REVIEW ARTICLE

Navigating the Polypharmacy Landscape: A Bibliometric Analysis of Computational Approaches for Predicting Adverse Drug Reactions

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ABSTRACT

Polypharmacy, the concurrent use of multiple drugs in a patient due to complex diseases or multiple morbidities, poses potential hazards through adverse drug reactions (ADRs). Conventional in vivo and in vitro ADR identification methods are challenging, making computational alternatives vital for minimizing patient risk. This study evaluates the scientific outputs of computational approaches to predict ADRs associated with polypharmacy through bibliometric analysis. A comprehensive literature search was conducted on Web of Science, Scopus and PubMed, which yielded 258 selected publications. Quantitative variable analysis was performed, and VosViewer was used to visualise networks and co-occurrences. The United States and China lead in publications, with 'drug-drug interaction' being the most frequent keyword. The Journal of Biomedical Informatics was ranked top, followed by BMC Bioinformatics and Briefings in Bioinformatics. The results indicate a growing global interest in computational methods for predicting adverse drug reactions associated with polypharmacy, primarily focusing on drug-drug interactions.
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INTRODUCTION

The term "polypharmacy", used over 150 years ago (1), refers to the usage of many medications, which indicates excessive or inappropriate prescribing. Although there is no official definition, it commonly refers to patients taking four or more medications (2), or the simultaneous use of five or more medications (3,4). Polypharmacy is rather prevalent in elderly patients and those with multiple morbidities needing more medications (2–4). The main reason for polypharmacy is poor health conditions and it is caused by the growing prevalence of multimorbidities (5). According to some studies, the most common chronic conditions associated with polypharmacy are obstructive pulmonary disease, diabetes, depression, heart disease, hypertension, and pain (5). These complex diseases need more than one medication to be effectively treated or controlled through different mechanisms of action. However, the use of multiple drugs can be linked to poor adherence, hospitalization, and higher healthcare expenses (3), and can trigger health risks such as adverse drug reactions (ADRs), side effects, and severe toxicities (6). One of the main causes of polypharmacy-induced ADRs is drug interactions (DIs) (6–10). DIs refers to an alteration in the pharmacological effect of a drug by another co-administrated drug (10,11) that can be beneficial or harmful. However, harmful DIs are significant because they account for 10–20% of preventable ADRs that require hospitalization (11,12). Predicting ADRs due to polypharmacy and DIs during preclinical and clinical phases can be costly and time-consuming. On the other hand, polypharmacy ADRs are rare and cannot be identified during clinical trials (10). DIs may be determined using *in silico*, *in vitro*, and *in vivo* studies; however, the latter two looks to be exceedingly expensive and, in some circumstances, difficult to carry out (8). Polypharmacy ADRs are subject to particular conditions that are hard to anticipate during preclinical and clinical studies. Additionally, patients with multiple chronic diseases or frailty are excluded during randomised controlled trials. As a result, there is limited understanding of the possible risk of taking multiple

medications in an older or multi-morbid population that is likely to be on a polypharmacy regimen (4). Hence, there is a strong tendency to develop computational methods for expediting procedures and lowering social, financial, and health expenses (13).

During the last decades, compound activity and biological data have been produced and gathered due to information technology and automation advancements. They helped reduce costs and time by increasing patient survival and quality of life or exploring alternate research avenues that led to personalized treatments (14,15). Recently, methods were developed to predict the possible ADRs induced by polypharmacy using artificial intelligence (AI). These approaches can expedite and simplify the drug development pipeline in preclinical investigations and clinical trials (14,16).

Bibliometric analysis is a mathematical and statistical approach to evaluate the progression of research activities in a specific field qualitatively and quantitatively. It can analyze and predict the development trend in a certain field over a period of time. Moreover, the approach can assess the contribution of authors, institutions, and countries and it is helpful to find out research trends, gaps, and future perspectives in a specific field (17–19). Thus, this study aimed to explore the scientific outputs of computational approaches for predicting polypharmacy-related ADRs through bibliometric analysis.

