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TOPICAL REVIEW

A Systematic Review of Graph Neural Network in Healthcare-Based Applications: Recent Advances, Trends, and Future Directions

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ABSTRACT Graph neural network (GNN) is a formidable deep learning framework that enables the analysis and modeling of intricate relationships present in data structured as graphs. In recent years, a burgeoning interest has arisen in exploiting the latent capabilities of GNN for healthcare-based applications, capitalizing on their aptitude for modeling complex relationships and unearthing profound insights from graph-structured data. However, to the best of our knowledge, no study has systemically reviewed the GNN studies conducted in the healthcare domain. This study has furnished an all-encompassing and erudite overview of the prevailing cutting-edge research on GNN in healthcare. Through analysis and assimilation of studies, current research trends, recurrent challenges, and promising future opportunities in GNN for healthcare applications have been identified. China emerged as the leading country to conduct GNN-based studies in the healthcare domain, followed by the USA, UK, and Turkey. Among various aspects of healthcare, disease prediction and drug discovery emerge as the most prominent areas of focus for GNN application, indicating the potential of GNN for advancing diagnostic and therapeutic approaches. This study proposed research questions regarding diverse aspects of GNN in the healthcare domain and addressed them through an in-depth analysis. This study can provide practitioners and researchers with profound insights into the current landscape of GNN applications in healthcare and can guide healthcare institutes, researchers, and governments by demonstrating the ways in which GNN can contribute to the development of effective and efficient healthcare systems.

INDEX TERMS Graph neural network, deep learning, graph neural network review, graph representation learning, healthcare application.

I. INTRODUCTION

Graphs, as fundamental mathematical structures, have proven to represent and analyze complex relationships in various domains, including medical healthcare. A graph interconnected by edges consists of nodes or vertices, which capture the connections or associations between medical entities such as patients, diseases, medications, and healthcare providers.

In recent years, the application of graph theory in the context of ML and data analysis has extended to the medical healthcare field [1]. GNN has emerged as a specialized class of machine learning (ML) models tailored to operate on graph-structured data within the healthcare domain [2], [3], [4]. GNN offers a transformative approach to extracting valuable insights from interconnected medical entities, enabling accurate predictions, and performing various tasks crucial for healthcare applications [5]. With medical graphs' inherent structure, GNN offers an efficient and effective approach to making predictions at the edge, node, and graph levels, unlocking valuable insights into healthcare data [6], [7]. By iteratively updating the hidden representations of nodes, GNN captures and integrates

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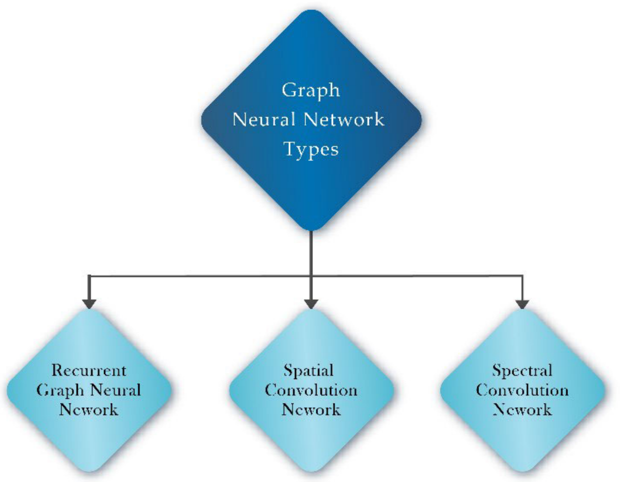

FIGURE 1. Types of graph neural network.

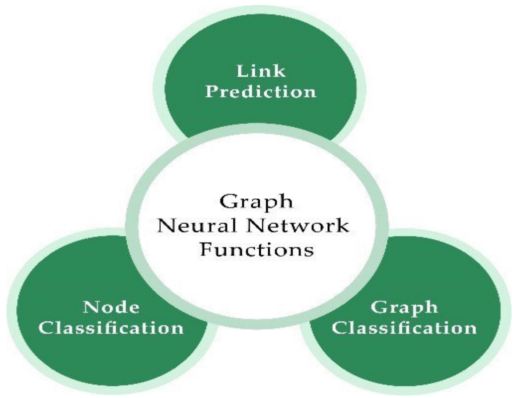

FIGURE 2. Functional overview of GNN.

relevant information from neighboring nodes, incorporating the attributes of medical entities (e.g., patient demographics, clinical data) and the structural characteristics of the healthcare graph. This integration enables GNN to learn rich representations that capture the complex relationships and dependencies within the medical data, paving the way for enhanced decision-making and improved patient outcomes [8], [9]. GNN can be categorized into three main types, each playing a crucial role in addressing healthcare challenges and improving patient outcomes (see Fig. 1) [10].

Recurrent GNN (R-GNN) finds significant applications in medical healthcare, extending the concept of recurrent neural networks (RNNs) to analyze graph-structured medical data. R-GNN can adapt to the changing topology and temporal dependencies within the medical graph by updating node representations based on their previous states and neighboring nodes. This capability allows R-GNN to track the progression of medical conditions, monitor treatment effectiveness, and provide personalized patient care based on dynamic graph data [10], [11].

Spatial convolutional networks (S-GNN) have proven to be a valuable framework within medical healthcare by adapting the convolutional operation from traditional image-based convolutional neural networks to graph-structured medical data [1]. S-GNN leverage the spatial locality and patterns within medical graphs to capture local relationships and extract meaningful features. By performing spatial convolutions iteratively across multiple layers, S-GNN can capture hierarchical relationships and learn increasingly abstract features from different regions of the medical graph, which aid in uncovering spatially-dependent patterns and dependencies essential for various medical applications [10].

Spectral convolutional networks (Spectral-GNN) have emerged as a valuable tool within medical healthcare by leveraging the spectral domain to analyze and process graph-structured medical data. Spectral-GNN can extract both local and global structural information by considering the influence of different spectral components at various scales. However, the spectral decomposition process can be computationally expensive, particularly for large medical graphs. Spectral-GNN may encounter difficulties in handling dynamic or evolving medical graphs since the spectral components are based on the fixed structure of the graph [10]. From Fig. 2 in the medical field, GNN can be categorized into three main categories based on their functionalities and applications.

Node classification is one of the fundamental tasks that GNN excels at performing in the context of medical healthcare. In node classification, the objective is to assign a specific label or class to each node in a medical graph based on its features and the information obtained from its neighboring nodes. GNN can generalize and accurately predict the class labels of unlabeled nodes, aiding in various medical classification tasks. By effectively integrating information from neighboring nodes, GNN can uncover insightful patterns and dependencies that might not be apparent at the individual node level.

Link prediction is another crucial function that aims to forecast the presence or likelihood of connections between nodes. GNN leverages the medical graph's structural properties and connectivity patterns to infer missing or potential links, empowering them to anticipate future interactions or relationships. By assimilating information from the graph's topology and node features, GNN can effectively capture the intricate dependencies and latent knowledge that contribute to the formation of links. The ability to anticipate and infer links within the medical graph enables healthcare professionals and researchers to gain insights into disease mechanisms, identify novel therapeutic targets, and facilitate personalized treatment strategies.

Graph classification is a crucial function that involves entire graph labeling based on its structural properties, node attributes, and connectivity patterns. GNN is particularly well-suited for this task due to its ability to capture hierarchical relationships and dependencies within the graph. GNN can learn to extract informative representations that effectively capture the discriminative features of the entire medical graph. By leveraging the power of DL, GNN can effectively model and learn the complex structural characteristics and patterns inherent in graph-structured medical data [4], [12]. This, in turn, facilitates the development of intelligent decision support systems, patient risk stratification, disease prognosis, and treatment recommendation systems, thereby enhancing the quality of healthcare delivery and patient outcomes [10], [11].

GNN is a powerful tool which has emerged as for analyzing graph-structured data in medical healthcare, capable of extracting meaningful insights, accurate predictions, and improved decision-making [13]. The integration of GNN in medical healthcare has the potential to revolutionize the industry, enhance clinical decision-making, and contribute to the development of innovative healthcare solutions [14], [15]. GNN has found numerous applications in the healthcare sector, ranging from disease diagnosis and prognosis to drug discovery and predicting patient outcomes. By integrating GNN into drug-drug interaction (DDI) prediction through DDI-GCN, researchers achieve superior accuracy and mechanistic insights, enhancing drug safety and patient well-being [16]. Leveraging medical knowledge graphs, a knowledge-grounded conversation generation model is enriched to create contextually accurate and engaging medical dialog systems, improving healthcare accessibility, quality, and cost-effectiveness [17]. Operationalizing secondary medical knowledge via GNN-based graph rewriting augments clinical practice guidelines, enabling comprehensive decision support for multimorbid patients while mitigating adverse interactions, thereby advancing patient care [18].

Through connected graph data and learning methods like apriori, personalized health assistance systems are developed, exemplified by a graph-based dynamic context model for medication assistance and heart rate monitoring, enhancing healthcare delivery amidst digitalization and demographic shifts [19]. GNN can enhance protein-ligand binding affinity prediction in drug design, implement unsupervised clustering of single-cell RNA sequencing data for cellular subpopulation identification, and improve brain-computer interface systems [20], [21], [22]. Further innovation emerges in evidence-based medicine through GNN. An approach using a domain knowledge graph and statistical inference methods extracts structured knowledge from pre-clinical studies, aiding complex domain understanding like spinal cord injuries [23]. LIGHTED, an integrated DL model combining LSTM and GNN, enhances opioid overdose risk prediction by leveraging electronic health records, empowering clinical decision support and addressing the opioid crisis [24]. A two-stage framework with a novel 3D contextual transformer enhances CT airway segmentation, overcoming challenges in bronchoscopy planning and COPD assessment [25]. GNN revolutionize patient care management by clustering similar patients through electronic health records, enabling personalized recommendations and optimizing healthcare delivery [26]. Phenomenal strides are made in multi-modal applications. AER-GCN augments multi-label lesion annotation through knowledge graphs, enhancing chest X-ray image classification for improved diagnostics [27]. Cutting-edge variational graph autoencoders predict drug-protein interactions in the context of Covid-19, contributing to novel therapeutic options [28]. Moreover, GNN enables the development of predictive models for drug-target interactions [29], the segmentation of Covid-19-infected regions [30], and compressed sensing MRI reconstruction [31]. Gene selection based on social network analysis' bolsters microarray data classification, optimizing accuracy and efficiency [32]. CheXGAT, a hybrid model merging convolutional and GNN, advances multilabel chest X-ray classification with improved accuracy [33]. Genetic programming optimizes CNN structures for Covid-19 diagnosis from X-ray images [34]. Causal inference techniques unveil a framework for estimating interventions' impact in clinical settings [35]. MultiCoFusion transforms cancer diagnosis by integrating histopathological images and genomic data for survival analysis and grade classification [36]. Graph embedding and phenotypic frequency integration enhance phenotypic representation from the human phenotype ontology, advancing patient analysis and risk prediction [37]. Attribute-aware interpretation learning refines thyroid nodule diagnosis, promoting human-computer collaboration and accuracy [38]. LiNGAM, causal analysis identifies disease progression factors from medical checkup data, contributing to novel insights [39].

It's worth noting that GNN also facilitates accurate prediction of disease-related candidate lncRNAs [40], influenza outbreak forecasting [41], and drug response prediction with graph convolution operations [42]. Through these innovations, GNN revolutionized healthcare, addressing diverse challenges and redefining medical practice for improved patient outcomes.

To acquire a comprehensive understanding of the current research on GNN in healthcare-based applications, it is crucial to conduct a systematic review. This review study aims to provide a thorough and critical analysis of studies conducted on GNN in healthcare-based applications and identify current research trends, challenges, and future research directions in this field. The major contributions of this review study can be summarized as follows:

I. The systematic review provides a comprehensive overview of the utilization of GNN in various healthcare-based applications, highlighting its potential impact.
II. The review study emphasizes how GNN leverages the inherent structure of medical graphs to analyze intricate dependencies and relationships within healthcare data, enabling comprehensive analysis and improved decision-making.
III. This study defines and addresses state-of-the-art research questions, offering insightful solutions and valuable findings into the current state of knowledge in healthcare-based GNN applications.

