranial haemorrhage, priapism, rash/flushing, reflux, seizure, sinusitis, syncope/presyncope, thrombocytopenia/bleeding, transaminitis, visual changes (including ischaemic optic neuropathy)	F_1score, precision, recall. F_1 = 0.78, precision = 0.69, recall = 0.9	cTAKES: F_1 score on held out EHR data (38 notes for 12 patients) was 0.78. ADE rates differed between the EHR clinical notes and diagnostic codes. Of 40 potential ADEs examined, 6 (15 %) were identified significantly more frequently in the EHR clinical notes. An additional 13 potential ADEs were identified only in clinical notes but not in diagnostic codes. Only 1 potential ADE was identified significantly more frequently in the diagnostic codes. Some potential ADEs were similar in both data sources	Analysis of clinical notes generally identifies more potential ADEs than diagnostic codes in either EHR or insurance claims datasets, but certain diagnoses are better represented in structured data

Table 2 (continued)

Author, year	Aim	Methods	Data source	Drug-ADE	Evaluation metrics used	Results	Conclusion
Green 2019 [35] also in Hazlehurst 2019 [40]	Enhance automated methods for opioid overdose identification and classification in EHRs	Built a rule-based NLP knowledge module based on the MediClass system to identify and classify the opioid overdose from clinical notes of EHR encounter records. They used terms or concepts related to the indicators of overdose and type of overdose as variables to enhance a code-based algorithm. Each NLP-derived variable was tested using logistic regression analyses to determine whether or not its addition improved performance beyond that of each respective code-based algorithm. Used rule-based NLP tool for extraction	1006 ($n = 627$ used) records for the development dataset, 1696 ($n = 710$ used) records for the validation dataset, and 435 ($n = 305$ used) records for the portability dataset from two US health systems (ED, inpatient, outpatient, and telephone follow-up) compared to chart audit	Opioid—overdose	Sensitivity, specificity, PPV, NPV Identification of the substance involved in ADR: PPV = 0.32, NPV = 0.89, Sensitivity = 0.24, specificity = 0.93	The NLP method performed well in identifying overdose (sensitivity = 0.80, specificity = 0.93), intentional overdose (sensitivity = 0.81, specificity = 0.98), and involvement of opioids (excluding heroin, sensitivity = 0.72, specificity = 0.96) and heroin (sensitivity = 0.84, specificity = 1.0). However, it performed poorly at identifying adverse drug reactions and overdose due to patient error and moderately at identifying substance abuse in opioid-related unintentional overdose (sensitivity = 0.67, specificity = 0.96)	Accurately identified overdoses in EHR text and some types of overdoses. Performed well overall but poorly on some classifications. The NLP-enhanced algorithms for suicides/suicide attempts and abuse-related overdoses perform significantly better than code-based algorithms and are appropriate for use in settings that have data and capacity to use NLP

Table 2 (continued)

Author, year	Aim	Methods	Data source	Drug-ADE	Evaluation metrics used	Results	Conclusion
Harpaz 2013 [37]	Develop a better signal detection strategy for potentially novel ADRs by requiring signalling from both AERS of the Food and Drug Administration and EHRs in both sources	Used a rule-based NLP system—MedLEE to extract and normalize medications, diseases, and signs and symptoms. Temporal information corresponding to admission, discharge, and visit dates was also extracted. Laboratory test data directly available in structured form and based on internal New York Presbyterian Hospital (NYPH) codes were linked to each of the narratives, and, together with the data dimensions extracted from the narratives, formed the set of clinical variables used for statistical signal detection Used rule-based NLP tool for information extraction, and statistical analysis to estimate surrogate measures of association between specific drug-event (outcome) combinations	Full dataset consisted of 7 years (2004–2010) of data, around 1.2 million narratives, and 178,000 patients from unstructured HER—clinical narratives—corresponding to discharge summaries, admission notes, and outpatient office visits compared to over 4 million FAERS reports	Any drug –rhabdomyolysis, acute pancreatitis, and QT prolongation	Precision at K (signals selected), recall at k, $F_1$and average precision. For the union of the established and plausible classes of ADRs: precision at $K = 85$, recall at $k = 20$, F_1score = 30	The combined AERS and EHR system outperforms the AERS system for all values of K examined, and often by a large margin	Replicated signalling in AERS and EHRs can enhance signal detection under certain operating scenarios and objectives. This approach leads to improved accuracy of signal detection when the goal is to produce a highly selective ranked set of candidate ADRs. Such a system is not intended to replace, but rather augment, the portfolio of existing approaches

