

The Use of Machine Learning in Real-World Data: A Systematic Review of Disease Prediction and Management

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Submitted to: JMIR Medical Informatics
on: November 17, 2024

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The Use of Machine Learning in Real-World Data: A Systematic Review of Disease Prediction and Management

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Abstract

Background: Machine learning (ML) and big data analytics are revolutionizing healthcare, particularly in disease prediction, management, and personalized care. With vast amounts of real-world data (RWD) from sources like electronic health records (EHRs), patient registries, and wearable devices, ML offers significant potential to improve clinical outcomes. However, data quality, transparency, and clinical integration challenges remain.

Objective: This study aims to systematically review the use of ML in real-world data for disease prediction and management, identifying the most common ML methods, disease types, study designs, and sources of real-world evidence (RWE).

Methods: A systematic review followed the PRISMA guidelines to identify studies that utilized machine learning methods for analyzing real-world data in disease prediction and management. The review focused on extracting data related to the machine learning algorithms used, disease categories, types of studies, and sources of RWE, such as electronic health records (EHRs), patient registries, and wearable devices.

Results: The systematic review revealed that the most frequently employed machine learning methods were Random Forest (RF), Logistic Regression (LR), and Support Vector Machine (SVM). These methods were applied across various disease categories, with cardiovascular diseases, cancers, and neurological disorders being the most common. Real-world evidence primarily originated from EHRs, patient registries, and wearable devices, with a predominant focus on predictive modeling to improve clinical outcomes.

Conclusions: ML and big data hold significant promise for enhancing healthcare through better disease prediction and management. However, data quality, model interpretability, and generalizability must be addressed to integrate ML models fully into clinical practice.

(JMIR Preprints 17/11/2024:68898)

DOI: <https://doi.org/10.2196/preprints.68898>

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Original Manuscript

Review

The Use of Machine Learning in Real-World Data: A Systematic Review of Disease Prediction and Management

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Abstract

Background: Machine learning (ML) and big data analytics are rapidly transforming healthcare, particularly in disease prediction, management, and personalized care. With the increasing availability of real-world data (RWD) from diverse sources such as electronic health records (EHRs), patient registries, and wearable devices, ML techniques present substantial potential to enhance clinical outcomes. Despite this promise, challenges such as data quality, model transparency, generalizability, and integration into clinical practice persist.

Objective: This systematic review aims to examine the use of ML in analyzing real-world data for disease prediction and management, identifying the most commonly employed ML methods, prevalent disease types, study designs, and the sources of real-world evidence (RWE) utilized. The review also explores the strengths and limitations of current practices, offering insights for future improvements.

Methods: A comprehensive search was conducted following the PRISMA guidelines to identify studies utilizing ML techniques for analyzing RWD in disease prediction and management. The search focused on extracting data regarding the machine learning algorithms applied, disease categories studied, types of study designs (e.g., clinical trials, cohort studies), and the sources of RWE, including EHRs, patient registries, and wearable devices. Studies published between 2014 and 2024 were included to ensure the analysis of the most recent advances in the field.

Results: The review identified 58 studies that met the inclusion criteria, with a total sample size of over 150,000 patients. The most frequently applied ML methods were Random Forest (RF) (24 studies), Logistic Regression (LR) (21 studies), and Support Vector Machines (SVM) (18 studies). These methods were predominantly used for predictive modeling across disease areas, including cardiovascular diseases (19 studies), cancer (9 studies), and neurological disorders (7 studies). RWE primarily came from EHRs, patient registries, and wearable devices. A significant portion of studies (68%) focused on improving clinical decision-making, patient stratification, and treatment optimization. Among the 58 studies, 14 (24.1%) focused on decision-making, 13 (22.4%) on healthcare outcomes such as quality of life, recovery rates, and adverse events, and 11 (19.0%) on survival prediction, particularly in oncology and chronic diseases. For example, RF models for cardiovascular disease prediction demonstrated an area under the curve (AUC) of 0.85 (95% CI, 0.81–0.89), while SVM models for cancer prognosis achieved an accuracy of 83% ($p < 0.05$). Despite the promising outcomes, many studies faced challenges related to data quality, model interpretability, and ensuring generalizability across diverse patient populations.

Conclusions: This systematic review highlights the significant potential of ML and big data analytics in healthcare, especially for improving disease prediction and management. However, to fully realize the benefits of these technologies, future research must focus on addressing the challenges of data quality, enhancing model transparency, and ensuring the broader applicability of ML models across diverse populations and clinical settings.

KEYWORDS

machine learning; big data; real-world data; disease prediction; healthcare management; real-world evidence

Introduction

Advances in big data analytics and the growing availability of real-world data (RWD) are transforming healthcare by enabling new applications of machine learning (ML) to improve health

outcomes [1]. Real-world evidence (RWE) generated from diverse data sources like electronic health records (EHRs), patient registries, and wearable devices has become central to informed decision-making in clinical practice [2, 3]. When combined with ML, RWD presents a promising avenue to enhance disease prediction, personalize patient management, and optimize therapeutic effectiveness. By providing a comprehensive view of patient histories and real-world health outcomes, ML applications in healthcare can drive actionable insights across various domains, including disease diagnosis, treatment planning, and chronic disease management [4, 5]. Real-world data captures information about patients in naturalistic settings, revealing how healthcare is delivered and its outcomes. Unlike clinical trials that operate within controlled conditions, RWD offers a more representative view of patient experiences, treatment responses, and health outcomes [6]. The rise of big data technology and data management systems has facilitated the integration of vast, heterogeneous data types, allowing ML algorithms to identify complex patterns within high-dimensional datasets [7, 8]. These capabilities allow healthcare providers to predict health outcomes, identify at-risk populations, and tailor interventions based on individual patient factors, thus making strides toward precision medicine [9].

Despite its potential, ML applications in RWD and big data contexts face several challenges. Data quality remains a primary concern, as real-world data often features inconsistencies, missing values, and lack of standardization [10]. Unlike the structured data from controlled clinical trials, RWD demands extensive preprocessing, including advanced natural language processing (NLP) methods and imputation techniques to address data gaps. Such efforts are critical to enhancing ML model reliability and ensuring accurate, meaningful outcomes [11, 12]. Biases present another key issue. ML models trained on RWD may inherit biases from the data, often stemming from demographic imbalances or regional healthcare differences. Left unaddressed, these biases can lead to healthcare disparities, as ML-driven decisions might inaccurately represent minority populations or certain patient groups [13]. Incorporating fairness-aware ML algorithms and cross-validating models across multiple datasets can mitigate this challenge, though developing equitable ML models remains a high priority [14]. Another significant hurdle is the interpretability of ML models, especially deep neural networks, which are known for their "black box" nature. While complex models deliver high accuracy, their opaque decision-making process limits the ability to verify or explain predictions. Model transparency is crucial given the high stakes in healthcare, where ML-based recommendations can impact lives. Advances in interpretability tools like SHAP values and LIME have helped enhance model transparency, yet balancing interpretability with performance remains an area of active investigation [15, 16].

The integration of ML with RWD poses ethical and regulatory challenges, especially regarding patient privacy, data security, and informed consent. Regulations like the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in the European Union impose strict standards for data protection. However, adapting these laws to the context of ML in healthcare is complex due to the scale and diversity of data involved [17, 18]. Solutions such as de-identification, secure data-sharing protocols, and clear data management strategies have become crucial to ensuring patient confidentiality while maximizing data utility [19]. Ensuring equitable treatment outcomes is another ethical imperative. Given that ML models trained on data from predominantly certain demographics may perform poorly on underrepresented groups, addressing these disparities is critical. By incorporating fairness-aware ML models and building representative datasets, healthcare practitioners can ensure that ML applications benefit all patient groups, regardless of demographics [20]. Regulatory bodies are beginning to develop specific guidelines for the use of ML and RWD in healthcare. The Food and Drug Administration (FDA), for example, has issued draft guidance on using RWE for regulatory decisions, and the European Medicines Agency (EMA) has also recognized the importance of RWE in evaluating drug safety and efficacy [21]. As ML applications in healthcare continue to grow, a

solid regulatory framework will be necessary to safeguard patient health while supporting technological innovation.

The objective of this systematic review is to explore and critically analyze the applications, challenges, and future directions of machine learning in processing real-world health data and big data across various disease domains. Specifically, this review aims to identify the disease areas where ML with RWD has shown clinical utility, examine the ML algorithms and methodologies applied to big data in healthcare, and analyze the challenges related to data quality, bias, and model interpretability. Additionally, the review addresses the ethical and regulatory frameworks pertinent to the use of ML in healthcare, with an emphasis on patient privacy and fairness. Finally, it outlines future research needs and opportunities for innovation in using ML, RWD, and big data for precision medicine and public health.