MATERIALS AND METHODS

Data Source and Data Collection

Scopus, Thomas Reuters' Web of Science core collection, and PubMed were used as the primary data sources. The literature search was performed on a single day to avoid daily database update bias. The flowchart of search strategy is shown in Figure 1 for each database. The document type was limited to original articles and reviews, whereas no restriction was included in the term of the time frame. The information such as author name, article title, source of the article, affiliation, year of publication, keywords, and abstract for each article was exported in CSV formats. A total of 1063 duplicates were identified and removed from 2920 articles retrieved from the three databases, resulting in 1,857 articles available for further record screening.

Data Extraction

The exported files were imported into Microsoft Excel 365 (Microsoft, USA). Two independent researchers carried out the article screening for the inclusion and exclusion of articles. First, the selection was made based on the article title. The selected articles were then evaluated by reading their abstract, and in some cases, followed by the full-text reading to determine the article relevancy to the analysis. Extracted data from selected papers include authors' names, article titles, source of the article, affiliation, year of publication, keywords, and the number of citations. Any disagreement between the researchers was discussed to reach a consensus.

Data Analysis and Visualization

The data were analyzed manually using Microsoft Excel 365 (Microsoft, USA). The data were statistically analyzed regarding the number of publications in a year, authors with the most publications, countries with the most publications, institutions with the most publications, journals, and keywords. The data were visualized using VOSviewer version 1.6.19 (http://vosviewer.com), a software used to visualise networks of scientific literature. It connects journals, authors, countries, and intimations regarding co-authorship, citation, co-citations, and co-occurrence analysis (19).

RESULTS

Global Trend and Citation

A total of 598, 1338, and 993 articles were retrieved from Web of Science, Scopus, and PubMed, respectively. Only 258 articles met the inclusion criteria containing 239 original and 19 review articles (Figure 1). The publications were cited 6331 times with an average of 25.2 citations per publication. The trend of global publication on computational approaches for polypharmacy side effects prediction has been increasing from 1987 (n=1) to 2022 (n=33), as shown in Figure 2. The first article was published in 1987; from 2022 until August 11, 33 articles were published.

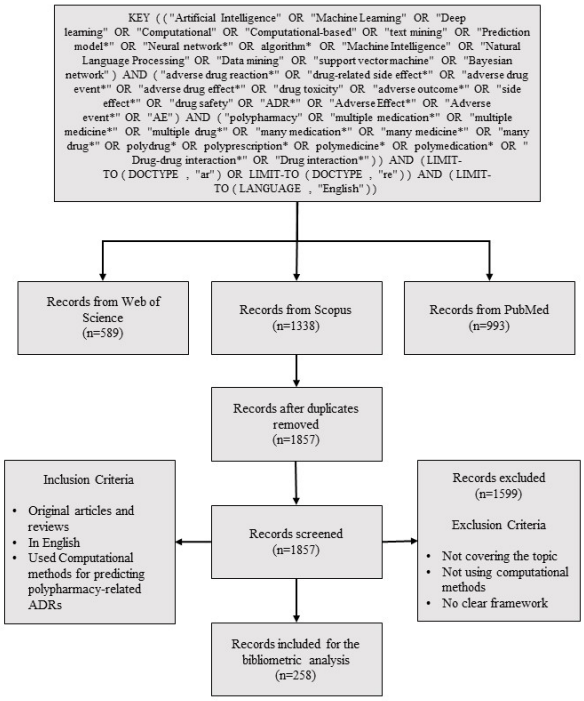

Figure 1 : Flowchart of search strategy

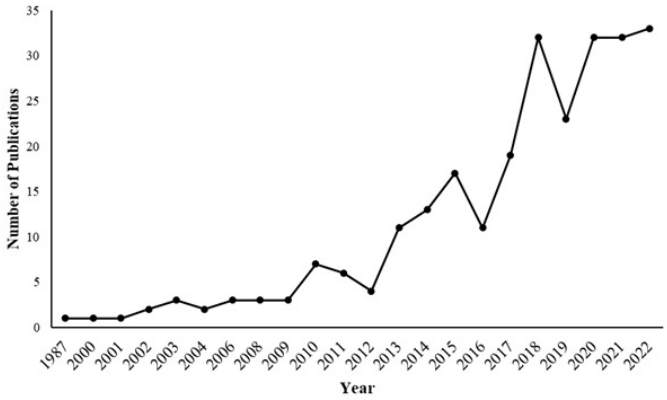

Figure 2 : Number of publications per year.