Table 2 (continued)

Author, year	Aim	Methods	Data source	Drug-ADE	Evaluation metrics used	Results	Conclusion
Lependu 2013 [43, 44]	Investigate adverse drug events in large volumes of free-text clinical notes	Used NLP pipelines to extract and normalize biomedical concepts such as drug, disease, device, and procedures. Uses ~5.6 million strings from existing terminologies; filters unambiguous terms that are predominantly noun phrases, uses the cleaned up lexicon for term recognition to tag or annotate the text; excludes negated terms or terms that apply to family and medical history; normalises all terms using the ontology hierarchies; and finally uses the time stamps of the note to produce a deidentified, temporally ordered patient–feature matrix. Compares to recalls or alerts or signals. Ontology based text processing workflow Extraction. Used rule-based NLP tool for extraction	Stanford Translational Research Integrated Database Environment, which spans 18 years of patient data from 1.8 million patients; it contains 19 million encounters, 35 million coded ICD-9, diagnoses, and >11 million unstructured clinical notes, which are a combination of pathology, radiology, and transcription reports	12 distinct ADEs, 78 distinct drugs, 28 positive cases, and 165 negative cases	Odds ratio, propensity score, ROC, AUROC Detecting 28 true positive associations from the single drug–adverse event reference set: AUROC (adjusted) = 0.804; a threshold of 1.0 on the lower bound of the 95 % CI, sensitivity = 0.39, Specificity = 0.975	Using the set of terms corresponding to the definition of the event of interest: sensitivity = 0.74, specificity = 0.96. For 28 true positive associations from the single drug–adverse event reference set: the overall performances of detecting associations between a single drug and its adverse event, with an AUROC of 75.3 % (unadjusted) and 80.4 % (adjusted). A threshold of 1.0 (a commonly used cut-off) on the lower bound of the 95 % CI of the adjusted ORs translates to 39 % sensitivity and 97.5 % specificity	Reproduced rofecoxib signal and other drug recalls or alerts. Provided methodology for mining clinical notes using NLP/terminologies to transform into structured data for pharmacovigilance. Analysis of textual clinical notes could detect adverse drug events 2 years before the official alert

Table 2 (continued)

Author, year	Aim	Methods	Data source	Drug-ADE	Evaluation metrics used	Results	Conclusion
Murphy 2023 [41]	Investigate drug-related AKI causes in ICU	Used keyword search to identify AKI and DAKI from clinical notes; and combined other data from the allergy module and diagnostic codes for an observational study on ICU data. Compares diagnosis codes (structured data), allergy module (semi-structured data), and clinical notes (unstructured data). Used keyword search for information retrieval	8124 ICU admissions were included, with 542 (6.7 %) ICU admissions experiencing AKI stage 2 or 3 from ICU data from a hospital in the Netherlands	Nephrotoxic drugs – drug-induced acute kidney injury	NA (keyword search)	18.8 % of AKI drug-related; all DAKI cases retrieved were documented in the clinical notes, none were retrieved by diagnostic codes	Highlighted limitations around identifying drug-associated AKI from unstructured documentation, informing the need for better NLP/ML to improve extraction, and reporting of ADEs

Table 2 (continued)