IV. This review study provides a comprehensive exploration of the current research trends, challenges, and future research directions, offering valuable insights for researchers and further advancements.

The study organization follows a logical and systematic flow, facilitating a comprehensive exploration of various aspects of GNN. In Section II, the review contextualizes the study by discussing related literature, outlines the methodology employed in the review process, and defines the research questions. The distribution analysis of the selected studies and current trends have been analyzed in Section III. Furthermore, in Section III, after an in-depth analysis, research questions have been addressed, providing insightful analysis and findings that fulfill the objectives of the study. The challenges encountered by researchers in implementing GNN and potential future research directions are discussed in Section IV. Finally, in Section V, the study concludes by summarizing the key findings and outlining the study's implications for future advancements in GNN.

II. REVIEW METHODOLOGY

The following sections provide an overview of the relevant research and outline the methodology employed for this systematic review.

A. RELATED WORK

In recent years, there has been a proliferation of review studies focusing on GNN. Those studies have examined and analyzed various aspects of GNN across diverse domains, those are analyzed here to explore and identify the current research gap.

Zhou et al. [43] conducted an extensive literature review on GNN, emphasizing their importance in various learning tasks involving graph data. In the study a comprehensive design pipeline for GNN models has been proposed, organizing different variants based on graph types, computation modules, and training types. They provide an overview of frameworks and theoretical analyses and categorize applications across structural, non-structural, and other scenarios. The review showcases the remarkable advancements of GNN, attributed to enhanced model flexibility, expressive power, and training algorithms. Moreover, the authors identify key challenges such as interpretability, robustness, pretraining, and complex structure modeling that require further attention in GNN research.

In another review, Wieder et al. [44] delve into the expanding application and importance of GNN in the realm of drug discovery. To effectively organize this rapidly evolving field, the study compiles and categorizes 80 GNN architectures from 63 publications, demonstrating their use in predicting over 20 molecular properties across 48 datasets. The study discusses the growing interest among pharmaceutical companies in integrating GNN methods into proprietary frameworks, with a specific emphasis on predicting molecular properties.

Zhou et al. [45] present an extensive review study that comprehensively examines GNN, focusing on taxonomy, advancements, and emerging trends. The study covers four essential dimensions: architectures, extensions and applications, benchmarks, and evaluation pitfalls. The authors provide detailed insights into various GNN architectures and explore diverse extensions of GNN. The review also puts forth four prospective areas for future research, encompassing highly scalable GNN, robust GNN, GNN beyond the WL test, and interpretable GNN.

Gao et al. [46] present an extensive examination of recommender systems based on GNN, highlighting their historical progression. Existing recommender systems are categorized based on stage, scenario, objective, and application, while GNN techniques are classified into spectral and spatial models. The survey delves into the motivations behind employing GNN in recommender systems, focusing on factors such as high-order connectivity, structural characteristics of data, and enhanced supervision signals. Furthermore, the study thoroughly analyzes the challenges associated with embedding propagation/aggregation, graph construction, model optimization, and computational efficiency.

Chen et al. [47] comprehensively appraise GNN-based fault diagnosis (FD). The study underscores the merits of leveraging graphs to represent data across diverse application domains. The review commences by scrutinizing FD techniques grounded in NNs, categorized by data representations encompassing time series, images, and graphs. Through meticulous experimentation on benchmark datasets, the study corroborates the efficacy of GNN-based FD methodologies, substantiating their supremacy in FD. Finally, the review engenders discourse concerning prospective challenges and offers insights for forthcoming research endeavors, aiming to facilitate a seamless transition from traditional NN-based FD to graph-structured data approaches while proffering guidance for future inquiries.

Wu et al. [48] present a comprehensive survey on applying GNN in data mining and ML fields. In the study, a new taxonomy is proposed, categorizing GNN into recurrent, convolutional, autoencoders, and spatial-temporal architectures. The survey covers applications of various GNN across domains and detailed insights into code which is open-source, datasets of benchmark, and evaluation of model. Furthermore, the study presents potential avenues for future research in this rapidly advancing field.

Ye et al. [49] present a comprehensive survey on utilizing GNN for multi-relational knowledge graphs (KGs), which represent factual information among diverse entities. The study highlights the challenges and research topics associated with KGs and the significant advancements made possible by GNN in recent years. The review focuses on four key KG tasks: knowledge graph alignment, link prediction, graph reasoning knowledge, and node classification. It provides an in-depth analysis of GNN-based approaches for each task, discussing their models, benefits, and contributions.

TABLE 1. Applied keywords.

Medical knowledge graph	Graph neural networks	Graph convolutional network	Applications	Graph attention network
Medical imaging	Graph autoencoder	Healthcare	Medical	Clinical
Disease	Patient	Drug	Diagnosis	Prediction
Outcome prediction	Healthcare informatics	Electronic health record	Graph discover	Medical data analysis
Graph representation	Machine learning	Artificial intelligence	Health data analytics	Electronic medical record

Wu et al. [50] thoroughly examine recommender systems based on GNN, focusing on the effective learning of user/item representations from interactions and side information. The study introduces a comprehensive classification framework for GNN-based recommendation models, categorizing them according to information used type and task of recommendation. The authors systematically assess the challenges associated with applying GNN to diverse data types and discuss the strategies employed in existing studies to overcome these challenges. Furthermore, the study puts forward novel perspectives for the future advancement of this field.

Munikoti et al. [51] present a thorough examination of the integration of deep reinforcement learning (DRL) and GNN within graph-structured environments. The analysis explores the advantages of combining DRL and GNN, such as enhanced adaptability and decreased computational complexity. Furthermore, the review identifies the main obstacles encountered when integrating DRL and GNN and proposes potential avenues for future research.

He et al. [52] provide a comprehensive survey on utilizing GNN in wireless networks, harnessing the computational capabilities of DL techniques. The study emphasizes the effective exploitation of graph-structured data and contextual information to optimize wireless networks using GNN. The classical paradigms of GNN are subsequently introduced, followed by exploring their applications in wireless networks, particularly in resource allocation and emerging fields. The survey underscores that the application of GNN in wireless networks is still at an early stage, necessitating further advancements to address existing challenges.

The preceding discourse reveals that numerous studies have been undertaken to examine diverse aspects of GNN within multiple domains. Nevertheless, there has been a scarcity of review research conducted to examine the utilization of GNN within healthcare-based applications. This study presented here fills a critical gap in the existing literature by offering a comprehensive review of GNN applications specifically within the healthcare domain. Unlike previous reviews, our study stands out in its systematic analysis of GNN studies, shedding light on current trends, persistent challenges, and future prospects in healthcare applications. Notably, this study goes beyond a mere survey, posing and addressing research questions to provide a deeper understanding of GNN's role in healthcare. Our study underscores the significant potential of GNN to advance diagnostic and therapeutic methodologies, offering valuable insights for practitioners, researchers, and policymakers aiming to enhance healthcare systems.

B. SEARCH STRATEGY

The systematic review process for identifying relevant studies on GNN in healthcare-based applications requires a structured and comprehensive search strategy. To facilitate the search for relevant studies, various search engines and databases have been utilized, and various keywords have been carefully selected and utilized with an amalgam of keywords to ensure that most of the relevant studies are included (see Table 1).

C. INCLUSION AND EXCLUSION CRITERIA

The established inclusion and exclusion criteria for this study are purposefully constructed to guarantee the incorporation of only pertinent studies. Any studies that fail to fulfill these criteria are excluded.

Inclusion criteria:

I. Studies that apply GNN for healthcare-based applications.
II. Studies that involve the use of medical data.
III. Studies that provide a comprehensive description of the GNN model and its parameters.
IV. Studies that evaluate the performance of the GNN model using appropriate metrics.
V. Studies that discuss the potential of GNN in improving healthcare outcomes.
VI. Studies that provide insights into the interpretability of GNN models.

Exclusion criteria:

I. Studies that only use GNN for non-healthcare applications.
II. Studies that are not relevant to the healthcare domain.
III. Studies that are not written in English.
IV. Studies with insufficient reporting of the GNN model architecture, training process, or evaluation metrics are used in the healthcare context.
V. Studies that are not relevant or do not contribute to the overall understanding of GNN in healthcare-based applications.

D. SELECTION OF THE STUDY

The meticulous selection of studies plays a pivotal role in ensuring the utmost quality of a systematic review. This research endeavor undertakes a systematic approach to identify and evaluate existing studies focusing on GNN. Through

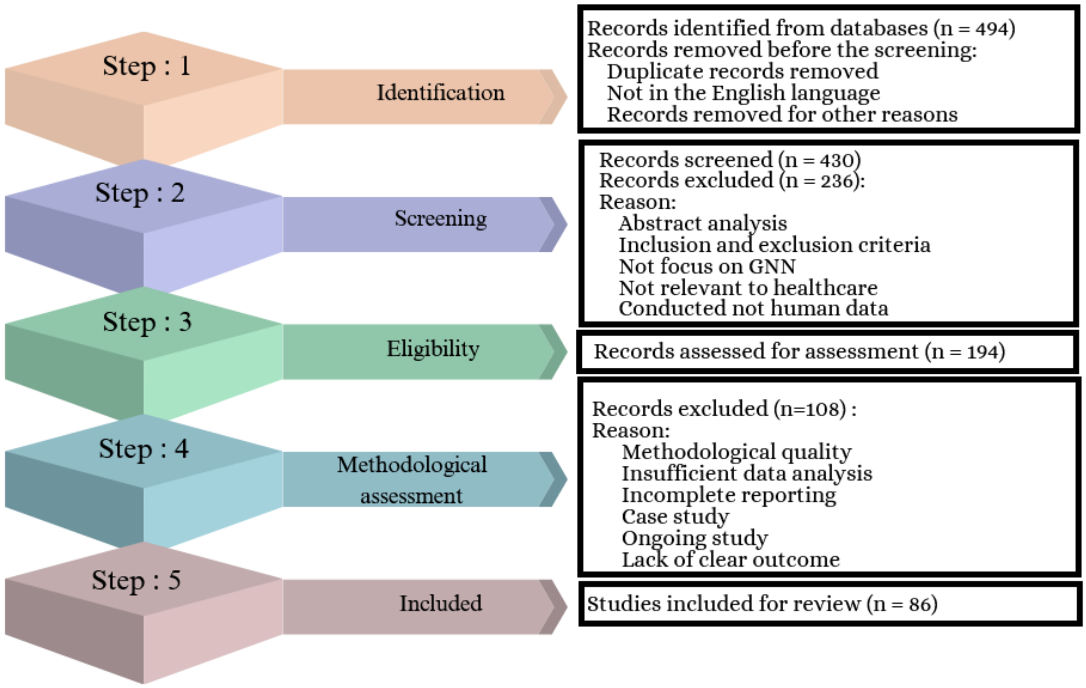

FIGURE 3. Workflow of the study section procedure.

the comprehensive search of various databases, a total of 494 studies have been yielded, as depicted in Fig. 3. In the initial step, 64 studies were excluded based on duplicated studies, not being in English, and other reasons. Subsequently, these studies underwent meticulous screening based on their titles, abstracts, inclusion and exclusion criteria, etc., resulting in a refined set of 194 studies. Further, a thorough assessment of the full-text versions of these studies was conducted to ensure the studies' methodological quality, leading to the exclusion of 108 studies based on the proper outcome, quality, sufficient analysis, etc.

Finally, the stringent application of the selection procedure resulted in a final selection of 86 studies that met the rigorous standards for inclusion in this systematic review.

