

## REVIEW

# Application of graph theory in liver research: A review

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## Abstract

Graph theory has emerged as a valuable tool in liver research, aiding in the assessment of complex interactions underlying liver diseases at different organizational levels. This has allowed significant advancements in the detection, treatment, and control of liver disorders. Particularly, graph theory is useful in identifying different liver diseases. Graph theory can be used to analyze liver networks and identify altered nodes and edges, which may serve as potential noninvasive biomarkers for disease detection. Furthermore, graph-based techniques, including graph neural networks and graph knowledge, have been employed to construct interaction networks, providing insights into the communication involved in focal liver diseases and related conditions such as coronavirus disease 2019 (COVID-19), hepatic muscular atrophy, and hepatic necrosis. Functional networks for the liver have also been developed with graph-based methods, providing insights into the metabolic processes occurring in the liver and the functional organization of the liver. Graph theory is also useful for image analysis, with applications such as image segmentation, registration, synthesis, and object identification. By representing images as graphs, it is possible to analyze and process them with graph-based algorithms, handling complex relationships among pixels and making them useful in boundary extraction and texture analysis. Overall, graph theory is an essential research tool for liver research, providing valuable insights into the complex interactions underlying liver diseases as well as innovative approaches for diagnosis and treatment.

## KEYWORDS

disease, graph knowledge, graph theory, liver, neural network

## Key points

- Graph-based techniques, including graph neural networks and graph knowledge, have been employed to construct interaction networks, providing insights into the communication involved in focal liver diseases and related conditions.
- The study provides examples of how graph theory can be applied to liver research, including the development of functional networks and the use of graph-based algorithms for image analysis.

## 1 | INTRODUCTION

In recent decades, liver diseases have risen to the forefront of global health concerns, constituting a significant burden on healthcare systems and contributing to

millions of deaths annually. Acute hepatitis, cirrhosis, and liver cancer stand as formidable adversaries, collectively responsible for over 4 million deaths in 2020 alone.<sup>1–3</sup> Among these, viral hepatitis emerges as a dominant force, representing a substantial portion,

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ranging from 50% to 90%, of liver disease cases.<sup>4</sup> Chronic liver diseases further compound the issue, affecting a notable 5%–15% of cases worldwide.<sup>5</sup> Moreover, liver cancer, accounting for 3%–10% of total cases, adds another layer of complexity to the already dire situation.<sup>6</sup> Given the gravity of these statistics, liver research has become increasingly dynamic and multifaceted, necessitating innovative approaches to combat these diseases effectively. While various methodologies have been proposed for disease diagnosis, lesion detection, and injury grading, the integration of graph theory emerges as a pivotal and promising avenue in this relentless pursuit of understanding and addressing liver disorders.<sup>7,8</sup> Graph theory offers a versatile framework that can be applied to model complex biological systems, including the intricate network of interactions within the liver. By representing biological entities as nodes and their interactions as edges, graph theory provides a powerful tool for elucidating the underlying mechanisms driving liver diseases. Moreover, graph-based approaches facilitate the analysis of large-scale biological data sets, such as gene expression profiles, protein–protein interactions, and metabolic pathways, enabling researchers to uncover hidden patterns and relationships that may hold critical insights into disease pathogenesis and progression.

Graph theory has gained popularity and has been applied in liver disease research in recent years.<sup>9</sup> Specifically, in the context of liver research, graph theory has proven instrumental in several key areas including network analysis, disease biomarker discovery, drug repurposing and target identification, and patient stratification and prognostication. Network models for liver diseases have been constructed using graph theory, which has helped explore relationships and regulatory mechanisms between imaging and diseases in liver research.<sup>10</sup> For example, graph theory has been used to construct bioinformatics networks for liver diseases, revealing interactions of DNA,<sup>11</sup> RNA,<sup>12</sup> proteins,<sup>13</sup> and metabolites<sup>14</sup> in the liver and their impacts on disease development, which may help better understand the pathogenesis of liver diseases and identify potential risk factors. Moreover, graph theory has been utilized to develop models for diagnosing and predicting many liver diseases, including diffusivity diseases such as hepatitis,<sup>15</sup> fibrosis,<sup>16</sup> and cirrhosis<sup>17</sup>; focal diseases such as liver cancer<sup>18</sup> and other related diseases. Graph theory can learn multimodal patterns and reveal interactions among different disease types, which may improve the accuracy and precision of clinical diagnosis. In addition, graph theory also has multiple applications in image processing. By representing images as graphs, graph-based approaches effectively capture complex spatial and structural relationships among image pixels or regions and enable efficient processing and analysis of images, including image registration, synthesis, and segmentation.<sup>19,20</sup>