Author, year	Aim	Methods	Data source	Drug-ADE	Evaluation metrics used	Results	Conclusion
Wang 2017 and 2018 [36, 42]	Screen for ADEs combining FAERS and EMRs	Used NLP techniques (MedTagger—CRF based ML model) to extract treatment outcome information from unstructured EMR text and then standardize the extracted terms using UMLS, and adopted a case-crossover design with drug use as the exposure. Proposes methods combine FAERS and EMR data. Compares with SIDER and ADReCS. Used CRF-based machine learning model for information extraction, and a case-crossover design with drug use as the exposure for association analysis	Rheumatoid arthritis patients with 15,826 notes from a US medical centre	Disease-modifying antirheumatic drugs—ADEs	Odds ratio, precision, recall, F1 score Precision = 0.1, Recall = 0.43, F1 = 0.156	For ADE signal detection of conventional DMARDs in rheumatoid arthritis patients: combining FAERS with EMR achieved better F1 scores in detecting ADEs. For instance. using ADReCS as gold standard, their approaches achieve 0.111 of F1 score on Methotrexate, and 0.153 of F1 score on leflunomide. Flexible mapping strategy helped improve recall, e.g., using SIDER as gold standard, 0.578 vs 0.376 of recall on methotrexate. Signals detected from EMR have considerably overlapped with signals detected from FAERS or ADE knowledge bases, implying the importance of EMR for pharmacovigilance	Recall was greatly increased when combining FAERS with EMR compared with FAERS alone and EMR alone. Combining data from clinical notes using NLP and FAERS data improved ADE detection

ADE adverse drug event, *AE* adverse events, *AERS* adverse event reporting system, *AKI* acute kidney injury, CRF conditional random fields, *cTAKES* clinical Text Analysis Knowledge Extraction System, *DAKI* drug-associated acute kidney injury, *DMARDS* disease-modifying antirheumatic drugs, *EHRs* electronic health records, *EMR* electronic medical record, *FAERS* FDA Adverse Event Reporting System, *FDA* US Food and Drug Administration, *HER* human epidermal growth factor receptor, *IBD* inflammatory bowel disease, *ICD-9* International Classification of Diseases 9th revision, *ICU* intensive care unit, *NLP* natural language processing, *NPV* negative predictive value, *PH* pulmonary hypertension, *PPV* positive predictive value, *TNFi* tumour necrosis factor inhibitor, UMLS Unified Medical Language System

between a single drug and its adverse event were reported [43, 44], with an area under the receiver operating characteristic (AUROC) curve of 75.3 % (unadjusted) and 80.4 % (adjusted). The unadjusted AUROC measures the raw association between drug and its ADEs; the adjusted AUROC is for cancelling the effect of potential confounders. Wang et al 2018 [36, 42] applied a ML-based NLP system (MedXN) [45] to extract and a Unified Medical Language System (UMLS) dictionary to normalise drugs and clinical outcomes from unstructured text, and then adopted case-crossover design to detect signals of association between drug and potential ADEs for patients with certain indications. They compared the extracted ADE from FAERS and Electronic Medical Record (EMR) against two ADE knowledge bases. Their finding showed that recall of ADE extraction greatly increased when combining FAERS with EMR compared with FAERS alone and EMR alone, especially for flexible mapping strategy. In addition, signals detected from EMR have considerably overlapped with signals detected from FAERS or ADE knowledge bases, implying the importance of EMR for pharmacovigilance.

Murphy et al (2023) [41] used keyword search to identify acute kidney injury (AKI) and drug-related AKI from ICU data. They highlighted limitations around identifying drug-associated AKI from unstructured documentation, informing on the need for better NLP/ML to improve the extraction and reporting of ADRs.

The comparisons with other data sources gave varying results but overall authors concluded that the addition of adverse events from unstructured data could improve pharmacovigilance. Lependu 2013 [43, 44] suggests that adverse events can be detected 2 years earlier with unstructured data. Others also indicate higher accuracy [37], higher recall [36, 38, 42], or new associations not visible by comparison sources [38, 39, 41]. However, some caution was recommended as certain adverse events are better represented in structured data [35, 38, 40]. For instance, in Green et al., the NLP performed well in identifying overdose and intentional opioid overdose but performed poorly at identifying overdose due to patient error [35, 40].