E. EXTRACTION OF THE DATA

To ensure accurate analysis, meaningful interpretation, and reliable results, a methodical and well-organized approach is implemented throughout the extraction process. In this step, predefined attributes are utilized to structure the gathered data, which include references and years, purpose, dataset, data characteristics, data instances, models, and contributions and findings. The selection of those attributes allows for a thorough exploration of GNN applications across healthcare area, leading to valuable insights into GNN potential and implications.

F. RESEARCH QUESTIONS

In order to delve into the applications and implications of GNN in healthcare, facilitating a deeper understanding of their capabilities and potential impact and address the complex challenges and explore the potential of GNN in healthcare, this research aims to investigate the following research questions:

- RQ1. What are the main applications of GNN in healthcare, and how have they been utilized to address specific healthcare challenges?
- RQ2. How do the specific structural characteristics of complex healthcare graphs and the diverse types of healthcare data integrated with GNN impact the effectiveness and practicality of GNN in extracting crucial insights and identifying meaningful patterns in healthcare data?
- RQ3. What is the comparative effectiveness of GNN versus traditional ML methods in healthcare-based applications, and what evidence supports the potential of GNN in improving decision-making and patient outcomes in healthcare?
- RQ4. What are the key determinants influencing the performance of GNN, and what are the limitations of the current GNN application?
- RQ5. How can GNN be utilized for the discovery and identification of rare disease subtypes or novel disease clusters while enabling interpretability and explain ability, which allows healthcare professionals to understand and trust the predictions and insights provided by these models?

III. ANALYSIS AND FINDING

In this section, selected studies, various distributions, trend analysis, and summaries of the studies have been conducted.

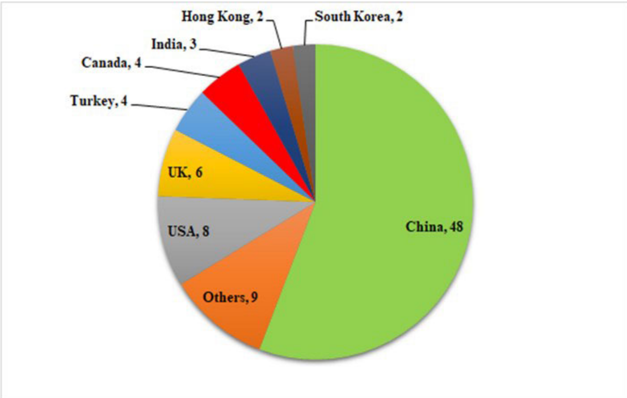

FIGURE 4. Geographical country-wise distribution of GNN studies.

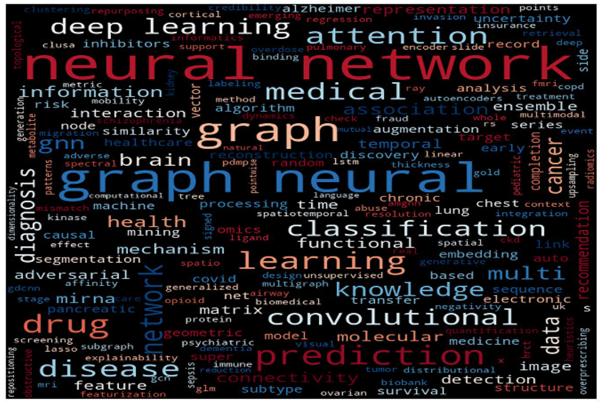

FIGURE 5. Keyword word cloud of selected studies in GNN.

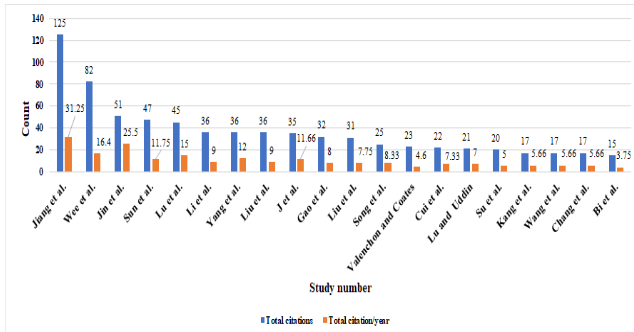

FIGURE 6. Top 20 studies in terms of citation.

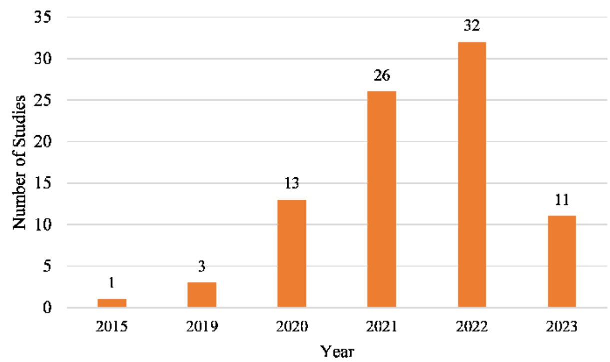

FIGURE 7. Year-wise distribution of studies.

Additionally, each of the proposed study questions has been addressed after careful, in-depth analysis and interpretation.

A. STUDIES DISTRIBUTION ANALYSIS

From Fig. 4, find out that China emerged as the most prominent contributor, with 48 studies dedicated to utilizing GNN in healthcare-based applications. Nine studies have been conducted, prompting other countries (such as the Netherlands, Finland, Singapore, Australia, etc.) to emulate the research. Following China, the United States exhibited a strong research presence with 8 studies, while the United Kingdom and Turkey closely followed with 6 and 4 studies, respectively. Moreover, within the chosen studies, 85% are sourced from several academic publications, while the remaining portion originates from conference proceedings.

Fig. 5 showcases a word cloud depicting the most frequently used keywords in the selected studies. In the figure the word "graph" stands out prominently, indicating the central role of graph theory in studies. Additionally, the terms "neural" and "network" appear prominently, reflecting the widespread utilization of neural network architectures in the domain of interest. Furthermore, the presence of keywords such as "prediction," "attention," and "deep learning" suggests a strong focus on predictive modeling and ML techniques. The terms "drug" and "disease" indicate the relevance of GNN in pharmaceutical and medical research, particularly in drug discovery and disease prediction.

In Fig. 6, an analysis of the top 20 most cited studies in the healthcare field related to GNN is presented. Among these notable works, Jiang et al. [53] focused on drug–target affinity prediction, Wee et al. [54] examined ad and mci diagnosis and transfer learning across populations, and Jin et al. [67] delved into antibody sequence-structure co-design. These studies, being highly cited, signify the significant interest researchers have shown in exploring GNN applications within the healthcare domain [55], [56], [57].

From Fig. 7, among the total included studies, one study was published in 2015, demonstrating an early interest in GNN for healthcare-based applications. The number of studies increased steadily over the years, with three studies in 2019, thirteen studies in 2020, and a significant rise to twenty-six studies in 2021, indicating a growing focus on GNN research. The year 2022 witnessed the highest number of studies, with thirty-two publications, suggesting a peak in research activity. The increasing number of studies during these years highlights the significance of GNN as a cutting-edge research area.

B. TRENDS ANALYSIS

The field of healthcare is experiencing a paradigm shift with the emergence of GNN. As healthcare data are inherently interconnected and structured as graphs, GNN offers a promising approach to extracting valuable insights and improving diagnostics, personalized treatments, and healthcare management by analyzing and modeling the intricate dependencies and patterns in healthcare data. A comprehensive summary of the included studies is presented in Table 2, and it is evident that GNN is utilized in a wide array of healthcare-based applications. The applications include clinical decision support, disease prediction, drug discovery, patient monitoring, and healthcare network analysis. Among these, disease prediction and drug discovery emerge as the most prominent areas of focus, indicating the potential of GNN for advancing diagnostic and therapeutic approaches.

The diverse landscape of methodologies in GNN studies presents a challenge for straightforward categorization. Predominantly, studies demonstrate a versatile approach, with researchers often opting to integrate mixed methodologies or combine them with various techniques [61], [90]. This tendency toward versatility serves to facilitate enhanced customization, feature extraction, and comprehensive analysis, making it challenging to confine these studies to rigid classification boundaries. The combination method showcased the potential for broader applications, emphasizing the effectiveness of integrating diverse GNN architectures for enhanced medical imaging tasks. Certain studies focus on recurrent GNN (R-GNN) [67], [68], [71], [79], [108], highlighting their utility in dynamically tracking medical conditions and providing personalized care by adapting to changing graph structures. This adaptability positions R-GNN as a valuable tool for patient-centric healthcare applications. On the other hand, studies delving into spectral convolutional networks (Spectral-GNN) [64], [88], [93], [103], [136] harness spectral domain analysis to extract crucial structural information. Despite facing computational challenges and limitations in handling dynamic graphs, Spectral-GNN contributes to insightful structural analysis. A notable trend emerges with the widespread utilization of spatial convolutional networks (S-GNN) [59], [60], [63], [69], [72], [74], [75], [78], [101], [102], [123], [124], [125], [126], [127], [128], underscoring their prominence and effectiveness in various medical graph applications, showcasing their adaptability to diverse healthcare research scenarios.

Regarding model focus and architecture, it can be observed that customization of the GNN model and the exploration of different architectures have been employed to tackle healthcare-related challenges. By leveraging these custom-designed architectures, researchers can enhance the performance and efficacy of GNN in healthcare, thereby enabling more accurate and insightful analyses, predictions, and decision-making processes.

This comprehensive analysis of GNN applications in healthcare classification tasks provides valuable insights into the diverse strategies employed by researchers. However, categorizing into classification methods proves challenging due to the prevalent use of versatile approaches and hybrid combination in the field of healthcare-based applications. In the study on medical triage chatbot diagnosis improvement [77], a hybrid combination approach is employed. This comprehensive mix of methodologies synergistically enhances the performance of the medical triage chatbot. Similarly, in the representation for predicting molecular associations [85], a hybrid combination involving LDA, MDA, PPI, and DDI is utilized within the LR-GNN framework. This approach effectively leverages the strengths of different techniques, demonstrating LR-GNN's efficacy in predicting molecular associations. The advantages of such hybrid combinations lie in their ability to capture diverse aspects of complex systems, providing a more comprehensive and accurate representation for improved diagnostic outcomes. Certain studies focus on specific classifications, reflecting a targeted approach in healthcare-based applications. Node classification proves to be a versatile tool in various healthcare applications. In the context of medical insurance fraud detection [60], node classification is employed to categorize 10,000 patients, contributing to anomaly detection and aiding in the identification of fraudulent activities. In the domain of medical knowledge graph reasoning [121], node classification plays a crucial role in personalized disease diagnosis by categorizing nodes within graph-structured datasets such as cora and citeseer. For predicting drug-target interactions [128], node classification helps categorize nodes representing different entities, facilitating the identification of potential associations between drugs and targets. Additionally, in the prediction of soft tissue deformation in image-guided neurosurgery [137], node classification is utilized to categorize nodes representing healthy and tumor tissues, contributing to accurate predictions of soft tissue deformations. Link classification plays a crucial role in various healthcare applications, as evident from the diverse studies presented. For instance, in the context of synthetic lethality prediction in human cancers [56], link classification with the proposed KG4SL model achieved exceptional performance, demonstrating its effectiveness in identifying gene pairs associated with synthetic lethality. In cancer survival prediction [76], link classification using the proposed MGNN model achieved an impressive accuracy, showcasing its capability to predict survival outcomes based on multimodal data and clinical profiles. Additionally, link classification in predicting deregulation types of miRNA-disease associations [84] with the SGNNMD model demonstrated good inductive capability and generalization to unseen miRNAs/diseases during training. In drug side effects prediction [92], the idse-HE model utilized link classification to reconstruct the original matrix and predict drug side effects based on drug chemical structure and network topology information. Furthermore, in lung cancer knowledge classification [108], the combination of the proposed PMI_2 + link method and GCNConv exhibited the best performance, highlighting the significance of link classification in categorizing documents related to lung cancer knowledge. Graph classification emerges as a pivotal approach across diverse healthcare studies, showcasing its versatility and impact on various tasks. In the context of drug similarity and binding strength analysis [58], graph classification, implemented through GNN, contributes to identifying kinase inhibitors with potential applications in treating Covid-19. In drug over-prescribing risk assessment [59], RxNet, employing graph classification techniques, outperforms baselines, enhancing precision-recall metrics. For radiotherapy target contouring [61], the GGP utilizes graph classification to achieve superior sensitivity in comparison to baseline models. In clinically interpretable pathway-level biomarkers discovery [62], MLA-GNN leverages graph classification for state-of-the-art performance in survival prediction, histological grading, and Covid-19 diagnosis. Chronic kidney disease prediction [63] involves graph classification using DeepLab V3+ and DGCNN, achieving high sensitivity and specificity for predicting eGFR levels. The prediction of Covid-19 cases [64] utilizes various graph-based models, including GNN, demonstrating their effectiveness in forecasting. These studies underscore the essential role of graph classification in advancing healthcare applications, from drug discovery to disease diagnosis and prognosis.