Methods

Eligibility Criteria

For this systematic review, we focused exclusively on clinical trials and cohort studies that utilized ML techniques to analyze RWD for disease prediction and management. Studies were included if they met the following criteria: (1) they were randomized controlled trials (RCTs), pragmatic clinical trials, observational clinical trials, or cohort studies; (2) they involved the application of ML methods (e.g., supervised learning, unsupervised learning, deep learning) to RWD for clinical decision-making, disease prediction, or management of common diseases such as cardiovascular diseases, diabetes, cancer, and chronic conditions; and (3) they used real-world health data sources such as EHRs, patient registries, or wearable health devices. Exclusion criteria included trials that did not apply ML techniques or used only data from controlled clinical trials rather than real-world settings.

Information Sources

The following information sources were utilized to capture the most relevant clinical trial and cohort studies: PubMed, Scopus, and the Cochrane Library. PubMed was specifically targeted for clinical trials and biomedical research, particularly studies published in leading clinical journals. Scopus and the Cochrane Library were also searched to gather clinical trial reports within the healthcare and ML domains. To ensure comprehensive coverage, Google Scholar was included to identify grey literature, such as theses and reports not indexed in traditional databases. These sources were selected to provide a broad overview of clinical trial data and their relevance to ML applications in disease management. Additionally, regulatory bodies such as the U.S. FDA and the EMA were consulted to gain insights into clinical trial guidelines and regulatory standards regarding the use of RWD in healthcare.

Search Strategy

A comprehensive search strategy was developed to identify clinical trials and cohort studies focused on ML applications in RWD. The search query incorporated key terms related to ML (e.g., "machine learning," "deep learning," "artificial intelligence") and clinical trials (e.g., "clinical trial," "randomized controlled trial," "pragmatic clinical trial") along with terms related to disease management (e.g., "disease prediction," "healthcare outcomes"). For example, the search used: ("machine learning" OR "deep learning") AND ("clinical trial" OR "randomized controlled trial" OR "pragmatic trial" OR "cohort study") AND ("real-world data" OR "electronic health records" OR "patient registries"). Boolean operators (AND, OR), truncation, and Medical Subject Headings

(MeSH) terms were employed to refine the search and ensure comprehensive coverage. The search was conducted across multiple databases, including Cochrane Library, PubMed, and Web of Science, covering the period from January 1, 2014, to December 31, 2024, ensuring that the full range of recent literature was captured. Additionally, relevant studies were identified through manual searches of reference lists from key articles and by reviewing clinical trial registries such as ClinicalTrials.gov to ensure comprehensive coverage of the clinical trials relevant to ML in disease management. Grey literature was identified by conducting targeted searches in Google Scholar and manually retrieving relevant documents suggested by domain experts. Only English-language publications were included. To enhance transparency and reproducibility, the full search strategy, including specific database queries and search filters, has been included in the **Multimedia Appendix 1**.

Study Selection

The study selection process was conducted in two stages: an initial screening of titles and abstracts by two independent reviewers, followed by a full-text review by the same two reviewers to ensure consistency and minimize bias. In the first stage, the titles and abstracts of all identified articles were assessed for relevance based on predefined inclusion criteria. Discrepancies between reviewers were resolved through discussion, with a third reviewer consulted when necessary. Studies that met the inclusion criteria proceeded to the second stage, where the full texts were retrieved for further evaluation (**Table 1**).

Table 1. Inclusion and exclusion criteria for study selection. This table outlines the specific inclusion and exclusion criteria used to guide the systematic screening and selection of studies for this review. It ensures clarity on how documents were evaluated at each stage based on study type, data source, analytical methods, focus, and reporting quality.

Criteria Type	Inclusion Criteria	Exclusion Criteria
Study Type	Clinical trials or cohort studies	Case reports, cross-sectional studies, reviews, editorials, letters, conference abstracts
Data Source	Studies using real-world data (RWD) such as electronic health records (EHR), patient registries, claims data, or wearable device data	Studies using simulated data, animal studies, or laboratory-based data
Machine Learning (ML) Application	Application of ML algorithms for disease prediction or management (e.g., supervised, unsupervised, deep learning models)	Studies using only conventional statistical models (e.g., logistic regression, Cox models) or expert systems
Clinical Focus	Studies addressing disease prediction, management, monitoring, or outcome prediction in healthcare	Studies unrelated to clinical decision-making, disease outcomes, or patient management
Outcome Reporting	Studies reporting ML model performance metrics (e.g., accuracy, AUC, sensitivity, specificity) and RWD sources	Studies lacking sufficient information on ML model performance or data sources

Language	Published in English	Non-English language publications
Publication Type	Peer-reviewed articles, indexed grey literature	Non-peer-reviewed sources (blogs, social media posts)

The evaluation of exclusion criteria was conducted independently by both reviewers, with disagreements resolved through discussion. To maintain transparency, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [22, 23] was used to document the number of studies at each review stage, including identification, screening, eligibility, and final inclusion. The PRISMA checklist can be seen in **Multimedia Appendix 2**.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized form. Key data points extracted from each clinical trial and cohort studies included study characteristics (e.g., author(s), year of publication, trial design), the specific machine learning methods employed (e.g., supervised learning, reinforcement learning, deep learning), disease areas targeted (e.g., cardiovascular diseases, diabetes, cancer), and the types of real-world data sources used (e.g., EHRs, patient registries, wearable devices). Additionally, we extracted the performance metrics of the ML models used, such as accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC), to evaluate their effectiveness in disease prediction and management. Information on the challenges and limitations of applying ML to RWD in clinical trials, such as data quality issues, biases, or model interpretability, was also collected. Any disagreements in data extraction were resolved through discussion. The extracted data were organized systematically to synthesize findings across studies.