Contribution of Countries

A total of 41 countries contributed to the topic. The United States had the most number of publications (n=105), followed by China (n=64), Spain (n=12), Japan (n=11), and South Korea (n=11). The co-authorship analysis of the countries (Figure 3a) revealed ten clusters with total links of 60. United States was at the center of the largest cluster with a total of 25 links and a link strength (TLS) of 51 which shows the country's close collaboration with different countries Such as China, Canada, India, Japan, France, Germany, Saudi Arabia, and Russia. Moreover, the second largest cluster belongs to China with 9 links and a TLS value of 34.

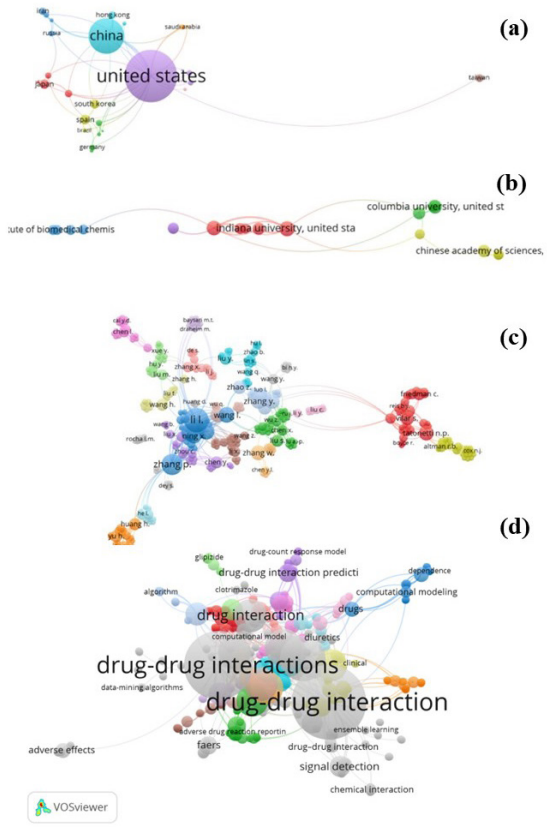

Figure 3 : Visualization of (a) countries, (b) institutions, (c) authors' co-authorship analysis, and (d) keyword cooccurrence analysis.

Contribution of Institutions

A total of 443 institutions contributed to the research on the topic. Among them, Indiana University of the United States contributed the most with 12 publications, followed by Ohio States University (n=11) and Columbia University (n=9) of the United States, and Northwestern Polytechnical University of China (n=8). However, the Stanford University of the United States, with 7 publications had the most total citations (n=862). Moreover, according to the co-authorship analysis, the visualization (Figure 3b) shows 5 clusters with a total number of 20 items and 32 links. The cluster in red was with most items that consisted of Indiana University, Ohio University, Harbin Engineering University, Regenstrief Institute, and the University of Pennsylvania. Moreover, Indiana University had the highest TLS (13).

Contributions of Authors

A total of 1037 authors from different countries contributed to the publications on computational approaches for polypharmacy side effects predictions. Among them, Li L. was ranked top with 16 publications and a total citation of 225 times. Zhang P. was ranked second with 12 publications, followed by Shen I. (n=8), Quinney S. K. (n=7), Wang I. (n=7), and Zhang Y. (n=7). However, Tatonetti N. P., with 6 publications had the most citations (403), followed by Zhang W., with a total citation of 321 times. As per co-authorship analysis, the visualization network (Figure 3c) shows 23 clusters with different numbers of items and 1739 links. Li L., Zhang P., Quinney S. L, Shen I., and Wang I. were at the center of the network with TLS of 111, 80, 63, 56, and 56, respectively, indicating the most collaboration between them.