However, comprehensive reviews that summarize the specific applications of graph theory in liver research are lacking. This study aimed to provide a thorough overview of the various applications of graph theory in liver research, including the creation of network models for liver diseases, the development of prognostic and

diagnostic models for liver diseases, and the design of programs for image processing in liver diseases. By highlighting the versatility and effectiveness of graph theory in liver research, this study provides significant insights into and recommendations for the prevention and management of liver diseases. These findings have significant implications for advancing the understanding of the underlying mechanisms of liver diseases and for developing novel diagnostic and therapeutic strategies.

## 2 | OVERVIEW OF GRAPH THEORY

Graph theory, a mathematical discipline focused on the study of graphs, has significantly evolved since its inception in 1736. It now encompasses diverse methodologies such as graph topology, knowledge graphs (KGs), graph neural networks (GNNs), and graph cut techniques. These advancements have found critical applications in liver research, offering innovative solutions for complex biological data analysis. For instance, graph topology has been used to map and predict changes in brain structures of patients with cirrhosis, while KGs have facilitated comprehensive data integration for a better understanding of liver diseases and drug interactions. GNNs have improved diagnostic and prognostic evaluations by enabling machine learning models to operate on graph-structured data, and graph cut techniques have enhanced image segmentation for accurate delineation of liver contours and cancer tissues. Visualization techniques further enrich this field by providing clear, interpretable representations of complex relationships in liver disease data. Collectively, these graph theory methods contribute to significant advancements in the diagnosis, treatment, and understanding of liver diseases.

### 2.1 | Graph topology

Graph topology was first proposed in 1736, as a branch of graph theory that focuses on the properties and characteristics of graphs, including the arrangement and connectivity of nodes and edges.<sup>21,22</sup> It has various applications in network analysis, data mining, and other fields involving the analysis of complex systems.<sup>23</sup>

Graph topology has been widely utilized to predict topological changes in the covariance network of brain structure in patients with cirrhosis and mild hepatic encephalopathy (Table 1).<sup>32–35</sup> To construct the vascular topology, Plantefevre et al. used graph topology and applied the shortest path algorithm in the minimum cost spanning tree to determine the optimal path.<sup>36</sup> Stegmaier et al. employed a combination of sequence analysis and graph topology to construct a de novo gene regulation network and performed whole-genome scanning in a liver cancer transgenic model.<sup>37</sup> Charnoz et al. computed the vascular skeleton using a topological representation of the graph and converted it into a graphical format to facilitate the diagnosis of liver diseases and cancer.<sup>38</sup> Hassenpflug et al. utilized

**TABLE 1** Overview of graph topology approaches applied in liver diseases and their applications.

Disease	Task	Application	Material	Year	Author
Hepatitis	Prediction	Predict HCV-Human protein interactions	HCVpro	2018	Indhumathy et al. <sup>24</sup>
Metabolic liver disease	Prediction	Predict alcoholic fatty liver disease	Clinical data	2022	Takamura et al. <sup>25</sup>
Fibrosis	Prediction	Predict children's survival	Clinical data	2022	Baldissera et al. <sup>26</sup>
Cirrhosis	Registration	Register vessel	Image (US)	2004	Hassenpflug et al. <sup>27</sup>
Failure	Prediction	Predict disease association	Clinical data	2020	Campos et al. <sup>28</sup>
Cancer	Segmentation	Segment vasculature	Image (CT)	2012	Laura et al. <sup>29</sup>
Cancer	Classification	Classify cancer subtype	Image (CT)	2014	Pancoska et al. <sup>30</sup>
Cancer	Classification	Classify cancer-specific gene	Genomic data	2020	Mallik et al. <sup>31</sup>
Hepatic encephalopathy	Prediction	Predict structural brain connectome alterations in cirrhotic patients with prior OHE	Image (MRI)	2018	Chen et al. <sup>32</sup>
Hepatic encephalopathy	Prediction	Predict the multilevel impairments of brain structural network in patients with MHE	Image (MRI)	2020	Gou et al. <sup>33</sup>