4 Discussion

In summary, this review evaluated the effectiveness of using NLP/ML to leverage unstructured EHR data to enhance pharmacovigilance. A total of 7 studies in 10 articles published between 2013 and 2023 were included, the majority of which were observational in design and conducted in healthcare settings to investigate a range of adverse drug events such as AKI, hypoglycaemia and arthralgias. Overall, these studies showed that NLP and ML approaches have potential for extracting clinically useful information on adverse events from unstructured EHR/EMR data. The same finding is also shown in prior research [46]. Various approaches in the fields of NLP and ML were utilised, including rule-based systems [34–44], statistical models [36, 37, 39, 42–44], and ML-based NLP tools [36, 42].

The overall performance of these models was reasonably high across most studies based on metrics such as sensitivity, specificity, F1 scores, and AUROC [39, 43, 44]. The NLP has facilitated the creation of unstructured datasets amenable to pharmacovigilance tasks including signal detection, risk identification, and detection of underreported adverse event-drug pairs [36, 42]. However, significant variability exists in techniques, data sources, evaluation methods, and pharmacovigilance outcomes examined. Only one study [36, 42] validated findings in external datasets or across multiple sites, which may limit the generalisability of the evidence. For future work of assessing ML/NLP studies in detecting ADEs from EHR notes, we refer readers to the prior study [47].

Performance varied across models and tasks, highlighting the need for continued research and validation on diverse clinical applications. Moreover, there is currently no widely accepted set of guidelines or criteria for reporting and critically evaluating NLP/ML research in analysing EHR notes. While a few well-known benchmark datasets [48] and shared tasks [49] exist for evaluating NLP/ML methods on detecting ADEs in EHR notes, they were not widely adopted in our included studies. As this emerging field continues to develop, it will be essential to establish standards for methodology and reporting to enhance the quality of studies and facilitate effective synthesis of evidence [50]. There is also no consensus on the best techniques for representative data sampling, addressing class imbalance, optimising models, and evaluating model performance. Three studies developed their own rule-based NLP methods [39, 41, 43, 44] for information extraction or information retrieval, while the remaining four studies leveraged existing tools, including three rule-based NLP tools [35, 37, 38, 40] and one ML-based tagger [36, 42]. For more detailed information on the effectiveness and characteristics of different NLP/ML methods for analysing EHR notes, we refer readers to a systematic review of NLP/ML methods applied to clinical notes [51, 52]. Additionally, studies focusing on information extraction and information retrieval [35, 36, 39, 40, 42–44] failed to compare their methods with widely used clinical NLP tools like cTAKES [53] and MetaMap [54] for analysing EHR data.

By leveraging the comprehensive information contained within EHRs, researchers can gain access to contextual documentation pertaining to medication usage patterns and their associated effects at scale [55]. Nevertheless, it is worth mentioning that NLP or ML in isolation cannot yield conclusive proof of causal connections between medications