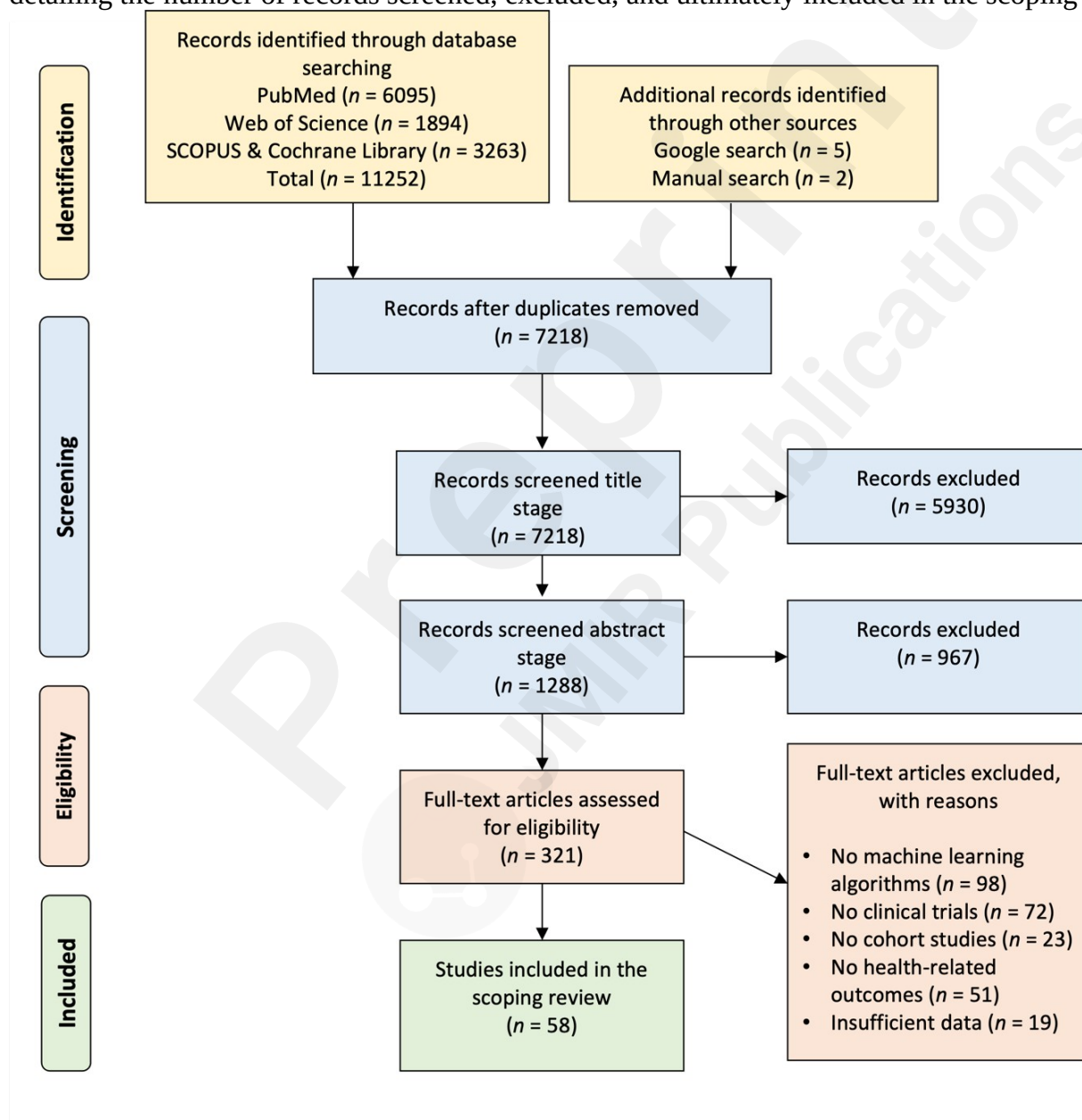
Results

Systematic Literature Search and Study Selection Workflow

The systematic literature search was conducted to identify studies applying machine learning (ML) techniques to real-world data (RWD) in clinical trials and cohort studies, with a focus on disease prediction and management. The search covered multiple databases, including PubMed, Scopus, Web of Science, and the Cochrane Library, to capture a broad range of studies from biomedical, clinical, and healthcare research fields. This search yielded a total of 11,252 records, as illustrated in the PRISMA flow diagram (**Figure 1**). To ensure comprehensive coverage, an additional 7 records were identified through external sources such as Google searches, manual hand-searching of non-indexed journals, grey literature, and other nontraditional academic sources. After removing duplicates, 7,218 unique studies remained for screening. The selection process followed a rigorous, multi-stage workflow. Title screening was first performed to assess relevance based on predefined inclusion criteria. Studies with titles not indicating the application of ML to RWD in clinical or disease management contexts were excluded, resulting in the removal of 5,930 records and leaving 1,288 studies for abstract screening. During the abstract screening, each abstract was carefully evaluated for inclusion criteria, including the use of ML techniques, relevant RWD sources (such as electronic health records, patient registries, or wearable device data), and relevance to disease prediction or management. This led to the exclusion of 967 studies that did not meet these criteria, most commonly for reasons such as lack of ML application (e.g., use of conventional statistical models only) or irrelevance to clinical disease management. A total of 321 studies proceeded to full-text review. At this stage, articles were assessed in detail to confirm adherence to all inclusion

criteria. 263 studies were excluded for specific reasons: 98 lacked ML algorithms (using conventional statistics instead), 72 were unrelated to clinical trial methodologies, 23 did not involve study cohorts, 51 were unrelated to healthcare outcomes, and 19 lacked sufficient information on ML model performance or data sources. Following this thorough, systematic, and transparent selection process, 58 studies met all eligibility criteria and were included in the final scoping review. These selected studies represent a diverse range of clinical applications, disease areas, ML methodologies, and RWD sources, offering a comprehensive overview of the current role of ML in clinical trials and cohort studies for disease prediction and management.

Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram depicts the study selection process from initial identification to final inclusion, detailing the number of records screened, excluded, and ultimately included in the scoping review.



The results of this review highlight that, although the initial literature search identified a substantial number of records (11,252 in total), only a small proportion met the rigorous and well-defined inclusion criteria required for evaluating the application of ML techniques in RWD for disease

prediction and management in clinical trials and cohort studies. After removing 3,306 duplicates, 7,218 unique records remained for title-based screening. In this initial screening step, 5,930 records were excluded because their titles indicated clear irrelevance to the research topic. These included studies not related to healthcare, studies focusing solely on basic science, molecular biology, or traditional statistical methods, and those not involving ML, RWD, or clinical applications. The remaining 1,288 records proceeded to abstract screening, where a more detailed examination was conducted against predefined inclusion criteria. At this stage, 967 studies were excluded for several specific reasons: (1) lack of ML implementation, with some studies using only conventional statistical approaches like logistic regression or decision trees without learning-based model development; (2) irrelevance to clinical trials or cohort study frameworks, instead focusing on simulations, animal studies, or non-human data sources; (3) absence of disease prediction or management applications, such as papers limited to healthcare policy, infrastructure, or economic modeling without patient-centered outcomes; and (4) insufficient use of RWD sources, as studies often used synthetic or trial-generated data rather than EHRs, registries, claims databases, or wearable device data. This process left 321 articles for full-text review, where the inclusion criteria were strictly applied in their entirety. Of these, 263 were excluded for well-documented, specific reasons: 98 articles were excluded for lacking ML algorithms, relying instead on conventional statistics or rule-based expert systems; 72 were excluded because they did not pertain to clinical trials, longitudinal cohort studies, or real-world clinical settings; 23 lacked clear use of study cohorts, instead using case reports, cross-sectional designs, or simulated data; 51 did not address health outcomes or disease prediction and management, focusing on other objectives like healthcare operations or data infrastructure; and 19 were excluded for providing insufficient details on the ML models applied or the RWD sources utilized, preventing adequate appraisal of study validity or relevance. This systematic, multi-stage exclusion process was critical for refining the final study set to include only those that genuinely addressed ML applications in RWD for disease prediction and management in clinical trials or cohort study contexts. The rigorous selection underscores the challenges researchers face when navigating an initially large and heterogeneous body of literature in a specialized, multidisciplinary research area. Ultimately, 58 studies were retained for inclusion in this scoping review. **Table 2** summarizes these studies, while key findings and methodological details are provided in **Multimedia Appendix 3**.

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Table 2. A summary of the studies included in the scoping review, outlining the study characteristics, diseases/medical conditions, type of study, source of real-world evidence (RWE), and machine learning (ML) methods used.

Study; Year	Database	Diseases/ Medical Conditions (Category)	Type of Study	Type of Real-world Evidence (RWE)	Machine Learning (ML) Methods	Model Performance Metrics
Wissel, BD. et al [24], 2023	PubMed	Epilepsy (Neurological diseases)	Evaluation of healthcare outcomes	Electronic health record (EHR)	Natural language processing (NLP)	AUC: 0.79 (95% CI = 0.62–0.96), Sensitivity: 0.80 (95% CI = 0.29–0.99), Specificity: 0.77 (95% CI = 0.64–0.88), Positive predictive value: 0.25 (95% CI = 0.07–0.52) Negative predictive value: 0.98 (95% CI = 0.87–1.00).
Ayers, B. et al [25], 2021	PubMed	Orthotopic heart transplantation (Cardiovascular diseases)	Survival prediction	Patient registries	Deep neural network (DNN), random forest (RF), and adaptive boosting (AdaBoost)	AUROC: RF: 0.691 (95% CI, 0.671-0.711) DNN: 0.691 (95% CI, 0.671-0.712) Adaboost: 0.653 (95% CI, 0.632-0.674)
Nadarajah, R. et al [26], 2023	PubMed	Atrial fibrillation (Cardiovascular diseases)	Disease prediction	EHR	FIND-AF machine learning algorithm	AUROC: 0.824 (95% CI 0.814 to 0.834)
Yadgir, SR. et al [27], 2021	PubMed	Cognitive impairment (Neurological diseases)	Disease prediction	EHR	Extreme gradient boosting (XGBoost)	AUC-ROC: 0.720
Liu, Y. et al [28], 2023	PubMed	Peripheral artery disease (Cardiovascular diseases)	Survival prediction	EHR	Logistic regression (LR), gradient boosting machine (GBM), RF, decision tree (DT), XGBoost, neural network, Cox regression, and random survival forest (RSF)	C-index: 0.788 (compared to 0.730 for GermanVasc Score)
Hill, NR. et al [29], 2022	PubMed	Atrial fibrillation (Cardiovascular diseases)	Disease prediction and cost-effectiveness	EHR	Prediction of Undiagnosed atrial fibrillation using a machine learning Algorithm (PULsE-AI)	Sensitivity : 50% Specificity: 90%
Sheth, SA. et al [30], 2019	PubMed	Acute ischemic stroke (Cardiovascular diseases)	Disease prediction	EHR	Convolutional neural network (CNN)	AUC-ROC: 0.88–0.90
Barton, C. et al	PubMed	Sepsis	Disease	EHR	XGBoost	AUROC of 0.88, 0.84, and 0.83