Abbreviations: CT, computed tomography; HCV, hepatitis C virus; HCVpro, hepatitis C virus protein interaction database; MHE, minimal hepatic encephalopathy; MRI, magnetic resonance imaging; OHE, overt hepatic encephalopathy; US, ultrasound.

graph topology to generate attribute-relation vascular maps from three-dimensional (3D) ultrasound images, which were subsequently utilized for the intraoperative registration of image-guided liver surgery.<sup>27</sup> In the domain of graph mining, Mallik et al. assessed the design and features of graph and rule-based machine learning algorithms with the aim of increasing their usefulness in the classification and prognosis of cancers.<sup>31</sup>

## 2.2 | KG

KG involves representing factual data through entities and relationships, providing a structured and organized tool to store and access knowledge in both tangible and abstract concepts. Current studies in the field of KG have focused on techniques such as knowledge representation learning<sup>39</sup> and KG embedding.<sup>40</sup> These approaches aim to convert entities and relationships into low-dimensional vectors.

KG is considered a crucial method in liver research due to its ability to effectively represent and organize complex data in a well-structured and meaningful manner (Table 2). It allows for a comprehensive analysis of drug interactions, as a valuable tool for drug development and safety evaluation. KG has been employed for predicting adverse drug reactions by integrating data from multiple sources, including genetics, biochemistry, and pharmacology.<sup>42–44</sup> Additionally, it may help identify biomarkers and therapeutic targets by integrating various data types such as imaging, genomics, and clinical information.<sup>45–49</sup> The management of nonalcoholic fatty liver disease (NAFLD) has also benefited from the integration of diverse metabolic pathways and the identification of potential drug targets, using KG.<sup>41</sup> KG has even been used to identify potential liver donors by integrating data on donor features and medical histories.<sup>50</sup> To implement KG in various settings, different techniques are required, including constructing graphs to represent

relationships among entities,<sup>41,46</sup> extracting knowledge from graphs to identify subgraphs or patterns,<sup>49</sup> and developing question-answer systems to query graphs.<sup>45</sup> Despite their benefits, existing KGs in liver disease have limitations. For instance, they lack comprehensive coverage of disease-specific entities and relationships. To enhance the usefulness of KG in liver disease research, data integration, and standardization should be improved.

## 2.3 | GNNs

The original GNNs were first proposed in 2005, with the goal of enabling machine learning models to operate directly on graph-structured data.<sup>51</sup> Graph convolutional networks (GCNs) extend GNNs by applying convolution operations to the graph structure, facilitating the learning of abstract feature representations for each node through message passing.<sup>26</sup> More recently, graph attention networks have been developed, which leverage the attention mechanism to weigh the sum of features of neighboring nodes.<sup>10</sup>

GNNs have emerged as a versatile tool in the field of liver disease research (Table 3).<sup>29,58–72</sup> Additionally, GNNs integrate preoperative data into organs during surgery, compensating for the limited details provided by intraoperative imaging and enabling adaptive responses to changes in organ shape. To this end, Garcia Guevara et al. developed an automatic elastic registration technique that integrates preoperative data into organs during surgery, thereby responding to changes in organ shape and compensating for the limited details provided by intraoperative imaging.<sup>64</sup> Laura et al. developed a graph-to-graph matching algorithm that considers the entire graph structure rather than just separate trees, with potential application in problems where an entire graph structure is required.<sup>29</sup> Overall, GNNs have great potential in advancing the field of liver disease research, providing