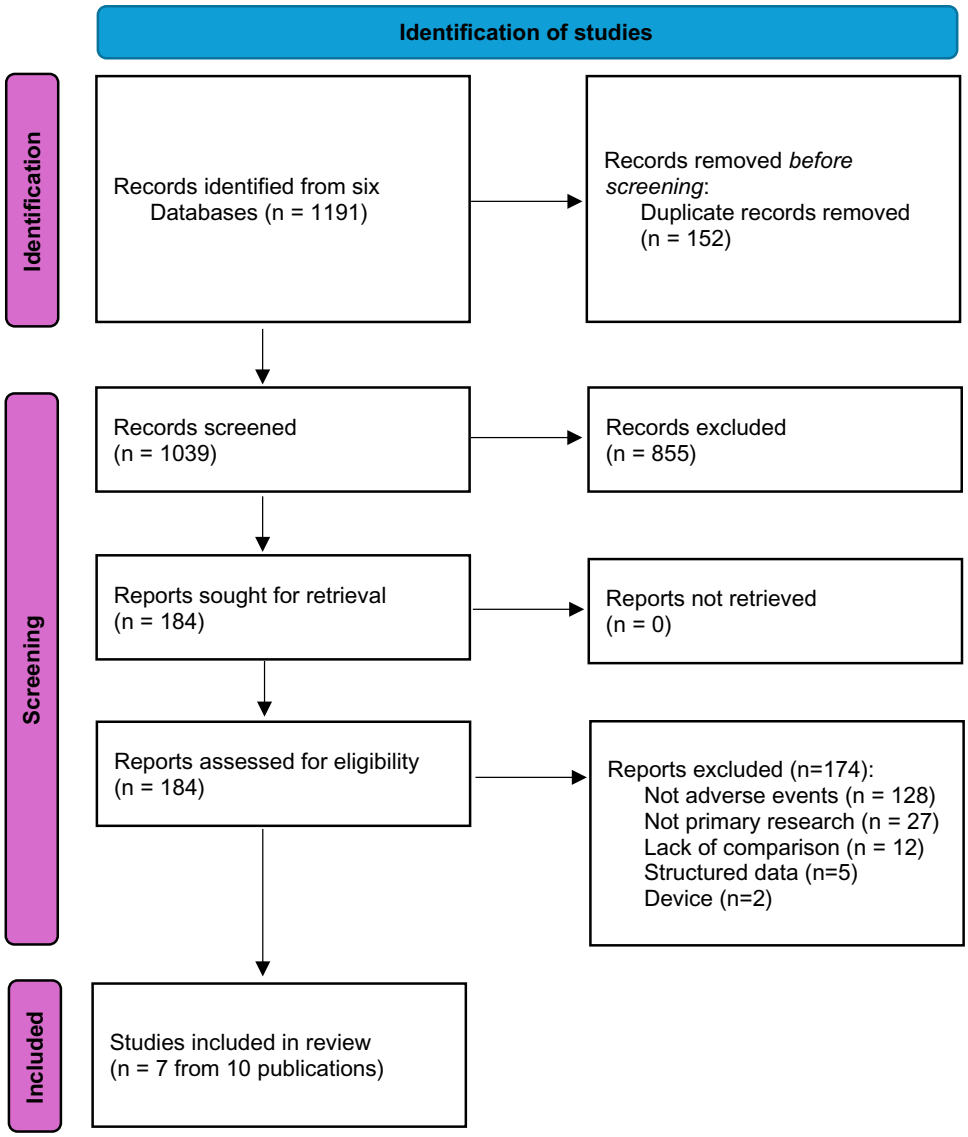


Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram for included studies

and adverse drug reactions. To establish such relationships, a comprehensive appraisal of all accessible evidence must be conducted [56]. Moving forward, the next crucial step involves assessing the real-world effectiveness of integrating information derived from unstructured data with other evidence obtained from EHRs and EMRs [57].