Study; Year	Database	Diseases/ Medical Conditions (Category)	Type of Study	Type of Real-world Evidence (RWE)	Machine Learning (ML) Methods	Model Performance Metrics
[31], 2019		(Infectious diseases)	prediction			for sepsis onset and 24 and 48 h prior to onset, respectively
Kao, YT. et al [32], 2023	PubMed	Atrial fibrillation (Cardiovascular diseases)	Disease prediction	EHR	DT, support vector machine (SVM), LR, and RF	AUROC: 0.74 Specificity: 98.7%
Kim, M. et al [33], 2022	PubMed	Atrial high-rate episodes (AHREs) (Cardiovascular diseases)	Disease prediction	Wearable devices	RF, SVM, LR, and XGBoost	AUROC RF: 0.742 SVM: 0.675 XGB: 0.745 LR: 0.669
Park, HB. et al [34], 2023	PubMed	Coronary artery disease (Cardiovascular diseases)	Disease prediction	Patient registries	Bayesian quantile regression (BQR)	AUC: 0.67, 0.65, 0.78, and 0.73 for per-patient, LAD, LCx, and RCA, respectively
Hilbert, A. et al [35], 2019	PubMed	Acute ischemic stroke (Cardiovascular diseases)	Healthcare outcomes and decision-making	Wearable devices	Residual Neural Network (ResNet)	Functional outcome (average AUC of 0.71) and for all folds for reperfusion (average AUC of 0.65)
Chen, W. et al [36], 2021	PubMed	Ewing sarcoma (Tumors)	Survival prediction	Patient registries	Boosted DT, SVM, nonparametric RF, and neural network	Sensitivity: 77/83% Specificity: 91/94%
Koutsouleris, N. et al [37], 2017	PubMed	Schizophrenia (Neurological diseases)	Healthcare outcomes and decision-making	Patient registries	Non-linear SVM	Test-fold balanced accuracy (BAC): 75%
Strömblad, CT. et al [38], 2021	PubMed	Colorectal and gynecology cancer (Cancers)	Healthcare outcomes	EHR	GBM and LR	N/A
Wang, SV. et al [39], 2019	PubMed	Atrial fibrillation (Cardiovascular diseases)	Decision-making	EHR	DT	N/A
Tan, TH. et al [40], 2021	PubMed	Influenza (Infectious diseases, respiratory diseases)	Healthcare outcomes	EHR	RF, XGBoost, and LR	RF model for hospitalization (0.840), pneumonia (0.765), and sepsis or septic shock (0.857) XGBoost for intensive care unit admission (0.902) LR for in-hospital mortality (0.889)
Goerigk, S. et al	PubMed	Depression	Decision-making	Patient registries	LR, SVM, RF, tree-based stochastic	LR: 0.75 accuracy, 0.76

Study; Year	Database	Diseases/ Medical Conditions (Category)	Type of Study	Type of Real-world Evidence (RWE)	Machine Learning (ML) Methods	Model Performance Metrics
[41], 2020		(Neurological diseases)			gradient boosting, and XGBoost	sensitivity, 0.73 specificity, 0.792 AUC SVM: 0.88 accuracy, 0.85 sensitivity, 0.91 specificity, 0.939 AUC RF: 0.89 accuracy, 0.88 sensitivity, 0.91 specificity, 0.957 AUC XGBoost: 0.88 accuracy, 0.85 sensitivity, 0.91 specificity, 0.954 AUC
Kijpaisalratana, N. et al [42], 2024	PubMed	Sepsis (Infectious disease)	Decision-making	EHR	RF, XGBoost, LR, and SVM	AUROC of ML in early sepsis identification was significantly higher than qSOFA, SIRS, and MEWS
Sharma, A. et al [43], 2019	PubMed	Acute coronary syndrome (Cardiovascular diseases)	Survival prediction	Patient registries	Cox regression	N/A
Singhal, L. et al [44], 2021	PubMed	Acute Respiratory Distress Syndrome (ARDS) (Respiratory diseases)	Disease prediction	EHR	Machine learning algorithm called 'eARDS' (Neural Networks, SVM, RF, LR, and XGBoost)	AUROC: 0.89 (95% CI = 0.88-0.90) Sensitivity of 0.77 (95% CI = 0.75-0.78) Specificity 0.85 (95% CI = 0.85-0.86)
Kanchanatawan, B. et al [45], 2018	PubMed	Schizophrenia (Neurological diseases)	Disease prediction	Patient registries	SVM and RF	SVM AUROC: 0.931 RF AUROC: 0.898
Huang, J. et al [46], 2022	PubMed	Ischemic stroke (Cardiovascular diseases)	Survival prediction	EHR	Naive Bayes (NB), XGBoost, and LR	NB AUROC: 0.767 XGBoost AUROC: 0.989 LR AUROC: 0.627
She, H. et al [47], 2023	PubMed	Sepsis (Infectious disease)	Disease prediction	Patient registries	SVM and RF	AUC: 0.98
Sundar, R. et al [48], 2022	PubMed	Gastric cancer (Cancers)	Survival prediction	Patient registries	RF	F-measure: 0.71 AUC: 0.75 (95% CI 0.50 to 0.99)
Alaa, AM. et al [49], 2019	PubMed	Cardiovascular disease risk (Cardiovascular diseases)	Disease prediction	Patient registries	Linear SVM, RF, neural networks, AdaBoost, and XGBoost	AutoPrognosis model improved risk prediction (AUC-ROC:

Study; Year	Database	Diseases/ Medical Conditions (Category)	Type of Study	Type of Real-world Evidence (RWE)	Machine Learning (ML) Methods	Model Performance Metrics
						0.774, 95% CI: 0.768-0.780) Framingham score (AUC-ROC: 0.724, 95% CI: 0.720-0.728, p < 0.001) Cox PH model with conventional risk factors (AUC-ROC: 0.734, 95% CI: 0.729-0.739, p < 0.001) Cox PH model with all UK Biobank variables (AUC-ROC: 0.758, 95% CI: 0.753-0.763, p < 0.001)
Azimi, P. et al [50], 2017	PubMed	Lumbar spinal canal stenosis (LSCS) (Spinal diseases)	Decision-making	EHR	Artificial neural network (ANN) and LR	AUC: 0.89
Baxter, SL. et al [51], 2019	PubMed	Glaucoma (Ocular diseases)	Decision-making	EHR	Multivariable logistic regression (MLR), RF, and ANN	AUC: 0.67
Anderson, JP. et al [52], 2015	PubMed	Type 2 Diabetes (Metabolic diseases)	Disease prediction	EHR	RF and SVM	AUC: 0.78
Bannister, CA. et al [53], 2018	PubMed	Stroke and myocardial infarction (Cardiovascular diseases)	Survival prediction	Patient registries	Cox regression	C-index is 0.59, 0.69, 0.64 and 0.66, 0.70, 0.70 for the GP and Cox regression models respectively. AUROC: 0.89
Scheer, JK. et al [54], 2017	Web of Science	Spinal deformity surgery (Spinal diseases)	Decision-making	Patient registries	DT and ANN	
Rau, HH. et al [55], 2016	Web of Science	Liver cancer (Cancers)	Disease prediction	EHR	ANN and LR	ANN Sensitivity: 0.757 Specificity: 0.755 AUROC: 0.873 AUC: 0.78 Sensitivity: 78%
Ramezankhani, A. et al [56], 2016	Web of Science	Type 2 Diabetes (Metabolic diseases)	Disease prediction	Patient registries	DT	
Pei, D. et al [57], 2019	Web of Science	Type 2 Diabetes (Metabolic diseases)	Disease prediction	EHR	DT	Accuracy: 94.2% Precision: 94.0% Recall: 94.2% AUC: 94.8%