**TABLE 2** Overview of knowledge graph approaches applied in liver diseases and their applications.

Disease	Task	Application	Material	Year	Author
Metabolic liver disease	Construction	Facilitate discovering research connections between bioinformatics and clinical researchers	Clinical data	2020	Frey et al. <sup>41</sup>
Injury	Prediction	Predict DILI	PGxLOD	2021	Bresso et al. <sup>42</sup>
Injury	Prediction	Predict disease association	Literature	2021	Fan et al. <sup>43</sup>
Injury	Prediction	Predict adverse drug reaction	DILI rank Database	2022	Joshi et al. <sup>44</sup>
Cancer	Question & answer	Answer questions about drugs, diseases, and symptoms related to primary liver cancer	SemMedDB	2019	Cao et al. <sup>45</sup>
Cancer	Construction	Construct a hepatocellular carcinoma knowledge graph	SemMedDB & SemRep	2020	Li et al. <sup>46</sup>
Cancer	Prediction	Predict changes in the expression of biological components	KEGG	2020	Folschette et al. <sup>47</sup>
Cancer	Prediction	Active drugs and compounds	PubChem & ChEMBL & DrugBank & STITCH & BindingDB & Binding MOAD & KEGG & SIDER & DCDB & HMDB & T3DB	2021	Cetin-Atalay et al. <sup>48</sup>
Cancer	Identification	Subgraph	TCGA	2022	Winkler et al. <sup>49</sup>
COVID-19	Prediction	Liver dysfunction	Literature	2020	Marhl et al. <sup>50</sup>

Abbreviations: BindingDB, Binding Database; Binding MOAD, Binding of Mother of All Databases; ChEMBL, Chemical Biology Information Resource; COVID-19, coronavirus disease 2019; DCDB, drug combination database; DILI, drug-induced liver injury; DrugBank, The DrugBank database, a comprehensive, freely accessible, online database containing information on drugs and drug targets; HMDB, Human Metabolome Database; KEGG, Kyoto Encyclopedia of Genes and Genomes; PGxLOD, Pharmacogenomics Linked Open Data; PubChem, Public Chemical Database; SemMedDB, Semantic MEDLINE Database; SemRep, Semantic Knowledge Representation and Extraction System; SIDER, Side Effect Resource; STITCH, Search Tool for Interactions of Chemicals; T3DB, Toxic Exposome Database; TCGA, The Cancer Genome Atlas.

**TABLE 3** Overview of GNNs approaches applied in liver diseases and their applications.

Disease	Task	Application	Material	Year	Author
Fibrosis	Detection	Detect fibrosis patterns	Clinical data	2021	Wojciechowska et al. <sup>22</sup>
Cirrhosis	Prediction	Predict microbe-metabolite-disease association	gutMDisord & MASI & VMH & HMDB & MIND	2022	Feng et al. <sup>14</sup>
Injury	Prediction	Predict DILI	DIList & TDCbenchmark	2022	Lim et al. <sup>52</sup>
Cancer	Prediction	Predict cancer association	Clinical data	2021	Ma et al. <sup>18</sup>
Cancer	Enhancement	Enhance liver cancer	Image (MRI)	2021	Xu et al. <sup>53</sup>
Cancer	Segmentation	Segment cancer	Image (MRI)	2022	Mo et al. <sup>54</sup>
Cancer	Localization	Localize Cancer	Image (CT)	2022	Shao et al. <sup>55</sup>
Cancer	Detection	Detect blood	Clinical data	2022	Kim et al. <sup>56</sup>
COVID-19	Prediction	Predict disease association	Graph	2022	Toor et al. <sup>57</sup>
Amyotrophy	Prediction	Predict gene-disease and disease-drug networks	GLDS & SPOKE	2021	Manian et al. <sup>13</sup>

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; DILI, drug-induced liver injury; DIList, Drug-induced liver injury severity and toxicity; GLDS: GeneLab Data System; GNNs, graph neural networks; gutMDisord, gut Microbiome Disorders Database; HMDB, Human Metabolome Database; MASI, microbiota-active substance interactions database; MIND, Mouse Integrative Network Database; MRI, magnetic resonance imaging; SPOKE, Scalable Precision Medicine Open Knowledge Engine; TDCbenchmark, The Tuned Distributional Context Benchmarking; VMH, Virtual Metabolic Human.

medical professionals with a valuable tool to improve diagnosis, prognostic evaluation, and preoperative planning.