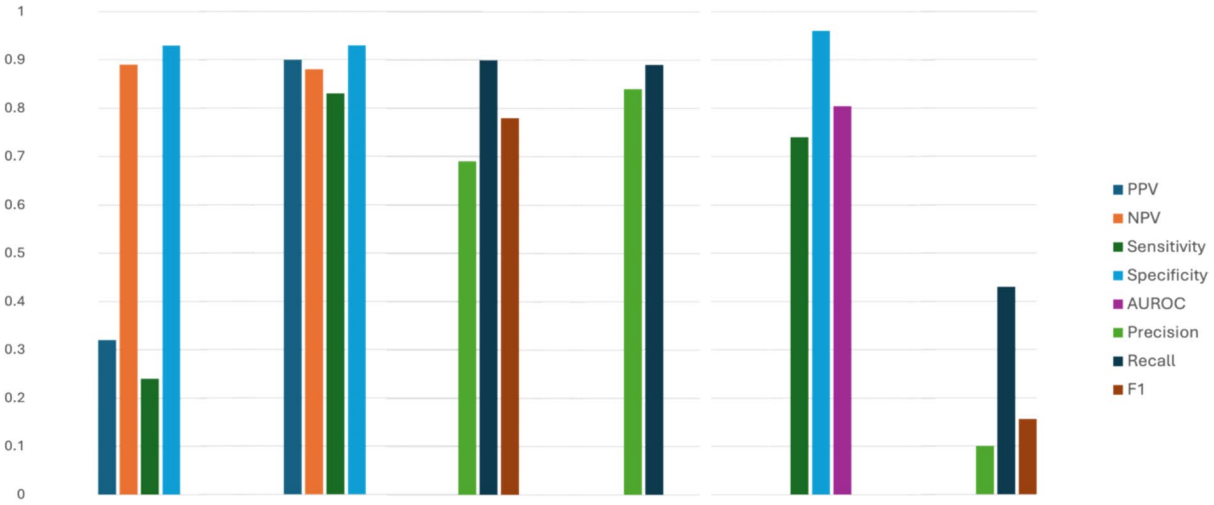
This review focuses on studies that assess the detection of specific adverse drug events from unstructured EHR data compared to other sources in order to improve patient safety. In contrast, previous reviews [58, 59] provide a general overview of using NLP for pharmacovigilance from diverse data sources or focus solely on technical issues.

This review synthesises evidence on the impact of unstructured EHR/EMR data on key pharmacovigilance metrics like adverse event detection, safety signals, risk identification, and documentation practices. Prior reviews in this field [46, 60] show a lack of such evidence.

Overall, there was a consensus that unstructured data have the potential to improve pharmacovigilance by being an adjunct to other sources. However, caution should be applied as variations in the performance of detecting adverse drug events were apparent according to adverse event type, and currently there is insufficient understanding of why such discrepancies exist.

4.1 Limitations

Certain limitations of this review must be acknowledged when interpreting the results. The exclusion of non-English studies could introduce potential language bias.



Author, Year	Green, 2019, incl. Hazlehurst, 2019	Cai, 2016	Geva, 2020	Harpaz, 2013	Lependu, 2013 AB	Wang, 2018
NLP/ML Methods	Rule-based	Not reported	cTAKES	MedLEE[b]	ontology based text processing workflow	MedTagger (CRF based ML model)
Data	627 notes	10,743 patients	286 patients	1.2 million notes	9,078,736 notes	15,826 patient's notes
	Classification Model	NER/IE Models				

[a] Excludes Murphy, 2023, as no performance metrics were reported.
[b] Results reported for original MedLEE model.
PPV = positive predictive value, NPV = negative predictive value, AUROC = area under the receiver operating characteristic, F1 = F1 score, CRF = conditional random fields, ML = machine learning, NER = named entity recognition, IE = information extraction

Fig. 2 Overview of system performance for included studies[a]

Most NLP/ML studies focused on simulated datasets or single research groups, limiting insights into real-world effectiveness and generalisability. Insufficient information regarding institutional data sources, patient demographics, model specifications, and evaluation methods in certain papers can also limit the analysis. Lastly, as this was a scoping review we did not conduct formal quality assessment of the studies. However, given the lack of a validated quality assessment tool for these types of studies, rigorous quality assessment with these studies would have been challenging.

Given the preliminary research stage in this area, caution should be exercised despite the potential of NLP/ML technologies for clinical use. Conducting well-designed validation studies and fostering interdisciplinary collaboration is crucial to establish effective frameworks for incorporating these tools into pharmacovigilance practice. While this review emphasised the current possibilities, it also emphasised substantial gaps that must be addressed through rigorous research and comparison to existing pharmacovigilance systems before widespread implementation.