Study; Year	Database	Diseases/ Medical Conditions (Category)	Type of Study	Type of Real-world Evidence (RWE)	Machine Learning (ML) Methods	Model Performance Metrics
Oviedo, S. et al [58], 2019	Web of Science	Postprandial hypoglycemia (Metabolic diseases)	Decision-making	Wearable devices	SVM	Specificity: 79% Sensitivity: 71%
Mubeen, AM. et al [59], 2017	Web of Science	Alzheimer's disease (Neurological diseases)	Disease prediction	EHR	RF	AUC: 0.87 Accuracy: 80.2%
Lopez-de-Andres, A. et al [60], 2016	Web of Science	Type 2 Diabetes (Metabolic diseases)	Survival prediction	Patient registries	ANN	ROC curve for Elixhauser comorbidity model: 91.7% (95% CI 90.3-93.0) Charlson comorbidity model: 88.9% (95% CI; 87.590.2)
Kwon, JM. et al [61], 2019	Web of Science	Cardiac arrest (Cardiovascular diseases)	Survival prediction	Patient registries	DNN, LR, SVM, and RF	AUROC: DNN 0.953 [95% confidence interval 0.952-0.954] LR (0.947 [0.943-0.948]) RF (0.943 [0.942-0.945]) SVM (0.930 [0.929-0.932])
Kim, I. et al [62], 2019	Web of Science	Breast cancer (Cancers)	Decision-making	EHR	Two-class Decision Jungle and Two-class Neural Network	AUC of the ROC curve 0.917 in the high RS group and 0.744 in the low RS group in test set
Khanji, C. et al [63], 2019	Web of Science	Hypertension and dyslipidemia (Cardiovascular diseases)	Healthcare outcomes	EHR	LR	cvAUCs: 0.73 for hypertension, 0.64 for dyslipidemia, and 0.79 for diabetes
Karhade, AV. et al [64], 2019	Web of Science	Lumbar disc herniation (Spinal diseases)	Decision-making	EHR	LR, RF, XGBoost, ANN, and SVM	AUC: 0.81
Jovanovic, P. et al [65], 2014	Web of Science	Cholelithiasis (Gastrointestinal diseases)	Decision-making	EHR	ANN	AUROC: 0.884 (95% CI, 0.831-0.938; P < .001)
Kang, AR. et al [66], 2020	Web of Science	Postinduction hypotension (Anaesthesia-related complications)	Healthcare outcomes	EHR	NB, LR, RF, and ANN	AUC-ROC (95% CI) NB: 0.778 (0.650-0.898) LR: 0.756 (0.630-0.881) RF: 0.842 (0.736-0.948) ANN: 0.760 (0.640-0.880)
Isma'eel, HA. et al [67], 2018	Web of Science	Coronary artery disease (Cardiovascular diseases)	Healthcare outcomes	EHR	ANN	Sensitivity 91% [81%-97%] Specificity 65% [60%-79%]
Hill, NR. et al [68], 2019	Web of Science	Atrial fibrillation (Cardiovascular diseases)	Disease prediction	EHR	RF, SVM, and Cox regression	AUROC RF: 0.827 SVM: 0.725

Study; Year	Database	Diseases/ Medical Conditions (Category)	Type of Study	Type of Real-world Evidence (RWE)	Machine Learning (ML) Methods	Model Performance Metrics
Dong, Y. et al [69], 2019	Web of Science	Chinese Crohn's disease (Gastrointestinal diseases)	Decision-making	EHR	RF, LR, SVM, DT, and ANN	AUROC RF: 0.9864 LR: 0.9538 SVM: 0.9497 DT: 0.8809 ANN: 0.9059 AUROC: 0.7
Bowman, A. et al [70], 2018	Web of Science	Carpal tunnel syndrome (Musculoskeletal diseases)	Healthcare outcomes	EHR	LR and ANN	
Bertsimas, D. et al [71], 2018	Web of Science	Breast, lung, ovarian cancers (Cancers)	Survival prediction	EHR	DT	AUROC: 0.83 – 0.86
Manz, CR. et al [72], 2020	Cochrane Library	Cancer-related serious illness (Cancers)	Decision-making	EHR	RF and SVM	N/A
Tian, D. et al [73], 2023	Cochrane Library	Lung transplantation (Respiratory diseases)	Survival prediction	EHR	Random survival forests (RSF)	AUROC: 0.879 (95% CI, 0.832-0.921)
Li, E. et al [74], 2022	Cochrane Library	Latent profile analysis (Cancers)	Decision-making	EHR	GBM	N/A
Tedeschi, SK. et al [75], 2021	Cochrane Library	Pseudogout (Rheumatic diseases)	Disease prediction	EHR	NLP	AUC: 0.86
Wissel, BD. et al [24], 2023	Cochrane Library	Epilepsy surgery (Neurological diseases)	Decision-making	EHR	NLP	AUC: 0.79 (95% CI = 0.62–0.96) Sensitivity: 0.80 (95% CI = 0.29–0.99) Specificity: 0.77 (95% CI = 0.64–0.88) Positive predictive value: 0.25 (95% CI = 0.07–0.52) Negative predictive value: 0.98 (95% CI = 0.87–1.00)
Ambwani, G. et al [76], 2019	Cochrane Library	Cancer biomarkers (Cancers)	Healthcare outcomes	EHR	LR	Sensitivity: 97.3%
Jorge, A. et al [77], 2019	Cochrane Library	Lupus (Autoimmune disease)	Disease prediction	EHR	LR	Specificity: 97% Sensitivity: 64%

Study; Year	Database	Diseases/ Medical Conditions (Category)	Type of Study	Type of Real-world Evidence (RWE)	Machine Learning (ML) Methods	Model Performance Metrics
Shimabukuro, DW. et al [78], 2017	Cochrane Library	Sepsis (Infectious diseases)	Healthcare outcomes	EHR	LR	AUROC: 0.952 (0.946 to 0.958) Specificity: 0.900 (0.870 to 0.930) Sensitivity: 0.900 (0.878 to 0.922)
Sarraju, A. et al [79], 2021	Cochrane Library	Atherosclerosis (Cardiovascular diseases)	Healthcare outcomes	EHR	RF, GBM, XGBoost, and LR	XGBoost AUC 0.70 (95% CI 0.68 to 0.71) in the full CVD cohort and AUC 0.71 (95% CI 0.69 to 0.73) in patients with ASCVD, with comparable performance by GBM, RF and Lasso.
Ye, B. et al [80], 2019	Cochrane Library	Myopia (Ocular diseases)	Healthcare outcomes	Wearable devices	SVM	AUC: 0.99

Implementation of Machine Learning (ML) in Real-World Data (RWD) for Disease Prediction and Management

Machine learning (ML) methods have become integral tools in analyzing real-world data (RWD) for disease prediction and management. These methods analyze complex medical data, helping clinicians make informed decisions for better patient care. Random Forest (RF) is one of the most widely used ML methods, appearing in 24 studies (**Table 3**). It is an ensemble learning technique that builds multiple decision trees and combines their outputs to improve model stability and generalizability [81]. Several reviewed studies have reported that RF performs well in handling large datasets with numerous variables, particularly electronic health records (EHRs), which are common medical data sources. Its robustness against overfitting and ability to handle missing data make it a frequently chosen method in clinical applications, where data quality can vary [82, 83]. While RF has been widely applied in predictive modeling for disease outcomes, treatment responses, and patient risk assessments, further comparative studies are necessary to directly evaluate its performance against other ML models in real-world healthcare settings [84]. It is often applied to predict disease outcomes, assess treatment responses, and identify patient risk factors.

Table 3. The frequency of machine learning methods used in studies included in this review.

Machine Learning Method	Number of Studies
Random Forest (RF)	24
Logistic Regression (LR)	21
Support Vector Machine (SVM)	18
Extreme Gradient Boosting (XGBoost)	12
Artificial Neural Network (ANN)	11
Decision Tree (DT)	9
Gradient Boosting Machine (GBM)	4
Natural Language Processing (NLP)	3
Cox Regression	3
Deep Neural Network (DNN)	2

Logistic Regression (LR) is a fundamental method used for binary classification tasks and was employed in 21 studies. LR estimates the probability of a particular class, which is essential for predicting binary outcomes such as disease presence or absence. It is a simple yet powerful tool that works well with smaller datasets and provides results that are easy to interpret, making it particularly useful in clinical settings where transparency is crucial [85, 86]. LR is commonly used for disease risk prediction, helping clinicians assess the likelihood of a patient developing a condition based on their medical history and other clinical factors. Its interpretability allows for clear communication of results to healthcare providers, enhancing decision-making [87, 88]. Support Vector Machine (SVM), employed in 18 studies, is known for its ability to handle high-dimensional data, making it suitable for complex medical datasets, including genomic and imaging data. SVM works by finding the optimal hyperplane that separates different classes in the feature space [89-91]. This method

is beneficial in clinical settings where the relationship between variables is non-linear and can be adapted for classification and regression tasks. SVM is applied in disease prediction, particularly when the dataset has many features relative to the number of observations. It is also useful for classifying patients based on genetic or demographic factors, making it a powerful tool for precision medicine [92, 93]. Extreme Gradient Boosting (XGBoost) appears in 12 studies and is a highly effective method for improving predictive accuracy through boosting. XGBoost builds models sequentially to correct errors made by previous models and uses regularization to prevent overfitting. This method is precious in handling large datasets, common in clinical studies, and where computational efficiency is essential [94, 95]. XGBoost is often used for survival analysis and disease outcome prediction, where it can effectively manage the complexity of large datasets and missing data. Its flexibility allows it to be applied across various disease areas, from cancer prognosis to cardiovascular risk assessment [96, 97].