## 2.4 | Graph cut

Graph cut, a method for partitioning a directed graph into two disjoint sets, is commonly utilized in image segmentation by generating a graph representation of image pixels and their respective neighborhood relationships, and minimizing the energy or cost function to create a cut between the regions.<sup>65</sup>

In liver disease research, graph cut is considered a reliable and effective approach for accurate segmentation of liver contours,<sup>66–71</sup> cancer tissues,<sup>72–75</sup> and hepatic vessels<sup>73,76</sup> across multiple modalities (Table 4). To enhance the diagnosis and treatment of various diseases,<sup>87</sup> several automatic<sup>78</sup> and semi-automatic<sup>88</sup> segmentation techniques have been developed. These tools also facilitate computer-assisted interventional liver resection,<sup>85</sup> liver transplantation,<sup>83</sup> and other surgical procedures, providing more precise and effective tools for clinical treatment and intervention. For instance, Tang et al. developed an automatic multiorgan segmentation method based on 3D abdominal computed tomography (CT) findings utilizing graph partitioning methods.<sup>89</sup> Moreover, the combination of graph cut techniques with other machine learning and deep learning approaches has been used to improve the accuracy and reliability of liver segmentation, providing potential improvements in the diagnosis and treatment of multiple liver diseases. Overall, the graph cut has demonstrated usefulness in liver disease research, playing a crucial role in enhancing liver disease diagnosis, treatment, and surgical planning, which provides a valuable tool in this field.

## 2.5 | Visualization

Graph visualization constitutes a powerful approach for representing and visually analyzing graph structures.<sup>90</sup> Clustering visualization, a broadly used technique, groups nodes with similar characteristics or topological features.<sup>91</sup> Meanwhile, layout visualization arranges nodes and edges in two-dimensional (2D) or 3D space to generate a more accurate representation of their associations and hierarchy.<sup>92</sup> Interactive visualization enables users to interact with the graph structure and associated data by exploring subsets of nodes or edges, modifying the layout, or adjusting clustering algorithm parameters.<sup>93</sup> Moreover, time-series visualization is another powerful method for analyzing temporal changes in graphs, for example, the emergence of new nodes or the evolution of clustering patterns.<sup>94</sup>

Graph visualization of liver diseases has extensively applied graph theory, as reported previously.<sup>95</sup> For example, graph-based clustering and visualization methods have been utilized to identify and visualize the subtypes of liver cancers based on genomic data.<sup>96</sup> Furthermore, graph-based methods have been utilized to generate disease networks, revealing the intricate relationships among different liver disorders and their associated genes and pathways.<sup>97</sup> Additionally, visualization methods have been used to reveal the complex relationships between liver diseases and clinical indexes,<sup>98</sup> providing substantial insights into the mechanisms underlying the development and progression of liver diseases. Ultimately, these visualization techniques have great potential to significantly enhance our understanding of liver diseases, which may contribute to the development of personalized therapeutic strategies.

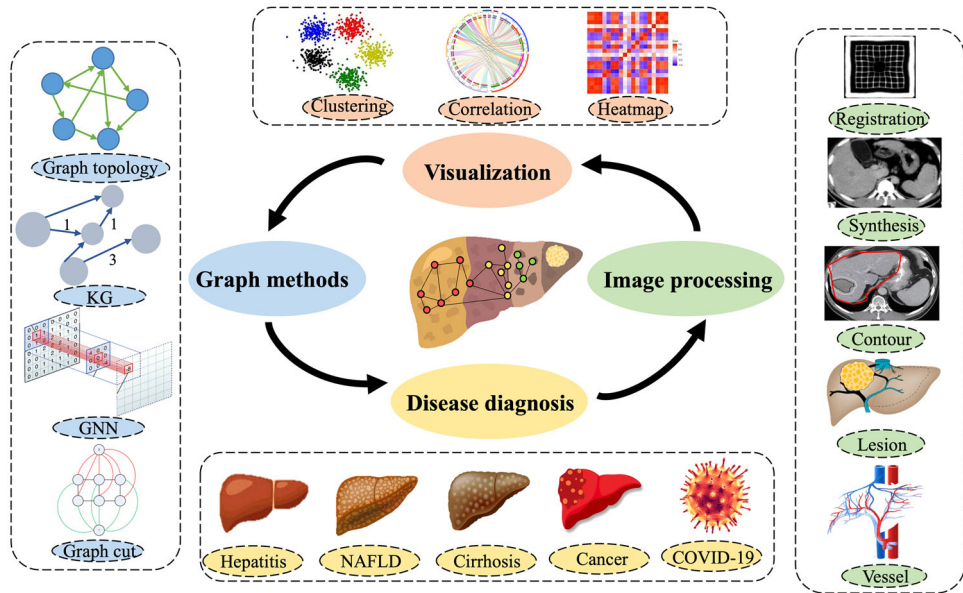
Graph theory, KG, graph convolutional neural networks (GNNs), graph cut, and other methods are widely used for liver disease diagnosis, including liver cirrhosis