4.2 Implications for Practice and Research

This review has significance for how future research will be undertaken and incorporated into pharmacovigilance practice. First, it re-affirms that NLP/ML systems cannot provide evidence of causality between drugs and adverse event outcomes [49]. Their importance comes from strengthening signal detection and structured/unstructured data processing to enable more proactive safety surveillance [61]. Second, collaboration between data scientists and clinical domain specialists is necessary to successfully design, develop, and use these systems [62]. Third, synthesising higher-quality evidence would be made possible by developing methodological standards and reporting criteria specifically for NLP/ML health research [63]. Finally, before considering large-scale clinical deployment of AI technologies, comprehensive multi-site prospective studies are essential to confirm utility across varied settings and populations [64], which help to optimise resources and prevent health disparities.

Overall, while this review reveals the promising potential of NLP and ML techniques for extracting insights on adverse

drug events from unstructured EHR data, much work must be done to establish the best methods, determine the utility in detail, and incorporate these novel approaches into applied pharmacovigilance practice. The review summarises the available research progress while identifying the drawbacks, biases, and knowledge gaps that must be addressed in subsequent studies. The use of these instruments to enhance patient safety will depend on standardised guidelines, multidisciplinary cooperation, and cautious evaluation.

The integration of unstructured data and NLP/ML algorithms demonstrates the potential value of clinical data embedded in narrative notes for pharmacovigilance [65]. Nevertheless, the absence of standardised frameworks and varying systems for unstructured EHR/EMR data poses obstacles to implementation.

4.3 Recommendations for Future Research

To improve future research in the use of NLP or ML on methods on EHR data, we propose several key recommendations. First, the development and adherence to standardised reporting guidelines specific to NLP/ML studies in healthcare, such as those suggested by Stevens et al. [47], is crucial. These guidelines recommend reporting detailed descriptions of data sources, preprocessing steps, model architectures and rationale, and evaluation metrics. To provide a full assessment of a model's performance, comprehensive evaluation metrics, including precision, recall, F1-score, and AUROC, should be consistently reported with confidence intervals and statistical significance tests [66]. Systematic comparisons between NLP/ML approaches and traditional pharmacovigilance methods, as well as established clinical NLP tools like cTAKES and MetaMap, are essential. These tools have been widely used in the clinical setting and are well established as baseline methods, which can be used as comparators for different datasets. Transparency and reproducibility can be enhanced by providing detailed documentation of cohort inclusion criteria, data collection and preprocessing, model development steps, and whenever possible, making code and de-identified datasets publicly available [67, 68]. Robust study designs should include multi-site investigations to assess generalisability, prospective validation in real-world clinical settings, and utilisation of larger, more diverse datasets to improve model performance and reduce bias [69, 70]. Finally, the development and utilisation of standardised benchmark datasets for evaluating NLP/ML models in pharmacovigilance would enable fair comparisons across different approaches and studies [49]. By following these recommendations, future research can produce more robust, comparable, and clinically relevant results, ultimately advancing the integration of NLP and ML techniques into pharmacovigilance practice.

5 Conclusion

This comprehensive scoping review indicates that utilising NLP and ML techniques has shown the potential to enhance pharmacovigilance by leveraging unstructured EHR/EMR data. These approaches have demonstrated proficiency in identifying specific adverse events and uncovering previously unknown safety signals that would not have been apparent through structured data alone. It is important to point out the significant differences in approach among various studies, and that the levels of validation and comparison to other data sources in terms of ease of use, utility, and effectiveness remain limited. To ensure reliability and effectiveness, practicality in healthcare settings, and definitive improvement in patient outcomes, it is essential to undertake further comprehensively planned studies involving multiple sites and comparisons.

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Declarations

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Conflicts of Interest None declared.

Ethics Approval Not applicable. Secondary analysis of publicly available literature.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material The data supporting the findings of this scoping review are derived from published studies and are publicly accessible. A comprehensive list of the studies included in the review, along with the excluded sources, can be found in the text and supplementary materials of this manuscript. For any additional inquiries regarding the data, please contact the corresponding author.

Code Availability Not applicable.

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