Journal Analysis

The extracted publications on the topic were published in 134 Journals. The top 10 journals published 95 articles (Table I). The Journal of Biomedical Informatics was ranked top with 16 publications and a total citation of 722 times. BMC Bioinformatics and Briefing Informatics were both ranked second with 12 publications each, followed by Studies in Health Technology Informatics (n=10), Drug Safety (n=8), and Scientific Reports (n=8).

Keywords Analysis

A total of 557 keywords occurred 886 times in 258 articles. Drug-drug interaction and drug-drug interactions were the most occurred keywords, with an occurrence of 41 and 36 times, respectively. Machine learning, adverse drug reaction, deep learning, pharmacovigilance, and polypharmacy were the other most used keywords, with 18, 13, 11,11, and 10 occurrences, respectively. As shown in Figure 3d, the co-occurrence analysis divided all the identified keywords into 44 clusters. The most prominent clusters were "drug-drug interaction" and "drug-drug

Table I : Top journals contributed to the topic

Rank	Source Title	TP	TP (%)	TC	C/P
1	Journal of Biomedical Informatics	16	6.20%	722	45.13
2	BMC Bioinformatics	12	4.65%	350	29.17
-	Briefings in Bioinformatics	12	4.65%	128	10.67
3	Studies in Health Technology Informatics	10	3.88%	105	10.50
4	Drug Safety	8	3.10%	234	29.25
-	Scientific Reports	8	3.10%	187	23.38
5	Bioinformatics	7	2.71%	532	76.00
6	PLoS Computational Biology	6	2.33%	205	34.17
-	PLoS ONE	6	2.33%	199	33.17
7	Journal of Cheminformatics	5	1.94%	34	6.80
-	Journal of the American Medical Informatics Association	5	1.94%	396	79.20
-	Amia Annual Symposium Proceedings	4	1.55%	60	15.00
8	Artificial Intelligence in Medicine	4	1.55%	103	25.75
-	Frontiers in Pharmacology	4	1.55%	107	26.75
-	Amia Summits on Translation Science Proceedings	3	1.16%	14	4.67
9	Clinical Pharmacology and Therapeutics	3	1.16%	186	62.00
-	Current Topics in Medicinal Chemistry	3	1.16%	88	29.33
-	IEEE Journal of Biomedical and Health Informatics	3	1.16%	16	5.33
-	Journal of Chemical Information and Modeling	3	1.16%	95	31.67

TP=Total Publications; TC=Total Citation; C/P=Citation per Publication

interactions". This indicates that the most prominent topics in polypharmacy side effects research are drug-drug interactions with TLS values of 160 and 159 respectively.

DISCUSSION

Polypharmacy is an emerging health concern that is caused by the growing prevalence of multimorbidities (5) as a needed strategy to treat complex diseases (2,20,21). However, it can cause severe ADRs due to the high occurrence of DIs (1,4,6,7). Determining and identifying polypharmacy-related ADRs during preclinical and clinical phases can be costly and in some circumstances, is impossible (8,10). Computational methods can be alternative approaches to detect polypharmacy-related ADRs in less time and cost (8,22–24).

The finding of this study showed that research in the field of computational methods for predicting polypharmacy side effects had an expansion, and the publications had an upward trend from 1987-2022. A total of 258 articles with 6331 cited times were published during the period. According to the findings of this study, the first paper referring to computational methods for detecting DIs was published in 1987 by Edmond et al.. The authors described algorithms that could determine DIs on any microcomputer in many languages (25). Recently, more advanced computational methods were developed to detect polypharmacy-related ADRs. These approaches are primarily designed to detect and identify DIs in a multi-medication regimen. According to a recent review by Qiu et al., the computational methods for detecting DIs can be classified into three main categories: (a) Literature-based extraction, which uses natural processing techniques to extract DIs from biomedical literature. A large amount of biomedical and drug information is hidden in literature, such as published articles, books, and scientific reports. The number of literature is growing exponentially. Models are designed to automatically detect and extract DIs from these sources. (b) Machine learning-based methods, with which the prediction models are built based on known DIs and drug features such as chemical and biological data to predict unknown DIs. (c) Pharmacovigilance-based data mining methods use statistical techniques to identify DI signals from different electronic databases that should be investigated further for any link with any potential ADR (13). This can be correlated with the findings of this study. As per the cooccurrence analysis of keywords, drug-drug interaction was the most used and occurred