**TABLE 4** Overview of graph cut approaches applied in liver diseases and their applications.

Disease	Task	Application	Material	Year	Author
Metabolic liver disease	Segmentation	Segment contour	Image (MRI)	2015	Casiraghi et al. <sup>77</sup>
Cirrhosis	Segmentation	Segment contour	Image (MRI)	2003	Lebre et al. <sup>78</sup>
Cirrhosis	Segmentation	Segment contour	Image (CT & MRI)	2019	Yan et al. <sup>79</sup>
Cancer	Classification	Classify cancer	Image (CT)	2012	Linguraru et al. <sup>80</sup>
Cancer	Segmentation	Segment contour	Image (CT)	2015	Li et al. <sup>81</sup>
Cancer	Segmentation	Segment contour	Image (CT)	2017	Cha et al. <sup>82</sup>
Cancer	Identification & Segmentation	Identify & Segment vessel	Image (CT)	2017	Zeng et al. <sup>83</sup>
Cancer	Segmentation	Segment contour & cancer	Image (CT)	2021	Kushnure et al. <sup>84</sup>
Cancer	Segmentation	Segment contour	Image (CT)	2021	Le et al. <sup>85</sup>
Cancer	Prediction	Investigate the important interactions between immune cells and their targeting drugs	GSE	2022	Mo et al. <sup>86</sup>

Abbreviations: CT, computed tomography; GSE, Gene Expression Omnibus Series; MRI, magnetic resonance imaging.

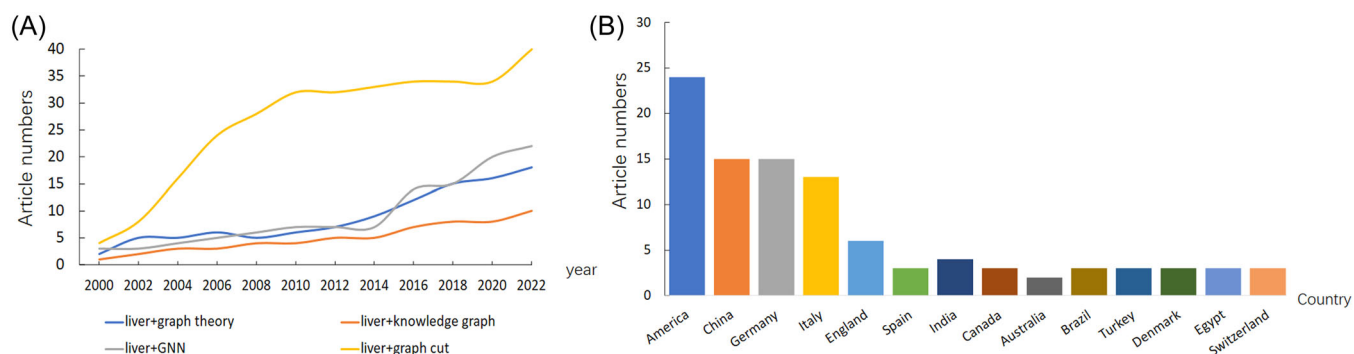


**FIGURE 1** Summary of graph theory methods and their applications in liver research. Graph methods: graph topology, knowledge graph (KG), graph convolutional neural network (GNN), and graph cut. Diseases: hepatitis, nonalcoholic fatty liver disease (NAFLD), liver cirrhosis, cancer, coronavirus disease 2019 (COVID-19). Image processing: segmentation of the liver, liver lesion, and blood vessel. Visualization: clustering, correlation, and heatmap.