Artificial Neural Networks (ANN), utilized in 11 studies, are powerful tools for modeling complex, nonlinear relationships in data. With multiple layers of interconnected neurons, ANN can learn intricate patterns from large datasets. It is widely used in applications that involve unstructured data, such as medical imaging and genetic data, where traditional models might struggle [98, 99]. ANN is frequently applied to predict disease progression, response to treatments, and identify potential biomarkers. In real-world data, ANN helps identify subtle patterns in complex datasets that simpler models might not capture, such as predicting cancer progression from radiological images [100, 101]. Decision Trees (DT), featured in 9 studies, are straightforward and interpretable models that split data into subsets based on feature values. DT models are highly useful in real-world healthcare settings, where interpretability is essential for clinical decision-making. They are often applied in clinical decision support systems (CDSS) to guide treatment decisions based on patient data [102, 103]. In healthcare, DTs predict disease outcomes, stratify patients by risk, and recommend treatment plans. Their transparency allows clinicians to understand the decision-making process, which is critical for patient trust and informed consent [104]. Gradient Boosting Machine (GBM) is used in 4 studies and is a powerful ensemble method that focuses on correcting errors made by previous models. It is effective in producing highly accurate predictions, particularly in the presence of noisy or incomplete data. GBM is more computationally intensive than other methods but often outperforms simpler models in accuracy. GBM is particularly useful for predicting disease progression and evaluating treatment efficacy in longitudinal studies, where multiple factors influence outcomes over time [105, 106].

Natural Language Processing (NLP), employed in 3 studies, is a subfield of AI focused on analyzing unstructured textual data. In healthcare, NLP extracts relevant information from clinical notes, electronic health records, and medical literature. It enables clinicians and researchers to analyze vast amounts of text data to identify trends, predict disease outcomes, and assess treatment effectiveness [107, 108]. NLP is crucial in extracting insights from EHRs and other textual data sources. It can help in disease prediction by identifying patterns from patient narratives, diagnostic codes, and clinician notes that would otherwise remain hidden in unstructured formats [109]. Cox Regression, used in 3 studies, is designed explicitly for survival analysis. It is widely applied in clinical research to model the time of an event, such as the onset of a disease or patient survival. This method is precious for understanding how various predictors affect the risk of an event occurring over time. In real-world data, Cox Regression is often used in cancer studies and other chronic diseases to predict survival times and assess the impact of different treatment regimens, making it indispensable in clinical trials and outcome-based research [110, 111]. Deep Neural Networks

(DNN), employed in 2 studies, are a more complex version of ANN with multiple hidden layers. DNNs identify intricate patterns and are increasingly used in healthcare applications involving large and complex data types such as medical imaging, genomics, and sensor data. DNN is particularly useful for analyzing high-dimensional data such as medical images (e.g., X-rays, MRIs) or genomic data, where the relationships between variables are complex and nonlinear. It helps identify disease markers and predict outcomes based on these complex datasets [112-114]. The diverse range of machine learning methods employed in real-world data for disease prediction and management demonstrates the adaptability of these techniques in clinical practice. From interpretable models like Logistic Regression and Decision Trees to more complex methods such as Deep Neural Networks and Extreme Gradient Boosting, each ML technique uniquely enhances predictive capabilities. These methods enable healthcare providers to make more accurate, data-driven decisions, ultimately improving patient outcomes and advancing personalized medicine.

Distribution of Diseases, Study Types, and Real-World Evidence (RWE) Sources in Machine Learning Applications

The distribution of disease types in studies utilizing ML for disease prediction and management reveals a strong emphasis on cardiovascular diseases, with 19 studies focusing on various conditions within this category (**Table 4**). This high representation can be attributed to the multifactorial and complex nature of cardiovascular diseases, which often involve a combination of genetic, environmental, and lifestyle factors. Conditions such as atrial fibrillation, heart transplantation, and peripheral artery disease are prominent in these studies, where advanced ML models are utilized to enhance predictive accuracy and improve patient management. For instance, studies on heart transplantation and atrial fibrillation highlight the potential of ML algorithms in survival prediction and early disease detection. A work demonstrated that ensemble models, combining random forest, deep neural networks, and adaptive boosting, significantly outperformed traditional logistic regression for predicting 1-year survival rates after orthotopic heart transplantation, with an AUROC of 0.764 [25]. Meanwhile, another study explored using the FIND-AF ML algorithm to identify undiagnosed atrial fibrillation using data from EHR, aiming to improve early detection and intervention. In addition, studies on peripheral artery disease (PAD) and atrial fibrillation in older adults underscore the utility of ML models in survival prediction and risk assessment [26]. A finding developed a predictive model for amputation-free survival post-revascularization, with the random survival forest model achieving the highest accuracy in predicting long-term outcomes [28]. Similarly, another study used various ML methods, including decision trees and random forests, to predict new-onset atrial fibrillation in older adults, achieving high specificity and performance, particularly with the random forest model [32]. Furthermore, the use of ML in acute ischemic stroke, including studies by Sheth et al. and Hilbert et al., illustrates the growing role of deep learning techniques, such as convolutional neural networks (CNN) and residual neural networks (ResNet), in improving diagnostic accuracy and predicting patient outcomes [35]. These advancements in ML can potentially revolutionize clinical decision-making and treatment selection, especially for conditions like stroke, where rapid and accurate assessment is critical.

A significant portion of studies also targeted cancers and tumors (9 studies), which are often characterized by their heterogeneity and the need for personalized treatment plans. Machine learning algorithms, such as RF and SVM, have enhanced early cancer detection, predicted disease recurrence, and assessed the effectiveness of different treatment protocols, offering great potential in oncology settings. One key area of focus is the prediction of disease outcomes. For instance, a study developed a series of ML models to predict the 5-year

survival rate for patients with Ewing sarcoma, a rare type of cancer. By utilizing data from 2,332 patients, including various algorithms such as boosted decision trees, SVM, random forests, and neural networks, the study found that the random forest method performed best, with impressive sensitivity and specificity. This model is now available through a web-based application, providing a valuable tool for clinicians to assess survival probabilities for Ewing sarcoma patients [36]. Another study employed a predictive ML model to improve surgical scheduling in cancer surgeries, specifically for colorectal and gynecologic cancers. This research utilized gradient boosting and linear regression techniques to predict surgical durations, reducing operational inefficiencies such as patient wait times and optimizing the use of surgical resources, demonstrating how ML can streamline healthcare operations while maintaining treatment quality [38]. Furthermore, in survival prediction, a study utilized a random forest model to develop a gene signature that predicts the response of gastric cancer patients to paclitaxel treatment. Their model, which identified a 19-gene signature, enabled the classification of patients into those who would benefit from the treatment, providing a novel approach to personalized cancer therapy [48].

Table 4. Disease categories and the number of studies included in this review.

Diseases	Number of Studies
Cardiovascular Diseases	19
Cancers and Tumors	9
Neurological Diseases	7
Infectious Diseases	5
Metabolic Diseases	5
Spinal Diseases	3
Gastrointestinal Diseases	2
Ocular Diseases	2
Respiratory Diseases	2
Other Diseases	4

The studies focusing on neurological diseases, including conditions like epilepsy, cognitive impairment, and schizophrenia, highlight the significant impact of ML in improving diagnosis, treatment prediction, and healthcare outcomes. These studies underscore the potential of ML to personalize patient care and optimize clinical decision-making. For instance, a study investigated the application of NLP embedded in EHR to automate alerts for pediatric epilepsy patients. This ML-driven clinical decision support system successfully increased referrals for epilepsy surgery, with a marked improvement in presurgical evaluation rates and even higher rates of actual surgery, illustrating how NLP-based interventions can influence healthcare outcomes by improving referral efficiency and treatment access [24]. Similarly, another study focused on the use of XGBoost, a machine learning algorithm, to identify older emergency department patients at high risk for cognitive impairment. This predictive model, using EHR data, demonstrated high sensitivity and specificity, with the potential to reduce the need for in-person screenings and prioritize high-risk patients. By streamlining screening processes, this approach could enhance the detection of cognitive impairments in older adults, potentially leading to earlier interventions and better management of conditions like dementia [27]. In schizophrenia, a study developed a non-linear SVM model to predict treatment outcomes for first-episode psychosis patients. The model was trained on pre-treatment patient-reported data and successfully predicted poor versus good treatment outcomes, thus supporting clinical decision-making in terms of which treatments might be more effective for certain patients, and identifying those at risk for non-adherence or poor prognosis [37]. These studies collectively demonstrate how machine learning methods like NLP, XGBoost, and Random Forest are revolutionizing the

management of neurological diseases. By enabling early detection, better prediction of disease outcomes, and more informed decision-making, these tools offer substantial improvements in both clinical and healthcare settings. Infectious diseases, metabolic diseases, spinal diseases, gastrointestinal diseases, ocular diseases, and respiratory diseases each had a smaller but notable presence in the studies (5 or fewer studies). These applications generally focus on disease prediction, early diagnosis, and treatment optimization. Machine learning models such as XGBoost and DNN have been employed to predict disease onset, assess risks, and improve patient management in these areas.