keyword in publications related to computational approaches for detecting polypharmacy side effects. This happened due to the direct relation between polypharmacy side effects and drug-drug interaction. As stated earlier, DIs are the main cause of ADRs due to polypharmacy (8,9,12). The keywords in an article indicate terms related to the main topic of the research. In the bibliometric analysis, the most occurred keywords reflect research trends in a specific topic (19). Moreover, most developed methods for predicting polypharmacy side effects are based on DIs information. For instance, Firdousy et al. developed a binary vector approach to predict DIs based on the functional similarity of drugs. The method was set on biological elements such as carriers, transporters, enzymes, and targets(8). Zitnik et al. developed another model for predicting polypharmacy side effects, called Decagon. It is a general convolutional neural network graph to predict the DIs that can identify the interdependence of different side effects types between any two drugs in the graph (24). Similarly, a network framework, developed by De Anda-Jaurengui, can analyze drug combination ADR that can potentially arise with a drug regimen and can quantitatively measure the possible interaction of a combination using high-throughout drug perturbation experiments (21). Recently, a new model for predicting polypharmacy side effects, called PSECNN, was introduced by Lakizadeh and Babaei. The multi-label, multi-class deep learning method combines basic drug features such as individual drug side effects, drug-protein interaction, chemical substructure, targets, and enzymes and creates a new drug feature that predicts the drugs' side effects (22). Kulenovic and Lagumdzija-Kulennovic developed a personalized medicine optimization method using the Electronic Medical Records repository of the Personal Genome Project (PGP), DrugBank. and Comprehensive Toxicogenomic Database to identify polypharmacy therapies with minimal DIs, drug-gene interactions, and DCI to avoid possible ADRs (26).

A total of 41 countries contributed to the topic; among them, the United States had the most publications followed by China. This shows that more papers may be published globally in the coming year since the topic is a growing concern. Moreover, nearly 92.6% of the publications were original articles, indicating that most of the published papers contained computational methods developed from scratch for the predictions of polypharmacy side effects. The quality and academic impact of the publications can be represented by the total times of citations of a country, journal, or institution. In this study, the United States was ranked first with the most cited times, followed by China. Additionally, most contributed institutions to the topic were from the United States and China. That makes both countries the most contributive ones among the others.

The collaboration between authors, institutions, and countries can be analysed by coauthorship analysis and means by TLS which indicates the frequency and closeness of collaboration between authors, institutions, and countries on a specific fluid. A high TLS value shows more frequent collaboration between them (19). In this study, Li L. and Zhang P. were found to have more collaboration with other authors on computational methods for predicting polypharmacy-related ADRs. Meanwhile, In terms of institutions, the Indiana University of the United States had a TLS value of 13 which can collaborate with the most collaborative country on the topic, the United States with a TLS value of 51. Journal of Biomedical Informatics, BMC Bioinformatics, and Briefings Informatics with impact factors of 6.317, 3.169, and 6.385, respectively, published most articles on the topic. Journals with high impact factors can have a high academic impact and attract high-quality papers (19).

CONCLUSION

Polypharmacy poses a significant health concern due to the potential for causing serious and life-threatening ADRs induced primarily by drug interactions. Identifying polypharmacy-related ADRS in the pre-clinical and clinical phases can be both expensive and, in some cases, unfeasible. Computational methods, however, offer a timely and cost-effective alternative for detecting such ADRs. These methods can reduce the potential risk of polypharmacy in a patient with complex diseases and ensure the safety of therapeutic plans and drug optimizations. The upward trajectory of this research focus indicates an ongoing commitment to addressing the complications of polypharmacy. This conclusion provides confidence in the continuation of this essential work in future years, likely driven by the ongoing academic interest and the necessity presented by complex patient care.

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