In the examination of training-testing data distribution across diverse studies in the systematic review on GNN in healthcare-based applications, distinct patterns emerge. Among the analyzed studies, a substantial portion (14) exhibits a prevalent preference for an 80% split, signifying a collective inclination towards constructing robust training datasets. Concurrently, another significant portion (10) opts for a 70% partition, showcasing a commonly employed and balanced percentage for training purposes. Additionally, a noteworthy number of studies (6) distinctly choose a 90% allocation, underscoring a deliberate emphasis on larger training sets to foster enhanced model learning. In contrast, a smaller yet notable portion (5) favors a 60% split, reflecting a tendency towards a comparatively more compact training dataset. Notably, insights into the test split also reveal diverse practices, with a majority of studies (17) prioritizing a 20% split for testing, demonstrating a common preference for a substantial test dataset. Many studies have prevalent 70% training data, where 10% used for validation dataset which explain the increased number of 20% test data split studies. Additionally, 14 studies opt for a 10% partition, while 5 studies choose a 30% split for testing, highlighting variations in test data allocation among the analyzed literature. The insights gleaned underscore the variability in the selection of training, and testing percentages across different studies, revealing nuanced preferences and considerations in model development.

The analysis of the GNN also reveals trends in terms of data coverage. It highlights the inclusion of diverse data types, such as electronic health records (EHRs), imaging data, genetic data, and healthcare network data. This indicates the potential of GNN to leverage different data sources for comprehensive healthcare analysis and decision-making. The trend analysis reveals that a larger number of studies focused on drug-target interactions, drug repurposing, protein structure prediction, and molecular property prediction. This reflects the growing interest in leveraging GNN for drug discovery and optimization in healthcare. The large number of utilized data instances highlights the capability of GNN to handle large-scale healthcare data, enabling more accurate and precise predictions.

C. ANALYSIS AND INTERPRETATION OF PROPOSED RESEARCH QUESTIONS

- RQ1. What are the main applications of GNN in healthcare and how have they been utilized to address specific healthcare challenges?

GNN has become increasingly popular in healthcare due to its ability to capture complex dependencies and relationships in healthcare data. One of the aims of this review study is to explore the main applications of GNN in healthcare and how they have been utilized to address specific healthcare challenges.

GNN has been widely used in recent years to discover biomarkers associated with various diseases and conditions and to analyze healthcare data [62]. One of the most promising applications of GNN in healthcare is clinically interpretable pathway-level biomarker discovery. This approach involves using GNN to analyze complex biological pathways and identify key biomarkers associated with specific diseases or conditions [62]. In the case of chronic kidney disease, GNN has been used to identify potential biomarkers that can help predict the progression of the disease and improve patient outcomes [117]. GNN can leverage dynamic graph convolutional networks with feature selection to extract high-quality omic-specific embedding information, aiding biomarker discovery in drug development [139], [140]. By analyzing large-scale patient data sets, GNN can identify patterns and relationships that can be missed by traditional statistical methods and provide a more comprehensive understanding of the underlying biology of the disease. GNN has also been used for Covid-19 drug discovery, enabling the identification of potential drug targets and the development of new treatments [86]. By analyzing molecular and clinical data, GNN can identify promising drug candidates, predict their effectiveness, and accelerate the development of new treatments, ultimately improving outcomes for patients affected by the Covid-19 pandemic [64], [133], [138].

GNN has emerged as a promising approach that is well-suited to analyzing brain network data because it can capture complex relationships between brain regions and identify subtle patterns that may be difficult for humans to detect [81]. By training GNN on large brain scans and clinical data datasets, researchers have developed models that can accurately predict the likelihood of an individual developing Alzheimer's disease [116]. GNN has also been used to identify biomarkers associated with the disease and used in drug repurposing for Alzheimer's disease, showing great promise in improving both the diagnosis and treatment of Alzheimer's disease [65] [100] [119].

TABLE 2. Summary of healthcare-related studies in GNN.

Ref and year	Purpose	Dataset	Data characteristics	Data instances	Models	Contributions and findings
[58], 2021	Drug similarity and binding strength analysis	Drug Bank and PubChem	Bio and chemical informatics, structure and descriptive info.	14556 drug entries, 110025926 chemical structures, and 96561 protein targets	Tanimoto algorithm, Atom Pair algorithm, and GNN	The kinase inhibitors obtained from the study can be used as Covid-19 alternative treatment.
[59], 2021	Drug over-prescribing risks	Collected	Descriptive information	2751137 prescriptions	Rx-refill LSTM, Dosing-Adaptive Network, and RxNet	RxNet outperforms all baseline techniques, improving prauc by 4.85% and F1-score by 6.35%.
[60], 2022	Medical insurance fraud detection	Municipal medical insurance bureau	Descriptive information	10000 patients	Bi-LSTM, GAT Metapath2vec, LR, RF GCN, HAN, StGNN	StGNN outperformed other models in node classification and anomaly detection tasks.
[61], 2019	Radiotherapy target contouring	Collected	PET-CT/RT-CT images	81 patients	2D U-Net, 3D U-Net, and GGP	GGP outperformed based line with sensitivity (GTV 80.5%, CTV 85.7%, PTV 92.2%).
[62], 2020	Clinically interpretable pathway-level biomarkers discovery	Glioma, Covid-19	240-dimensional RNAseq, proteomic data of the Covid-19 patient's sera	769 patients, and 70 patients	SLA-GNN, and MLA-GNN	MLA-GNN has state-of-the-art survival prediction, histological grading, Covid -19 diagnosis and achieved an accuracy of 93.05%.
[63], 2022	Chronic kidney disease prediction	Collected	Histopathology images	107471 images	DeepLab V3+ with ResNet-18, K-means clustering, DGCNN, and RF	At biopsy predicting high/low eGFR, achieved an accuracy of 95%. For eGFR changes prediction in one-year, accuracy of 84% is achived.
[64], 2021	Covid-19 cases prediction	Collected	Friendship ties, colocation probabilities, and district-specific, time-series	401 federal districts	XGBoost, DNN, GAM, MEAN, GNN, proposed (zip), and proposed negative binomial	The proposed model using the zip distribution obtained an RMSE of 3.931, while the proposed model using the negative binomial distribution obtained an RMSE of 4.094.
[65], 2021	Diagnosis of Alzheimer's disease	OASIS 3 database	T1 weighted MRI scans	121 scans	ADiag	ADiag has revealed a robust accuracy of 83%.
[66], 2021	Brain network-based disease analysis Framework	HIV, Bipolar	fMRI	70 samples from patients (positive), and 52 bipolar subjects	Proposed (BrainNNExplainer), M2E, MIC, MPCA, MK-SVM, GAT, GCN, and DiffPool, BrainNN	The BrainNNExplainer model was proposed for two datasets: the HIV dataset with an accuracy of 77.14% and auc of 75.00%, and the Bipolar dataset with an accuracy of 75.56% and an auc of 69.88%.
[67], 2022	Antibody sequence structure co-design	SAbDab	CDR sequences of heavy chains	4994 antibodies	Proposed (RefineGNN model)	Significantly outperforms on task of three antibody generation for sequence-based and graph-based approaches.
[68], 2021	Aiding medical diagnosis	ABIDE, ADHD-200	fMRI	971, and 794 d rs-fMRI scan	FFN, GCRN, GCN, and GAT	The GAT achieved an accuracy of 74%.
[69], 2022	Structure and position-aware for airway labeling	COPDGene	CT scans	220 COPD airway trees	CNN, GATS, and proposed (SPGNN)	The proposed method accuracy reaches 91.18% for 18 segmental airway branches labeling.
[70], 2022	Self-supervised context-aware learning for medical images	COPDGene	3D CT	3D CT images of 9180	Proposed MedicalNet, ModelsGenesis, MoCo, 3D CNN, and proposed	The proposed model achieved an accuracy of 65.3%.
[71], 2023	Boost temporal sensitivity in fMRI analysis	HCP S1200s, ID1000	fMRI	1093 healthy subjects, and 881 healthy subjects	SAGE, GCN, BrainGNN, BrainNetCNN, and proposed GraphCorr method	The GraphCorr model achieved 89.57% accuracy and roc score of 94.27%.
[72], 2023	Interpretable brain network-based psychiatric diagnosis	BA-2 Motifs, ABIDE, REST-meta-MDD	Graphs	1000 graphs, 528 patients, and 1604 participants	Linear-SVM, RBF-SVM, RF, LASSO, GCN, GAT, GIN, SIB, DIRGNN, GNNExplainer, PGExplainer, RC-Explainer, and proposed (CI-GNN)	For synthetic dataset, CI-GNN achieves 99.9% accuracy exceeding other baselines.
[73], 2023	Identify cancer genes	CPDB, Multinet, PCNet,STRING-db,Iref	Multiple gene-gene interaction networks and multi-omics	7753 non-cancer genes, 887 labeled cancer genes, and	Proposed (EMGNN)	The proposed (EMGNN) achieved an accurate and unified novel cancer gene prediction by integrating multilayer graphs.