The data reveals that Electronic Health Records (EHR) are the most frequently used form of RWE, accounting for 67.2% of the studies (39 out of 58). EHRs are a rich source of patient data, providing comprehensive records of patient health status, diagnoses, treatments, and outcomes over time. This makes EHRs particularly valuable for studies that require large-scale data to identify patterns, trends, and correlations in real-world clinical settings. The next most commonly used type of RWE is patient registries, which were utilized in 25.9% of the studies (15 out of 58). Patient registries typically collect data on specific patient populations with particular diseases or conditions, allowing for longitudinal tracking of disease progression and treatment outcomes. Wearable devices were the least utilized form of RWE, accounting for 6.9% of the studies (4 out of 58). Wearables are increasingly being used to collect real-time health data, including vital signs and activity levels, which can provide valuable insights into patients' health status outside of clinical environments. This distribution highlights the dominance of EHR as the primary data source in these studies, reflecting its accessibility and broad applicability in healthcare research.

Disease prediction emerged as the most widely studied area, represented by 34.5% of the studies (20 out of 58). This suggests a strong emphasis on using machine learning and data analytics to predict the onset, progression, or outcomes of various diseases. The next most studied area is decision-making, with 14 studies (24.1%), which underscores the growing interest in leveraging data-driven insights to inform clinical decisions and treatment strategies. Healthcare outcomes, such as quality of life, recovery rates, and adverse events, were the focus of 22.4% of the studies (13 out of 58), reflecting the importance of understanding how diseases and treatments affect patients' overall well-being. Survival prediction, accounting for 19.0% of the studies (11 out of 58), is another critical area of research, particularly in oncology and chronic diseases, where predicting patient survival and the effectiveness of interventions can guide clinical decision-making. This distribution indicates that disease prediction and decision-making are central to applying real-world evidence in healthcare, with a significant focus on improving patient outcomes and guiding treatment strategies.

Discussion

Principal Results

The findings of this study underscore the growing application of ML techniques in RWD for disease prediction and management. The results reveal that machine learning methods, particularly ensemble models like RF, play a crucial role in enhancing prediction accuracy and addressing the complexities of large and high-dimensional datasets common in healthcare. Among the top ML methods employed, RF was the most widely used, featured in 24 studies, showcasing its adaptability to a variety of clinical datasets such as EHRs and patient registries. RF's ability to handle missing data, its resistance to overfitting, and its effectiveness in managing imbalanced datasets made it a powerful tool in predicting disease

outcomes [115, 116], such as survival rates and complications in cardiovascular diseases and cancer. In terms of disease types, cardiovascular diseases dominated the studies, with 19 studies dedicated to predicting outcomes related to heart transplantation, atrial fibrillation, and peripheral artery disease. This concentration is likely attributed to the critical need for predictive tools in the early diagnosis and management of these conditions, which account for a significant burden on healthcare systems globally [117]. Machine learning applications, such as deep neural networks (DNN) and random survival forests (RSF), have been shown to improve the accuracy of survival predictions, assess treatment responses, and enhance patient stratification. Additionally, the study highlights the increasing application of ML in predicting conditions such as cancers, neurological disorders, and infectious diseases. These findings align with the broader trend of using RWD to bridge the gap between clinical trials and actual patient care by making predictions based on real-life data sources like EHRs and wearable devices. As evidenced in the studies reviewed, ML techniques can process vast amounts of medical data from various sources, facilitating early detection, timely intervention, and improved management of chronic conditions. Furthermore, these advancements in ML applications are subject to increasing regulatory oversight. Agencies such as the U.S. FDA and the EMA are actively exploring frameworks for the approval and regulation of ML-driven tools in healthcare. These regulations aim to ensure ML models' safety, efficacy, and transparency, especially in real-world applications where data variability and model interpretability remain key concerns. As regulatory bodies continue to define standards for using RWD and ML in clinical settings, ensuring compliance with FDA and EMA guidelines will be essential for the broader adoption and integration of these technologies into clinical practice.

Comparison with Prior Works

This systematic review aligns with and extends several recent literature reviews that have explored the application of ML to RWD in healthcare. Previous studies have highlighted the potential of ML models to transform healthcare by improving disease prediction and patient management [118, 119]. However, our review emphasizes a broader scope by including a wide variety of disease types, from cardiovascular diseases and cancer to neurological and infectious diseases, reflecting the growing versatility of ML tools in clinical settings. A notable comparison can be made with a study that focused on EHRs as the primary data source for ML models [120]. While their review identified the challenges associated with EHR-based studies, such as data sparsity and heterogeneity, our study similarly acknowledges these limitations but also expands the discussion to include wearable devices and patient registries as additional data sources. These emerging data sources provide a more complete picture of the patient's health status, significantly improving model performance and enabling better patient monitoring in real-world settings. Another key comparison is with a review that focused on ML's role in healthcare decision-making and its integration into clinical workflows [121]. While their work explored various ML algorithms in healthcare, our review places a stronger emphasis on the role of ensemble models like RF and their applicability across diverse healthcare datasets. One of the key contributions of our review, which sets it apart from prior works, is the focus on regulatory challenges associated with the deployment of ML models in clinical practice. While other reviews have discussed technical aspects of ML, we specifically address the urgent need for clearer regulatory frameworks from authorities such as the FDA and EMA to ensure the safe and effective approval of ML models in healthcare. This is an area that has received limited attention in prior reviews but is critical as healthcare systems begin to rely more heavily on automated systems for clinical decision-making. Overall, this review builds upon the foundations set by previous literature

but provides an updated and comprehensive analysis that incorporates new data sources, focuses on a broader range of diseases, and addresses the challenges of regulatory approval and model interpretability in the context of ML in healthcare.

Limitations

This review has several limitations. First, while a comprehensive search strategy was employed, it is possible that some relevant studies were missed, particularly those that did not explicitly use the selected keywords or were indexed in databases not included in this search. Additionally, the review was limited to English-language publications, which may have excluded relevant studies published in other languages. Another potential limitation is the application of strict inclusion and exclusion criteria, which, while ensuring the relevance and quality of the included studies, may have led to the omission of some studies that could have provided valuable insights. For example, studies with limited methodological details or those focusing primarily on deep learning applications were often excluded due to insufficient validation or performance comparisons. Future research could consider broader inclusion criteria to capture a wider range of studies. Furthermore, the variability in study designs and data sources posed challenges in synthesizing findings across different studies. The included studies utilized different types of RWD, ranging from EHRs and patient registries to imaging and wearable sensor data. This heterogeneity complicates direct comparisons and generalizability. Lastly, while efforts were made to minimize bias through independent study screening by two reviewers, inherent biases in study selection and data extraction may still exist. The reliance on published literature also introduces publication bias, as studies with negative or inconclusive results may be underrepresented. Future work could integrate unpublished data sources or conduct meta-analyses to provide a more comprehensive assessment of ML applications in RWD.

Future Work

While this scoping review aimed for comprehensive coverage by employing a broad search strategy across multiple databases and grey literature sources, the large disparity between the number of initially retrieved studies and those meeting the final inclusion criteria highlights an important area for improvement in future research. A more focused, topic-specific keyword strategy, combined with the application of advanced database filters, could increase the precision of future searches by limiting the retrieval of irrelevant studies. Additionally, integrating artificial intelligence-assisted search tools and natural language processing algorithms might further enhance the efficiency of systematic literature reviews by streamlining the identification of eligible studies based on more nuanced criteria. Future reviews may also benefit from targeting more narrowly defined subtopics within the broader field of ML applications in RWD, such as specific disease domains, ML model types, or clinical trial phases. These refinements would likely improve the overall relevance and manageability of retrieved records, ensuring a more efficient screening process and focused synthesis of findings.