TABLE 2. ***(Continued.)*** **Summary of healthcare-related studies in GNN.**

				14019 unlabeled genes		
[74], 2023	Adverse drug event detection	SMM4H, TwiMed-Pub, TwiMed-Twitter, CADEC	Documents, ADE, non-ADE	SMM4H (documents 2,418), TwiMed-Pub (documents 1,000), TwiMed-Twitter (documents 625), and CADEC (documents 7,474)	Proposed (KnowCAGE))	For the TwiMed-Pub dataset, the KnowCAGE (GAT) model achieved a precision of 89.6%, a recall of 83.4%, and an F1 score of 86.4%. On the SMM4H dataset, the KnowCAGE (GAT) model achieved a precision of 85.2%, a recall of 96.8%, and an F1 score of 90.6%. Lastly, on the CADEC dataset, the KnowCAGE model utilizing the DGCNN architecture achieved a precision of 86.1%, a recall of 92.9%, and an F1 score of 89.4%.
[75], 2023	Cancer molecular subtype classification	TCGA, BRCA	Multi-omics, molecular subtype labels	TCGA (9,027 samples), and BRCA [LumA 529, LumB 197, Basal 175, Her2 80]	Proposed [ETEMOGNN+ GAT], proposed [ETEMOGNN + GCN], FCNN, GCN, Multi-omics GCN, Multi-omics GCN , GrAMME, and Multi-omics GAT	GAT preferred for less information smaller graphs and GCN models preferred for extra information larger graphs.
[76], 2020	Cancer survival prediction	Lung cancer	Multimodal data, CAN profile, clinical	917 lung cancer patients, and 1903 valid breast cancer patient	LR, RF, SVM, MDNNMD, and proposed (MGNN)	The MGNN model achieved an accuracy of 94%.
[77], 2021	Medical triage chatbot diagnosis improvement	ChatBot, MIMIC-III	Online medical triage, EHR data	Node 3370, and node 423	MFBPR, GraphSAGE, Multi-relational GCN, Dipole, HGCN, and proposed (MHDP)	The proposed MHDP approach surpasses state-of-the-art baselines.
[78], 2021	Overprescribing detection	Collected	PDMP	2751137 prescriptions	LSTM, ON-LSTM, T-LSTM, StageNet, GraphSAGE, EvoNet, CTDNE, JODIE, TGAT, TGN, and proposed (RxNet)	RxNet consistently outperforms state-of-the-art methods in predicting patients at high risk of opioid overdose and drug abuse, with an average of 5.7% and 7.3% improvement on F1 score respectively.
[79], 2021	Medical assistant diagnosis	Collected	ICD tree, symptom description and basic information	200000 disease sample data	noGAT+MLP,GAT+MLP,treeLSTM+ATT,GAT+ATT, and proposed (GAT + ATT)	The proposed GAT+ATT model achieved an accuracy above 93% for the first five diagnoses.
[80], 2021	Pediatric sepsis diagnosis	Collected	Medical history, , blood gas analysis, physical examination, routine blood tests, coagulation tests, and serological tests	3298 patients	GCN, LSTM, Logistic, ResNet, MLP, SVM, RF, GBDT, DF, and proposed (MA-ARMA)	The proposed MA-ARMA model achieved an accuracy of 92.52% and a sensitivity of 77.78%.
[81], 2020	Brain network classification	Brain network	fMRI	354 samples	Proposed (GNEA)	In the brain network classification applications, GNEA achieves best graph representation ability with excellent learning performance.
[55], 2021	Topological feature extraction and visualization	Collected	Coarse segmentation maps	36 patients	WSI-GTFE	WSI-GTFE to flexibly summarize the key insights acquired from fitting any GNN model to histological data.
[82], 2022	Architecture for modeling spatiotemporal dynamics in resting-state	UK Biobank rs-fMRI database	rs-fMRI	35159 samples	Combined GNN and CNN	The proposed model could lay the groundwork for future DL architectures focused on leveraging the inherently and inextricably spatio-temporal nature of rs-fMRI data.
[83], 2023	Improving target-disease association prediction	NNM	Heterogeneous network	12015 nodes	Proposed (CreaTDA)	Drug discovery can be aided by CreaTDA's ability to detect novel target-disease correlations.
[84], 2021	Predicting deregulation types of miRNA-disease associations	HMDD v3.0 database	miRNA-disease	4264 miRNA-disease	Proposed (SGNNMD)	SGNNMD can generalize to unseen miRNAs/diseases and has good inductive capability.

TABLE 2. ***(Continued.)*** **Summary of healthcare-related studies in GNN.**

[85], 2021	Representation for predicting molecular associations	LDA, MDA, PPI, DDI	Biomedical network	LDA (6104 lncRNA, 451 disease nodes), MDA (1194 miRNA), PPI (75000 samples), and DDI (60000 samples)	Proposed (LR-GNN)	LR-GNN is effective for molecular association prediction.
[86], 2022	Covid-19 drug design	PDBbind-v2007, PDBbind-v2013, PDBbind-v2016, PDBbindv2019, SARS-CoVBA	Bench mark test	PDBbind-v2007 (1300), PDBbind-v2013 (2959), PDBbind-v2016 (4057), PDBbindv2019 (17652), and SARS-CoVBA (185)	Proposed (MP-GNN)	For prediction of protein–ligand binding affinity, state-of-the-art results has been achieved by Proposed model. Highly accurate in SARS-CoV/SARS-CoV-2 for the prediction of complexes of inhibitors.
[87], 2023	Immune therapy response in cancer	Gide, Liuand and Kim	Melanoma samples	600 patients	Proposed (DeepOmix-ICI (orICInetforshort))	The proposed model, with auc of 85%, demonstrated superior performance compared to other measures such as tumor mutational burden (auc = 62%) and programmed cell death ligand-1 score (auc = 74%).
[88], 2021	Brain multigraph prediction	ABIDE	Structural T1-w MRI	310 subjects	Proposed (topology-aware graph GAN architecture (topoGAN)), Adapted MWGAN, MultiGraphGAN, and Adapted MW-GAN (clustering))	In brain multigraph prediction of the proposed method domains of five target outperformance other method.
[89], 2020	Diagnosis prediction	Medical information mart for intensive care,real-world longitudinal EHR database	Benchmark	Data set I (patients 7499), and data set II (patients-14,060)	Proposed (GNDP)	GNDP outperforms attention-based, knowledge-guided clinical and RNN prediction models.
[56], 2021	Synthetic lethality prediction in human cancers	SynLethDB	Genes	72804 gene pairs	Proposed KG4SL	The KG4SL model achieved an auc of 94.70% and an aupr of 95.64%.
[90], 2022	Co-expression gene modules for disease diagnosis and prognosis	Glioma dataset, Covid-19	Transcriptomic, proteomic, omics	Patients 769, and patients 70	Proposed (MLA-GNN), SVM, RF, SNN and MORONET, SLA-GNN, HumanNet + MLA-GNN and PPI + MLA-GNN	MLA-GNN achieves impressive accuracy of 93.05%.
[91], 2020	Comorbidity aware chest radiograph screening	CheXpert	Images	223648 images	ResNet18 (S), ResNet18 (E), ResNet18 (GNN), DenseNet121 (S), DenseNet121(E), DenseNet121(GNN), Xception(S), Xception(E), and Xception(GNN)	GNN ensemble of DenseNet121 with an average auc of 82.1% across thirteen disease comorbidities.
[92], 2022	Drug side effects prediction	Studied	Drug	1020 drugs, 5599 side effects, and 133750 positive samples	Proposed (idse-HE)	idse-HE uses drug chemical structure, drug substructure sequence, and drug network topology information to reconstruct the original matrix and predict drug side effects.
[93], 2021	Classification of first-episode schizophrenia, chronic schizophrenia and healthy control	Collected	EEG	40 FESZ, 40 CSZ patients, 40 matched HC subjects	GNN, and SVM	The GNN classifier achieved an accuracy of 84.17% trained on the brain functional networks.
[53], 2020	Drug–target affinity prediction	Davis, KIBA	Benchmark	Davis (proteins 442), and KIBA (proteins 229)	Proposed (DGraphDTA), and DeepDTA	For DGraphDTA, MSE metric can reach 0.202 and 0.126 for two datasets. the prediction performance of DeepDTA is better than that of DGraphDTA, which achieves r_m^2 of 0.700 and 0.786.

TABLE 2. ***(Continued.)*** **Summary of healthcare-related studies in GNN.**

[94], 2021	Explainable drug-target binding affinity prediction	Davis, Filtered davis, KIBA, Metz, Human, C.elegans, ToxCast	Benchmark	Davis (proteins 442), Filtered davis (proteins 379),KIBA(proteins(229),Metz (proteins 170), Human (proteins 2001), C.elegans (proteins 1876), and ToxCast (proteins 37)	GNN-CNN,TrimNet-CNN, GraphDTA, DrugVQA(VQA-seq), TransformerCPI, MGNN-CNN (proposed), MGNN-MCNN (proposed), and proposed (MGraphDTA)	MGraphDTA can improve the capability of interpretation and generalization of DTA prediction modeling.
[95], 2022	Drug-drug interaction prediction	DrugBank,TWOSIDES	Drug	DrugBank (1706 drugs), TWOSIDES (645 drugs)	Proposed (SA-DDI)	SA-DDI can improve capability of interpretation and generalization of DDI prediction modeling.
[96], 2022	Lung radiomics features selection for copd stage	Collected	Images (chest HRTC scans)	465 participants	SVM, MLP, RF, LR, GB, LDA, AMGNN	AMGNN based on constructed novel lung radiomics combination vector performs best, achieving an accuracy of 94.3%, and recall of 94.3%.
[97], 2022	Prognostic prediction	NSCLC Radio genomics	Image	1705 patients	TNM model, and proposed	The proposed model achieved auc values of 78.5%.
[98], 2021	Prediction of ovarian cancer-related metabolites	PaDELdescriptor	Chemical structure	2325 dimensions	Proposed (GPS-OCM)	The auc and aupr of proposed method are 92% and 81%, respectively.
[99], 2022	Identify miRNA–disease associations	Human microRNA disease	Benchmark	16427 recorded	Sequence similarity based on CKSNP	Sequence similarity based on CKSNP achieved an auc of 93.71%.
[100], 2022	Alzheimer's disease classification	ADNI	MRI and tau PET scans	224 features	GNN	The GNN model, trained using the relabelled data, achieved an auc of 95.2%, which was higher than the auc obtained by a GNN trained on clinician diagnosis, which was 91.7%.
[101], 2022	miRNA–disease association prediction	IMCMDA	miRNA-disease	5430 miRNA–disease associations	Proposed (HLGNN-MDA).	The proposed (HLGNN-MDA) achieved promising performance in multiple metrics.
[102], 2021	Brain graph super-resolution	Connectomic	Brain and behavioral	277 subjects	Proposed AGSR-Net framework	The proposed AGSR-Net framework out- performed its variants for predicting high-resolution functional brain graphs from low-resolution ones.
[54], 2019	Ad and mci diagnosis	ADNI-2 cohort, ADNI-1 cohort	MRI scans	3089, and 3602	Graph-CNN	Find-tuned graph-CNN achieved promising CN vs. AD classification accuracy of 89.4%.
[103], 2020	Electronic health records	MIMIC-III	Health records	46,520 patients	Proposed (HSGNN)	HSGNN outperforms other baselines in the diagnosis prediction task.
[104], 2022	Prediction of drug-drug interaction	DDI	Drug records	1935 drugs and 589827 annotated drug-drug interactions	Proposed a novel method of GNN-DDI	The GNN-DDI model achieved an auc of 93.6% and a recall of 92%.
[105], 2023	Predicting emerging health risks	Collected	Behavioral pattern information, chronic disease patients' disease information, and mental health information	189 persons	Proposed GNN-based multi-context mining	The proposed GNN-based multi-context mining approach achieved a mse of 1% and a recall of 77.1%.
[106], 2020	Medical treatment migration prediction	Collected	Medical insurance	1000 patients	Proposed (Event-involved GCN (EGCN)), LSTM, GCN, R-GCN, GCN-ED, KGCN-sum, PinSage	The proposed EGCN achieved an accuracy of 82%.
[107], 2021	Drug relocation model	Drug–disease association	Real	Fdataset (drugs 593), Cdataset (drugs 663)	Proposed (HSSIGNN)	The proposed HSSIGNN achieved an area under the curve auc of 85%.
[108], 2022	Lung cancer knowledge classification	Hallmarks_of_cancer,wos_lung_cancer , lung_cancer_2	Documents			The combination of GCNConv and proposed PMI_2 + link method has achieved best performance.

TABLE 2. *(Continued.)* **Summary of healthcare-related studies in GNN.**

		016_2017, lung_cancer_2 018_2019, lung_cancer_2 020_2021		Article (1852,14170,3378,46 45,6147)	Proposed (PMI_2 + link method)	
[109], 2020	Document-level medical relation extraction	CDR, CHR	Documents	CDR (500 abstracts), CHR (7298 Pub-Med abstracts)	Proposed (SKEoG)	SKEoG achieves 70.7, 91.4 of F1-score on the CDR dataset and on the CHR dataset.
[110], 2020	Next-period prescription prediction	MIMIC-III	Medical	7121 patients	Proposed (RGNN)	For next-period prescription prediction proposed method is effective, and GNN and RNN are complementary mutually.
[111], 2021	Predicting chronic diseases	CBHS	CVD, CPD	1305 patients, and 528 patients	LR, SVM, RF, ANN, GCN, GAT, and proposed GNN	The proposed GNN model with attention mechanisms achieves an accuracy of 93.49% for CVD and 89.15% for CPD.
[112], 2021	Grading of colorectal cancer histology images	CRC, Extended (CRC), CoNSeP	Image	CRC (139 images), Extended CRC (300 images), CoNSeP (41 H&E stained images)	Proposed (HAT-Net)	The accuracy of propose HAT-Net for CRC and Extended CRC was 98.55% and 95.33%, respectively.
[113], 2021	Hierarchical medical entity embedding for healthcare applications	IQVIA dataset, eICU	Documents	119852 patients	Proposed ME2Vec	ME2Vec can improve downstream performance and interpretability as a general-purpose representation learning approach for EHR data.
[114], 2022	Lncrna-disease association prediction	lncRNA-disease association prediction	lncRNA-miRNA	2697 lncRNA disease associations, and 1002 lncRNA-miRNA	Proposed (HGNNLDA)	HGNNLDA has better prediction performance compared with five state-of-art rediction models, auc and aupr 97.86% and 88.91%, respectively.
[115], 2022	Hinsage learning from electronic medical records	EMR	Medical entities and relationships	53841 patients	RF, ANN, HinSAGE, and LR	The AUROC of HinSAGE was 95%.
[116], 2021	Diagnosis of Alzheimer's disease	TADPOLE	Multiple time point records and multimodal features	CN (N=413), MCI (N=865), AD (N=337) sMCI (N=315, pMCI (N=236)	Proposed (AMGNN)	The proposed (AMGNN) model provides accuracies of 94.44% and 87.50%.
[57], 2020	Disease prediction	EMR	Clinical	806 patients	GAT, GIN, and proposed	The proposed model can effectively generate embeddings and infer the embeddings for a new patient based on the symptoms reported to prediction on both rare and general diseases.
[117], 2022	Classification of chronic kidney disease	CK disease data	People	400 instances, 76 parameters, and 25 attributes	Proposed (GNN-DQL)	The proposed (GNN-DQL) classification accuracy of 99.93%.
[118], 2019	Predicting disease outcomes	TADPOLE	Disease	779 subjects	Linear SVM, MLP, RF, and MG-RGCNN	MG-RGCNN achieved an auc of 73.94%.
[119], 2022	Classification of Alzheimer's disease	EEG	EEG	20 AD patients	CNN, GNN, MLP, SVM-AM, and SVM-NS	The GNN achieved auc of 0.984 and 92% accuracy, whereas CNN has auc of 0.924 and 84.7% accuracy.
[120], 2020	Medication recommendation	MIMIC-III	Health	28936 patients single visit, and 6350 patients multi-visit	LR, LEAP, RETAIN, GAMENET, G-BERT, and GATE	The GATE model demonstrated significant performance with a Jaccard similarity of 47.42%, a PR with an auc of 70.87%, and an F1-score of 63.15%.
[121], 2022	Medical knowledge graph reasoning	Graph-structured	Cora and Citeseer, EMRNet	Citeseer (nodes 3327, edges 4732), EMRNet (nodels 4046, edges 19581)	GTGAT, LR, SVM, MLP, and TGAT	GTGAT surpasses the competing methods for personalized disease diagnosis.
[122], 2022	Chinese medical text classification	Chinese medical	Drugs, DA, RC, EM	Drugs (classes 88), DA (classes 42), RC (classes 24), and EM (classes 36)	Proposed (ConKGNN)	The proposed (ConKGNN) can serve as an efficient medical text classifier with excellent performance.
[123], 2022	Chinese medical named entity recognition	CCKS2017, CCKS2019	EMRs	CCKS2017 (13740 anatomy, 10142 Symptom, 1275 disease, 12689 exam, 1513 treatment), and CCKS2019 (1933 anatomy, 719	BiLSTM-CRF, Lattice LSTM, BERT-BiL STM-CRF, proposed	The proposed model exhibited impressive precision of 91.44% and recall of 92.30% for CCKS2017, as well as precision of 85.11% and recall of 86.74% for CCKS2019,

TABLE 2. ***(Continued.)*** **Summary of healthcare-related studies in GNN.**

				medicine, 2798 disease, 511 exam, 905 operation, 313 check)		
[124], 2022	CT segmentation	KiTS19 Challenge	CT images	210 patient studies	Proposed	The proposed model improved the segmentation of objects from adjacent tissues.
[125], 2023	Protein−ligand binding affinities from 3d structures	CSAR-HiQ	No name mentioned	13285 complexes	GIGN, PotentialNet, GNN-DTI, IGN, SchNet, and GNN	On three external test sets GIGN achieves state-of-the-art performance
[126], 2023	Classification of brain disorders	ABIDE, ADNI	rs-fMRI and non-imaging	871 samples, and 134 subjects	Proposesd (LG-GNN)	Proposed (LG-GNN) achieves highest performance in various evaluation metrics.
[127], 2022	Multifrequency electrical impedance tomography	Edinburgh mfEIT	Frequencies	4 × 8700 samples	M-STGNN	The M-STGNN achieved 10.7% improvement under the experimental setup.
[128], 2015	Predicting drug-target interactions	DTI-HN	Heterogeneous network	Total nodes (12015), and total edge types (4670850)	Proposed (DSG-DTI)	The proposed approach predicts drug-target interactions and can generalize to newly registered medicines and targets with minor performance degradation, exceeding other baselines.
[129], 2023	Cancer prognosis prediction and analysis	TCGA	Multiomics, mRNA, CNV, and DNA methylation	15 features, and sample 5350	Proposed (LAGProg), GCN	C-index values has been improved by 8.5% using LAGProg the other GNN method.
[130], 2020	Early diagnosis of pancreatic cancer	Collected	CT	936 pancreatic cancer cases, and 760 non-pancreatic cancer cases	Proposed method	The proposed method provides a valuable clinical tool for the early diagnosis of pancreatic cancer.
[131], 2022	Administrative medical	Collected	Medical	4639 diseases	Proposed	Novel GNN methods improve comorbidity identification using administrative medical datasets, surpassing statistical approaches.
[132], 2022	Super pixel-based brain tissue segmentation	Brainweb,MR BrainS ,iSeg-2019, IBSR	MRI	Brainweb (370 slices), MRBrainS (135 slices), iSeg-2019 (500 slices), and IBSR (1440 slices)	Proposed (GNN-SEG)	The proposed (GNN-SEG) has better segmentation performance than state-of-the-art CNN-based methods on four brain MRI datasets.
[133], 2021	Classification of Covid-19	SARS-COV-2 Ct-Scan Data set	CT images	1252 Covid -19 CT images, and 1230 non- Covid -19 CT scans	Proposed (NAGNN)	The proposed NAGNN achieved 99.29% of average accuracy on private data set and on the public SARS-COV-2 Ct-Scan Data set. achieved 97.86% average accuracy.
[134], 2022	Robust medicine recommendation	MIMIC-III	Patient	50000 patients	Proposed (KDGN)	KDGN outperforms the state-of-the-art model in 4 out of 5 evaluation metrics.
[135], 2022	Pancreatic cystic neoplasm classification	Collected	CT	No number mentioned	Proposed GNN-based model	The proposed GNN-based model shows good performance on the two tasks with accuracies of 88.926% and 74.497%.
[136], 2021	Secure and private IoMT	CE-MRI, public MRI	MRI	CE-MRI (233 patients), Kaggle (3264 brain MRI images)	Proposed (MRCG)	The proposed MRCG can achieve 88.64% mAP and 86.59% mAP, respectively.
[137], 2022	Predicting soft tissue deformation in image-guided neurosurgery	Healthy tissue, tumour tissue	Tissue	9118 node	Proposed (PhysGNN)	The proposed PhysGNN, promises accurate and fast soft tissue deformation approximations while promising enhanced computational feasibility, therefore suitable for neurosurgical settings.
[138], 2022	Diagnosis and prediction of Covid-19 severity	Collected	CT scans	1687 chest CT scan images	Proposed (SAGNN)	The proposed method achieves 86.86% in terms of auc and regression of 58% in terms of the correlation coefficient.

Furthermore, GNN contributes to multi-site autism spectrum disorder identification [141], interpretable Parkinson's disease classification [142], and the integration of geometric features for cancer prognosis [143]. Additionally, GNN plays a crucial role in creating a multi-model fusion framework for Alzheimer's disease prediction [144], effectively aggregating information from different populations and achieving superior predictive performance.

Antibodies are essential to the human immune system, and the co-design of antibody sequence structure involves identifying amino acid sequences and their corresponding three-dimensional structures that can effectively target and bind to specific antigens [83]. This process has significant potential for developing new treatments for various diseases, including cancer and infectious diseases. GNN has been utilized for antibody sequence-structure co-design, allowing for more efficient and effective identification of optimal sequences and structures. One significant advantage of using GNN for antibody sequence-structure co-design is that it can incorporate a wide range of data types, including genetic, biophysical, and clinical data. This can help researchers identify the most promising antibody candidates for further development and testing. GNN can also be used to optimize existing antibodies, improving their efficacy and reducing side effects [67].

GNN has demonstrated great potential in various aspects of cancer research. GNN-based approaches can identify potential cancer genes and their associated biological pathways [85]. Another area of cancer research is where, by analyzing gene expression data, GNN can identify patterns of gene expression that are associated with specific cancer subtypes and classify molecular subtypes of cancer. GNN has also been utilized in predicting the deregulation types of miRNA-disease associations and providing insights into the molecular mechanisms underlying disease development [99], [101]. Moreover, GNN has been applied to predict potential molecular interactions and identify new drug targets for various diseases, which can help accelerate drug discovery and lead to the development of more effective treatments [73], [74], [75], [76], [77].

In addition to the applications of GNN mentioned earlier, there are several other applications of GNN in healthcare. GNN can be used to analyze medical images such as X-rays, CT scans, and MRI scans to identify potential abnormalities or diseases [124]. Another application of GNN in healthcare is structure and position awareness for airway labeling [69]. GNN can also be used for context-aware self-supervised learning for medical images. This involves using GNN to analyze medical images and learn from the context of the images without the need for explicit labeling or supervision [70]. GNN can be used to improve the temporal resolution of fMRI data and help better understand brain function [71]. GNN can be used to analyze brain networks and identify potential biomarkers for psychiatric disorders [72], [102]. Overall, the main applications of GNN in healthcare involve analyzing healthcare data to identify patterns and relationships that can improve diagnosis and treatment, address specific healthcare challenges, and improve patient outcomes.

- RQ2. How do the specific structural characteristics of complex healthcare graphs and the diverse types of healthcare data integrated with GNN impact the effectiveness and practicality of GNN in extracting crucial insights and identifying meaningful patterns in healthcare data?

The integration of GNN with healthcare graphs that contain diverse types of data has the potential to improve the effectiveness and practicality of GNN in extracting crucial insights and identifying meaningful patterns in healthcare data.

The effectiveness and practicality of GNN in healthcare data analysis depend on the structural characteristics of the healthcare graphs used as input. Healthcare graphs can be highly complex, containing thousands of nodes and edges, and may be heterogeneous in nature, with different types of nodes and edges representing different healthcare concepts [83]. Moreover, healthcare graphs can be dynamic, with the relationships between nodes and edges changing over time. To address these challenges, GNN enables the propagation of information through the graph, capturing the relationships between nodes and edges and generating representations that capture the underlying structure of the healthcare data [83], [128].

Healthcare graphs may contain missing or incomplete data and contain noise or outliers, which can impact the ability of GNN to identify meaningful patterns and impact accuracy and generalizability. To address these challenges, several techniques have been proposed, such as imputation methods for missing data and outlier detection methods for noisy data. Chen et al. introduce the learnable graph convolutional network and feature fusion (LGCN-FF), addressing the limited exploration of discriminative node relationships and graph information in multi-view data. Their proposed framework, validated through superior performance in multi-view semi-supervised classification, integrates feature fusion and a learnable graph convolutional network. Chen et al.'s work highlights the importance of simultaneous consideration of both feature and graph fusion for enhanced learning accuracy [145]. Chen et al. [146] tackle the over-smoothing issue in graph convolutional networks by presenting an alternating graph-regularized neural network (AGNN). This model leverages a graph embedding layer derived from graph-regularized optimization to alleviate over-smoothing problems, and an Adaboost strategy is employed to aggregate outputs from distinct layers, demonstrating superior performance compared to existing models [146]. Li et al. [147] focus on the challenging problem of incomplete multi-view clustering (MVC), proposing graph structure refining for incomplete MVC (GSRIMC). GSRIMC avoids feature recovery steps and effectively handles biased error separation using tensor nuclear norm, achieving superior clustering results without accumulating mistakes during optimization [147]. Finally, Wu et al. [148] address the vulnerability of GNN to noise and adversarial attacks. Their proposed robust tensor graph convolutional network (RT-GCN) utilizes multi-view augmentation and a tensor GCN framework to enhance robustness, showcasing superiority over state-of-the-art models in resisting diverse adversarial attacks on graphs [148].