Conclusions

In conclusion, this review highlights the transformative potential of integrating machine learning (ML) techniques with real-world data (RWD) in healthcare, specifically for disease prediction and management. The use of advanced ML models, such as ensemble methods and deep learning, has demonstrated the ability to enhance predictive accuracy, improve patient

stratification, and facilitate more personalized and proactive healthcare. These advancements are poised to significantly impact clinical decision-making, enabling earlier diagnoses, optimized treatment strategies, and efficient resource allocation. However, despite these promising developments, several challenges remain. Issues related to data quality, generalizability across diverse populations, and the interpretability of complex ML models must be addressed to ensure their effective and widespread application. The lack of transparency in some ML algorithms, which often function as "black boxes," remains a significant barrier to their integration into clinical workflows. Improving the explainability of these models will be crucial in gaining the trust of healthcare professionals and enhancing the clinical utility of ML predictions. Additionally, regulatory frameworks for ML in healthcare are still evolving, with clear guidelines needed from regulatory bodies like the FDA and EMA. This will help ensure that ML models meet safety standards and are deployed in clinical settings in a manner that benefits both healthcare providers and patients. Furthermore, as healthcare data becomes increasingly heterogeneous, with sources ranging from electronic health records (EHRs) to wearable devices and patient registries, strategies for addressing data inconsistencies and ensuring data quality will be essential. Looking ahead, future research should focus on improving the robustness, transparency, and generalizability of ML models, particularly for underrepresented diseases and diverse patient populations. Establishing ethical and regulatory standards for the use of ML in clinical practice will be crucial for fostering public trust and ensuring equitable access to these innovations. Collaboration between clinicians, data scientists, and policymakers will be key to overcoming these challenges, with the ultimate goal of ensuring that ML-driven advancements in healthcare lead to improved health outcomes, better care delivery, and more equitable healthcare systems for all.

Data Availability

The original contributions presented in this study are included in the article/Multimedia Appendix, and further inquiries can be directed to the corresponding author.

Authors' Contributions

NHA and DD conceptualized the study, developed the methodology, and wrote the original draft of the manuscript. HFK contributed to the data collection, analysis, and interpretation. NHA, DD, and NA provided critical revisions and approved the final version of the manuscript. NA supervised the project study. All authors reviewed and approved the manuscript for publication.

Funding Statement

This work was supported and funded by the Deanship of Scientific Research at Imam Mohammad Ibn Saud Islamic University (IMSIU) (grant number IMSIU-DDRSP2501).

Conflicts of Interest

None declared.

Multimedia Appendix 1

Full search strategy.

Multimedia Appendix 2

PRISMA checklist.

Multimedia Appendix 3

A dataset of selected studies, including details such as the year of publication, authors' names, study title, database, diseases/medical conditions, disease category, study type, real-world evidence (RWE) type, machine learning (ML) methods used, and key findings.

Abbreviations

AdaBoost	: Adaptive Boosting
AHREs	: Atrial High-rate Episodes
ANN	: Artificial Neural Network
ARDS	: Acute Respiratory Distress Syndrome
AUC	: Area Under the Curve
AUROC	: Area Under the Receiver Operating Characteristic Curve
BQR	: Bayesian Quantile Regression
CNN	: Convolutional Neural Network
DNN	: Deep Neural Network
EHRs	: Electronic Health Records
EMA	: European Medicines Agency
FDA	: Food and Drug Administration
GBM	: Gradient Boosting Machine
GDPR	: General Data Protection Regulation
HIPAA	: Health Insurance Portability and Accountability Act
LR	: Logistic Regression
LSCS	: Lumbar Spinal Canal Stenosis
MeSH	: Medical Subject Headings
ML	: Machine Learning
MLR	: Multivariable logistic regression
NB	: Naive Bayes
NLP	: Natural Language Processing
PULsE-AI	: Prediction of Undiagnosed atrial fibrillation using a machine learning Algorithm
RF	: Random Forest
PRISMA	: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	: Randomized Controlled Trials
ResNet	: Residual Neural Network
RSF	: Random Survival Forest
RWD	: Real-world Data
RWE	: Real-world Evidence
SVM	: Support Vector Machine
XGBoost	: Extreme Gradient Boosting

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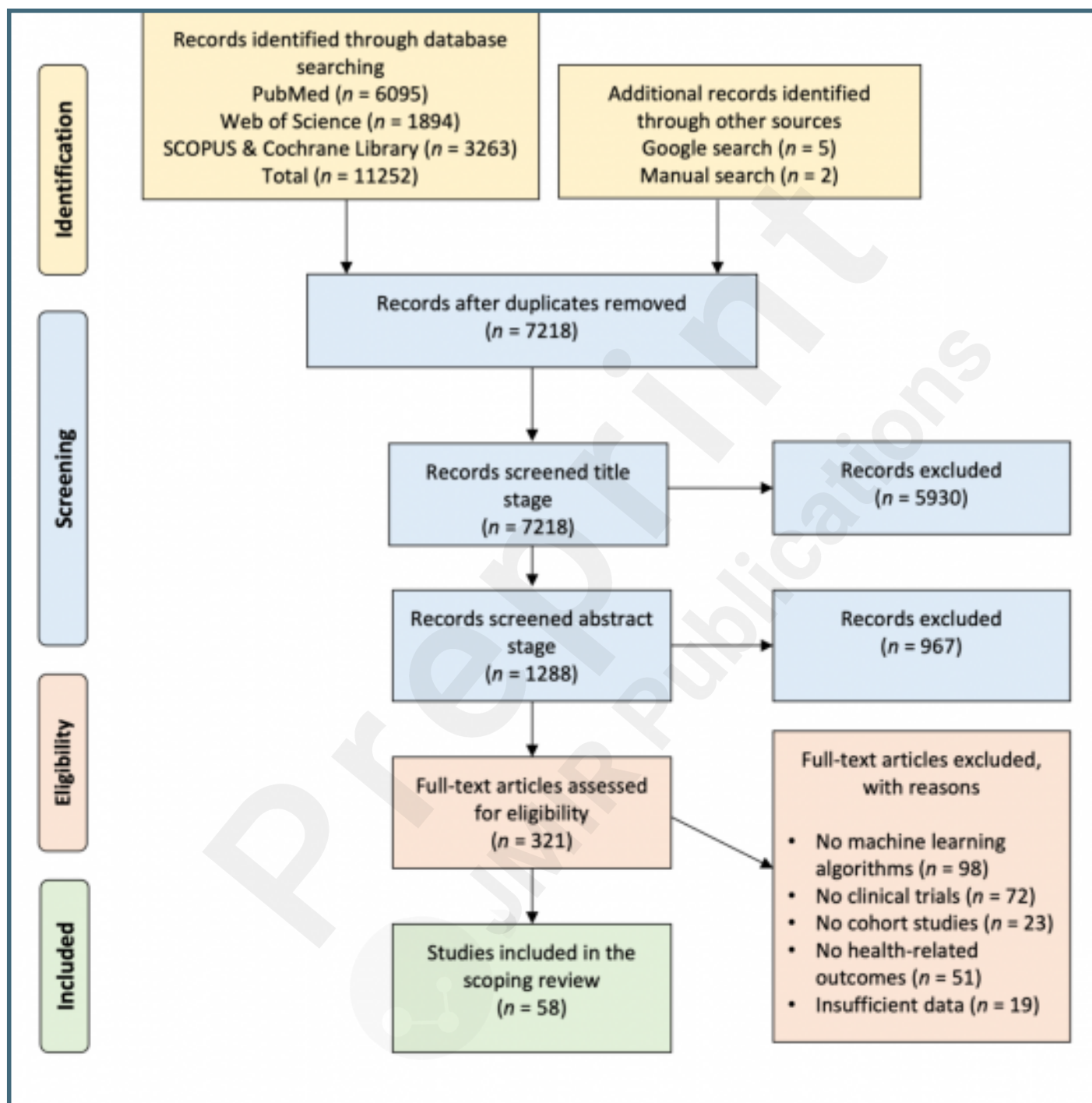
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Supplementary Files

Figures

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram depicts the study selection process from initial identification to final inclusion, detailing the number of records screened, excluded, and ultimately included in the scoping review.



Multimedia Appendixes

Full Search Strategy.

URL: <http://asset.jmir.pub/assets/8c623123031dcf0ad3639a0e39fefa72.docx>

PRISMA checklist.

URL: <http://asset.jmir.pub/assets/2c71171f2a9618e52eb70696f9c05c8e.pdf>

A dataset of selected studies, including details such as the year of publication, authors' names, study title, database, diseases/medical conditions, disease category, study type, real-world evidence (RWE) type, machine learning (ML) methods used, and key findings.

URL: <http://asset.jmir.pub/assets/4bf13f7216431aa9971e8752d6d0c0fe.xlsx>