Healthcare data is incredibly diverse and includes various types of data, each with unique characteristics and complexities that require specialized methods for processing and analysis. Integrating these different data types is also essential for a comprehensive view of a patient's health status. Many methods are designed to integrate different types of healthcare data and capture their relationships, generating representations that capture the underlying structure of the data. Imaging data can be combined with clinical data to predict the likelihood of a particular disease. The capability of GNN to handle multiple modalities of healthcare data has been demonstrated in various applications, including patient outcome prediction, disease classification, and drug discovery. For instance, in patient outcome prediction, MMGNN can integrate clinical, imaging, and genomic data to develop models that accurately predict patients' health outcomes.

However, integrating diverse types of healthcare data can also impact the effectiveness and practicality of GNN. The integration of high-dimensional imaging data with clinical data can increase the computational complexity of GNN, making it less practical for real-world applications. Additionally, integrating diverse data types may require specialized preprocessing techniques, such as feature extraction methods, to ensure that the data is compatible with GNN. To address described challenges, various techniques have been proposed, such as dimensionality reduction methods for high-dimensional data and data augmentation methods for data compatibility. These include imputation methods for missing data, regularization techniques to prevent overfitting, and attention mechanisms to handle the heterogeneous nature of healthcare data. To address the overfitting issue, regularization techniques such as L1 and L2 regularization can be used to penalize complex models and encourage simpler ones [135]. Attention mechanisms are used to handle the heterogeneous nature of healthcare data, which can include various types of data such as images, text, and numerical data.

- RQ3. What is the comparative effectiveness of GNN versus traditional ML methods in healthcare-based applications, and what evidence supports the potential of GNN in improving decision-making and patient outcomes in healthcare?

GNN in healthcare-based applications has the ability to handle complex data structures. GNN has garnered substantial interest and demonstrated prowess in healthcare applications, particularly in disease prediction and drug discovery. Compared to traditional ML methods, GNN offers several key advantages. However, the dynamic landscape of data analytics in healthcare introduces a spectrum of methodologies beyond GNN. Other tools, algorithms, and hybrid approaches exist that can also effectively extract complex healthcare data dependencies and relationships. It is essential to convey that the highlighted GNN applications showcase promising avenues, yet the field remains open to continued exploration and innovation. Recognizing the diversity of available tools ensures a comprehensive understanding of the broader possibilities for unraveling intricate healthcare data, thereby fostering a holistic approach to advancing diagnostic and therapeutic strategies. Traditional ML methods usually rely on tabular data structures, where data is organized in rows and columns [149]. However, healthcare data is often complex and heterogeneous, comprising different data types such as images, time series, text, and graphs. GNN, on the other hand, can handle these complex data structures effectively [150]. GNN can process graph-structured data, which is well-suited to representing complex relationships between entities in healthcare data. GNN can also be used for image and text-based healthcare data, where it can capture spatial and semantic relationships between different parts of the data [149].

Another advantage of using GNN in healthcare-based applications is its ability to handle incomplete data. Traditional ML methods struggle to deal with such data and often require complete data to make accurate predictions [149]. However, GNN can handle incomplete data and still make accurate predictions, as it can learn from the available information and fill in the gaps to create a complete picture of the data. GNN can also handle noisy data by identifying and filtering out irrelevant or erroneous data points. GNN can help fill the gaps and provide more accurate predictions and insights, ultimately improving decision-making and patient outcomes [151].

Furthermore, GNN has the ability to learn from multiple modalities, which is one of the key advantages of using GNN in healthcare-based applications compared to traditional ML methods [152]. GNN can integrate information from different modalities by constructing a graph that captures their relationships. In medical imaging, GNN can learn from the spatial and temporal relationships between different regions of interest within an image. In clinical notes, GNN can learn from the semantic relationships between medical concepts and conditions mentioned in the notes. In genomics, GNN can learn from the relationships between different genes and their expression levels, enabling better decision-making and improved patient outcomes [153].

GNN has the ability to capture temporal dependencies, which allows GNN to learn patterns of change and relationships over time that are difficult for traditional ML methods to capture. Temporal dependencies here refer to the relationship between events that occur over time. In predicting patient outcomes, GNN can capture how the patient's condition changes over time and how these changes relate to other variables to make accurate predictions about the patient's future outcomes [154]. Although GNN can effectively capture complex relationships and patterns within data, understanding how these models arrive at their predictions can be challenging. This lack of interpretability can be problematic in healthcare, where decisions made based on AI models must be explainable to healthcare providers and patients. While some methods for interpreting GNN exist, they can be complex and computationally intensive, which may limit their practical usefulness.

GNN can capture complex relationships between various factors, such as clinical variables, genetic information, and lifestyle factors, which can help healthcare professionals make more accurate and personalized predictions about patient outcomes. GNN can also be used to improve treatment outcomes by identifying optimal treatment plans and predicting treatment responses. GNN can extract features from images and use them to identify patterns and anomalies that are not easily visible to the human eye. This can help radiologists and other medical professionals make more accurate and timely diagnoses, leading to improved patient outcomes [43], [48], [155]. Overall, the evidence supports the effectiveness of GNN in healthcare-based applications, and GNN is likely to play an increasingly important role in the future of healthcare [156], [157].

- RQ4. What are the key determinants influencing the performance of GNN, and what are the limitations of the current GNN application?

GNN has emerged as a powerful framework for analyzing and modeling complex relationships within graph-structured data. However, the performance of GNN is influenced by several factors that impact its effectiveness and accuracy.

One of the key determinants of GNN performance is architectural design [74], [82], [88]. The design choices made in constructing the GNN, such as the node and edge representations, aggregation mechanisms, and message-passing strategies, can significantly affect its performance [60], [85], [121]. Different design configurations may have varying abilities to capture and propagate information through the graph, resulting in variations in performance. Understanding the impact of architectural design choices is essential for optimizing GNN models and improving their performance.

Another determinant that influences GNN performance is the selection and tuning of hyperparameters. Hyperparameters, such as the learning rate, number of layers, and regularization techniques, play a crucial role in determining the behavior and performance of GNN. These parameters need to be carefully selected and fine-tuned to ensure optimal performance [117]. The choice of hyperparameters can impact the model's ability to generalize, avoid overfitting, and converge to a suitable solution.

The quality and characteristics of the input graph data also significantly affect GNN performance. Factors such as the size of the graph, its sparsity, noise level, and structural properties can all influence how well the GNN can capture and utilize the underlying patterns and dependencies in the data [121]. Understanding the impact of data characteristics on GNN performance is essential for preprocessing and preparing the input data, ensuring that the GNN can effectively learn from the available information.

The nature of the specific application or domain plays a significant role in influencing the performance of GNN in the healthcare domain. Healthcare data is characterized by its complexity, diversity, and interconnectedness, which necessitates careful consideration when applying GNN to healthcare-related tasks. In clinical decision support systems, GNN can be employed to analyze patient data. However, the nature of clinical data, including its high dimensionality, heterogeneity, and temporal dependencies, poses challenges for GNN. The nature of disease data also impacts the performance of GNN in disease prediction tasks [73]. The nature of molecular data, including its structural complexity, chemical interactions, and vast search space, poses unique challenges for GNN [58], [92]. Developing GNN architectures that can effectively capture molecular features, learn from chemical graphs, and facilitate efficient exploration of the chemical space is crucial for improving the success rate and efficiency of drug discovery processes.

GNN in healthcare-based applications has the limitation of interpretability. While GNN can effectively capture complex relationships and patterns within data, understanding how these models arrive at their predictions can be challenging. Furthermore, GNN in healthcare-based applications has limited scalability. As the size of the graph increases, the number of edges between nodes increases exponentially, which can result in significant computational challenges. To address this limitation, researchers have explored techniques such as transfer learning, feature extraction, dimension reduction, ensemble methods, etc.

- RQ5. How can GNN be utilized for the discovery and identification of rare disease subtypes or novel disease clusters while enabling interpretability and explain ability, which allows healthcare professionals to understand and trust the predictions and insights provided by these models?

GNN has shown great potential for discovering and identifying rare disease subtypes or novel disease clusters. Rare diseases can be challenging to diagnose due to their diverse symptoms and a lack of understanding of the underlying genetic mutations that cause them [75]. GNN can analyze large and complex datasets of patient records, genetic data, and other clinical information to identify patterns and relationships of rare disease subtypes or novel diseases that may not be immediately evident to human researchers. In addition to identifying rare disease subtypes, GNN can also help identify novel disease clusters by analyzing various types of data. For instance, healthcare professionals can use GNN to analyze EHR to identify clusters of patients with similar disease patterns, such as comorbidities, symptoms, or lab results [77]. GNN can also be used to identify environmental or social factors that contribute to the emergence of specific disease clusters. GNN can also analyze large-scale genomic data to identify novel genetic mutations and biomarkers associated with specific disease clusters. This can facilitate the development of targeted therapies that are tailored to specific patient groups, improving treatment outcomes and reducing healthcare costs. GNN can also be used to predict the progression of certain diseases and assess the effectiveness of treatment interventions [96]. By analyzing patient data over time, GNN can identify patterns and relationships that can inform the development of personalized treatment plans and help healthcare professionals make better-informed decisions [97].

In addition to identifying rare disease subtypes and clusters, GNN can also help healthcare professionals identify the geographic locations of these diseases. GNN can identify areas with higher prevalence rates of certain rare diseases by analyzing patient data and demographic information. This can help healthcare professionals pinpoint the specific regions where the disease is most prevalent and identify potential environmental or genetic factors that may be contributing to the disease's incidence. Furthermore, GNN can also aid in the development of new drugs for those diseases [74], [128]. By analyzing large genetic and chemical data datasets, GNN can identify patterns and relationships between disease subtypes and potential drug targets. This can lead to the development of targeted drugs for rare disease subtypes, improving patient treatment options. GNN can also be used to predict the efficacy of different drugs and drug combinations, reducing the time and cost required to bring new drugs to market.

GNN can provide interpretability by using attention mechanisms, which allow the model to identify which parts of the input data are most relevant to its predictions. By identifying the most relevant data, GNN can provide healthcare professionals with a clearer understanding of how the model is making its predictions and allow them to make more informed decisions about patient care. GNN can use graph visualization techniques to show the relationships between different data points and how they contribute to the model's predictions, which can help healthcare professionals understand the reasoning behind the model's predictions [97]. By enabling healthcare professionals to understand how the model works and the reasoning behind its predictions, GNN can help bridge the gap between data-driven decision-making and clinical expertise. Additionally, GNN can be used to predict patient outcomes and identify potential interventions, such as drug therapies or surgical procedures, allowing healthcare professionals to make more informed decisions about patient care. Several studies in the domain of GNN architectures have embraced open-source practices by providing their code for public access. Notable examples include studies such as [53], [57], [69], [73], [82], [83], [85], [86], [87], [88], [92], [94], [95], [99], [100], [101], [102], [103], [104], [113], [116], [122], [125], and [134]. The decision to share code openly offers significant advantages in promoting transparency, collaboration, and reproducibility in scientific research. Open-source code allows fellow researchers and practitioners to scrutinize, validate, and build upon the proposed architectures, fostering a culture of trust and credibility within the scientific community. Additionally, it facilitates the dissemination of knowledge, enabling a wider audience to benefit from and contribute to advancements in GNN research for healthcare applications. Open-source practices also promote the rapid development of the field by encouraging the adoption of proven methodologies and fostering a collaborative environment for innovation and improvement.

IV. CHALLENGES AND FUTURE RESEARCH OPPORTUNITIES

This section outlines the current challenges that researchers encounter when implementing GNN in various healthcare-related applications. In addition, the prospective research opportunities and directions for researchers conducting healthcare-related research on the GNN are highlighted.

A. CHALLENGES

1. **Heterogeneous data integration:** Heterogeneous data integration in GNN involves combining diverse data types, formats, and sources, posing challenges in seamlessly merging and representing such data in a unified graph structure. Researchers sometimes face difficulties in handling varying data modalities, addressing data sparsity, and dealing with semantic differences between heterogeneous data elements, leading to suboptimal model performance.
2. **Interpreting GNN predictions:** Interpreting GNN predictions challenges involves determining the feature importance, attributing predictions to specific nodes or edges in the graph, and explaining GNN's behavior in complex graph-structured data. The nature of GNN can make it difficult to gain insights into the reasoning behind model's predictions, which may hinder GNN adoption in critical applications.
3. **Scalability for healthcare graphs:** Scalability for healthcare graphs refers to efficiently handling and processing large-scale, complex graph-structured data, such as electronic health records and patient networks. Researchers may encounter challenges in dealing with the complexity of healthcare graphs, leading to increased computational demands, storage requirements, and slower processing times, which can hinder real-time analysis and decision-making.
4. **Limited labeled data:** Limited labeled data refers to situations where there is a scarcity of annotated samples available for training GNN. Researchers often encounter challenges in achieving robust and accurate model performance due to insufficient training data, leading to overfitting and reduced generalization.
5. **Generalization of GNN:** Generalization across various healthcare-based applications of GNNs refers to the ability of GNN models to perform well on new, unseen data from different healthcare-subject than the one they were trained on. Researchers often encounter challenges in adapting GNN models to diverse subjects with varying data distributions, as the model may fail to generalize and yield suboptimal performance on new data.
6. **Ethical GNN applications:** Ethical GNN applications refer to responsibly deploying GNN while ensuring fairness, transparency, and avoiding biased outcomes. Researchers may encounter challenges in unintentionally perpetuating biases present in the data, leading to unfair or discriminatory predictions, and the lack of interpretability of GNN models may raise ethical concerns regarding their decision-making process. Addressing this challenge involves adopting fairness-aware methods, auditing, and mitigating bias in the data.
7. **Handling missing data:** Researchers often encounter challenges in effectively imputing missing values while preserving the graph structure and relationships, and improper handling of missing data may result in suboptimal model performance and skewed insights. Addressing this challenge may involves employing appropriate imputation techniques, to fill in missing values and retain the integrity and representativeness of the data for meaningful analyses and decision-making.
8. **Bias in GNN predictions:** Bias in GNN predictions can cause systematic errors or favoritism towards

specific groups or attributes in the data, leading to unfair and discriminatory outcomes. Researchers may fall into this problem when the training data is unrepresentative or contains biased information, and the GNN model learns and amplifies these biases during training, which may result in skewed predictions.

B. FUTURE RESEARCH OPPORTUNITIES

1. **Transfer learning in healthcare**: Researchers can explore novel GNN architectures, domain adaptation techniques, and transfer learning strategies that effectively adapt pre-trained models to new medical domains while preserving data privacy and ethical considerations. By collaborating with healthcare institutions and adopting multi-modal patient data, researchers can pave the way for more efficient and accurate GNN-based transfer learning approaches in a variety of healthcare applications.
2. **Personalized medicine applications**: Personalized medicine applications involve tailoring medical treatments and interventions to individual patients based on their unique characteristics and needs. Researchers can explore innovative GNN architectures that efficiently integrate multi-modal patient data, such as genomics, imaging, and clinical records, to create personalized predictive models for disease diagnosis, treatment response prediction, and patient risk stratification.
3. **Federated learning for privacy:** Federated learning for privacy involves training GNN models across decentralized data sources without sharing raw patient data, preserving data privacy and security. Researchers can explore advanced encryption and secure aggregation techniques tailored for GNN, ensuring privacy-preserving collaborative model training while maintaining model accuracy.
4. **Real-time clinical decision support:** Future research should focus on developing advanced AI and customized GNN algorithms and data stream processing techniques to enable real-time analysis of patient data from various sources, empowering healthcare professionals with actionable information at the point of care.
5. **Explainable GNN models:** Explainable GNN models involve developing techniques to provide interpretable and transparent insights into GNN predictions and decision-making processes. Future research should focus on exploring attention mechanisms, feature attribution methods, and visualization techniques to improve the interpretability of GNN models.
6. **Class imbalance in medical datasets:** Class imbalance in medical datasets refers to the unequal distribution of different classes in the data, leading to biased and inaccurate model performance. Researchers should focus on developing innovative techniques, to mitigate the impact of class imbalance and improve the generalization and fairness of models in medical applications.
7. **GNN for drug discovery and clinical trials:** GNN for drug discovery and clinical trials involves GNN architectures, graph representation learning techniques, and large-scale molecular graph datasets to enhance GNNs' accuracy and efficiency in drug discovery and to predict molecular properties, optimize drug candidates, and accelerate the drug development process.
8. **Disease progression modeling:** Future research should focus on developing innovative GNN architectures, incorporating longitudinal patient data and spatiotemporal graph structures, to enhance disease progression predictions and enable early detection and personalized treatment strategies.
9. **Graph-based patient clustering:** GNN for graph-based patient clustering involves grouping patients based on shared medical features and treatment responses. In this area, researchers should focus on developing novel GNN-based clustering algorithms, incorporating multi-modal patient data, and leveraging graph structures to enhance clustering accuracy and interpretability.
10. **GNN for rare diseases:** GNN for rare diseases involves using it to aid in early diagnosis, phenotype prediction, and therapeutic target identification for rare and underrepresented medical conditions. Researchers should focus on building comprehensive rare disease datasets, developing specialized GNN architectures, and exploring transfer learning and multi-task learning approaches to optimize model performance for limited and imbalanced data.
11. **Human activity monitoring:** Human activity monitoring involves utilizing GNN to analyze data from wearable sensors and IoT devices, tracking and interpreting human movements and behavior. Researchers should focus on developing GNN-based models that efficiently process and interpret sensor data, enabling real-time activity recognition and continuous patient monitoring.
12. **GNN for clinical decision-making:** GNN for clinical decision-making involves integrating into decision support systems to assist healthcare professionals in making evidence-based and timely clinical decisions. Researchers should focus on developing interpretable GNN architectures, incorporating heterogeneous patient data and medical knowledge graphs, to enhance the accuracy and transparency of GNN-based predictions.

V. CONCLUSION

This systematic review provides a comprehensive analysis of GNN in healthcare-based applications. The methodological procedure involved a systematic search and selection process, which resulted in a robust set of studies representing diverse healthcare-based GNN applications. The review encompasses a total of 86 studies that met rigorous inclusion criteria, ensuring a reliable body of evidence for analysis.

The review covers a wide range of applications, including clinical decision support, disease prediction, drug discovery, patient monitoring, and healthcare network analysis. This breadth of coverage demonstrates the versatility and potential of GNN in addressing various healthcare challenges. China, the United States, and Turkey emerged as prominent contributors to the field, showcasing their commitment to advancing GNN research in healthcare. The continuously increasing number of studies from 2015 to 2022 highlights the significance of GNN as a cutting-edge research area. The research questions posed in this study, which explores the application of GNN in healthcare-based applications, are effectively addressed through the systematic review and analysis of the included studies. By examining the healthcare domains and their specific applications of GNN, this study provides valuable insights into the potential of GNN in improving clinical decision-making, enhancing disease prediction accuracy, facilitating drug discovery, enabling patient monitoring, and optimizing healthcare network analysis. The systemic analysis provides valuable insights into the architectures, models, and purposes of the included studies. Furthermore, numerous obstacles have been identified that impede researchers in the healthcare domain when studying GNN, such as the interpretability of GNN models in healthcare applications, which remains a challenge due to their complex and opaque nature. Moreover, the limited availability of benchmark datasets and standardized evaluation metrics for GNN in healthcare poses challenges in assessing and comparing the performance of different models. Despite the comprehensive nature of this study, there are certain limitations that should be acknowledged. The inclusion of studies was restricted to those published in English, potentially excluding relevant research in other languages. Furthermore, it is possible that there are studies that have not been identified using the search keyword employed. Additionally, during the data extraction process, we may have overlooked some pertinent information.

Looking ahead, future research directions might focus on analyzing and summarizing the GNN architectures for specific healthcare tasks, enhancing the interpretability and explain ability of GNN models, addressing privacy and security concerns, and exploring the potential of federated learning approaches in healthcare. In addition, analyzing GNN research can help identify factors that influence the performance of GNN in the healthcare domain, which can revolutionize healthcare delivery, enhance patient outcomes, and promote innovation.

ABBREVIATIONS

Short form	Full form
GGP	Gated graph propagator.
FMRI	Functional magnetic resonance imaging.
HIV	Human immunodeficiency virus infection.
BP	Bipolar disorder.
SABDAB	Structural antibody database.
CDR	Complementarity-determining region.
ABIDE	Autism brain imaging data exchange.
EMGNN	Explainable multilayer graph neural network.
BRCA	Breast invasive carcinoma.
MGNN	Multimodal graph neural network.
MHDP	Multi-relational hyperbolic diagnosis predictor.
MA-ARMA	Multi-activations autoregressive moving average.
GNEA	Graph neural network with elm aggregator.
HN	Heterogeneous network.
CREATDA	Credibility-encoding graph neural network for tda prediction.
SGNNMD	Signed graph neural network method.
MP-GNN	Multi-physical graph neural network.
TOPOGAN	Topology-aware graph gan architecture.
GNDP	Graph neural network-based diagnosis prediction.
EEG	Electroencephalograph.
AMGNN	Auto-metric graph neural network.
CDR	Chemical-disease relation.
CHR	Chemical reactions.
RGNN	Hybrid method of rnn and gnn.
CVD	Cardiovascular disease.
CPD	Chronic pulmonary disease.
CRC	Colorectal cancer.
EXTENDED CRC	Extended colorectal cancer.
HAT-NET	Hierarchical transformer graph neural network.
CONSEP	Colorectal nuclear segmentation, and phenotyps.
AMGNN	Auto-metric gnn.
GNN-DQL	Graph neural network-based deep q learning.
GTGAT	Gated tree-based graph attention network.
CONKGNN	Contrastive knowledge integrated graph neural networks.
RW	Random walk.
GNN	Graph neural network.
GIGN	Geometric interaction graph neural network.
LG-GNN	Local-to-global graph neural network.
M-STGNN	Mask-guided spatial-temporal graph neural network.
DTI-HN	Drug-target interaction heterogeneous network.

LAGPROG	Local augmented graph convolutional network.
NHIRD	National health insurance research database.
ADNI	Alzheimer's disease neuroimaging initiative.
HLGNN	Heuristic learning based on graph neural networks.
MDA	Microrna–disease associations.
HSGNN	Heterogeneous similarity graph neural network.
EGCN	Event-involved gcn.
HSSIGNN	Hybrid similarity side information powered graph neural network.
MLP	Multilayer perceptron.
NAGNN	Neighboring aware graph neural network.
ICU	Intensive care unit.
KDGN	Knowledge-enhanced dual graph neural network.
PHYSGNN	Physics–driven graph neural network.
SAGNN	Structural attention graph neural network.
RF	Random forest.

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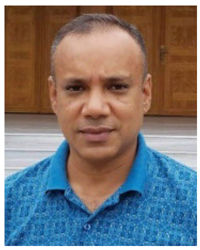

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