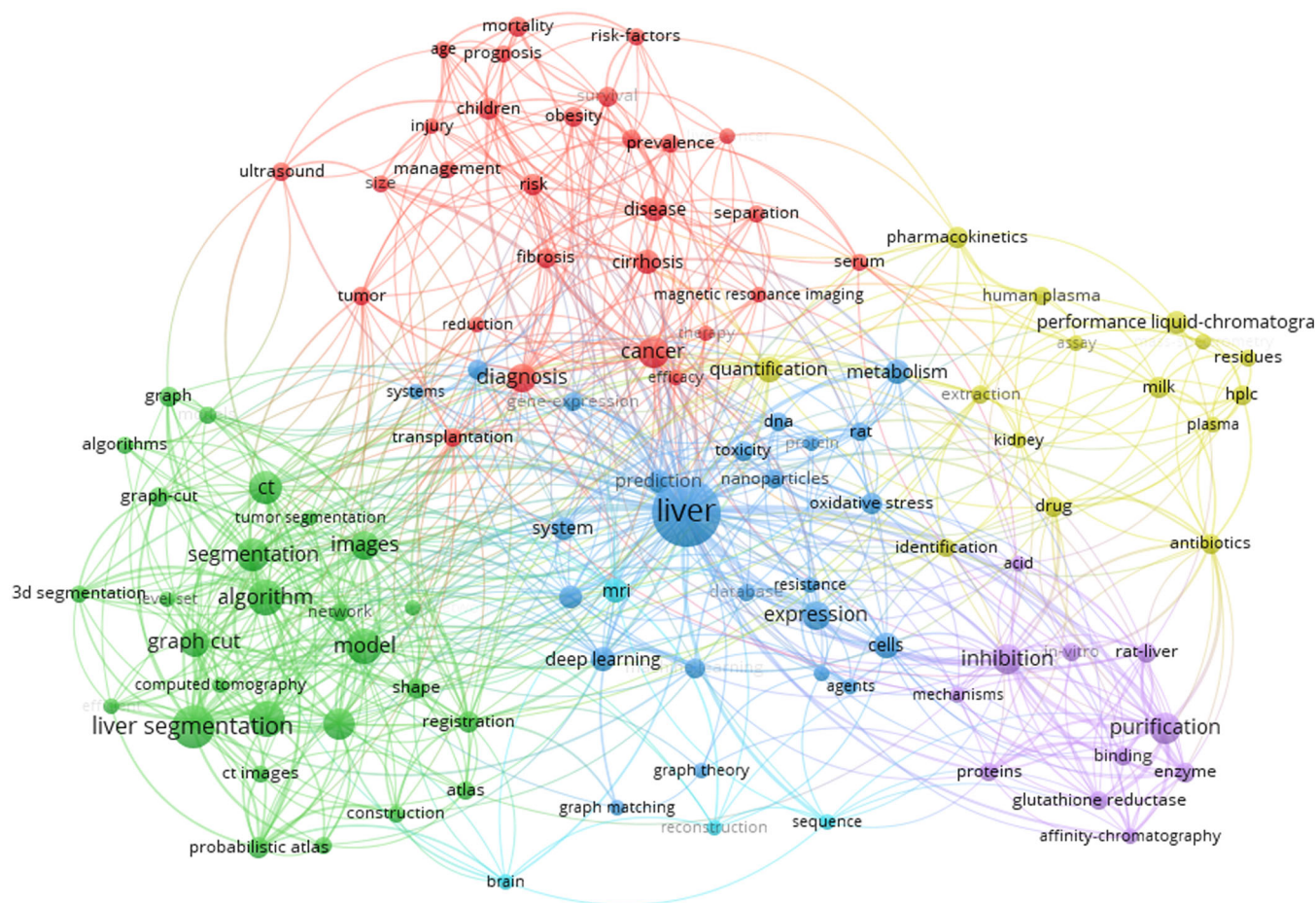
and nonalcoholic fatty liver. Additionally, these techniques contribute to improve the performances of imaging tools for liver and blood vessel segmentation. Furthermore, graph theory methods present vivid visualization results, enhancing the understanding of complex liver structures and functions (Figure 1).

We retrieved articles published by combining liver and different graph theory methods in the past 20 years. The number of articles published is steadily increasing. Among them, the number of articles published by combining liver and graph cuts was the highest. After 2016, with the extensive application of GNNs and KG, there has also been a substantial increase in the study of these methods in liver research. Among the countries that published related articles, European countries

accounted for a large proportion, followed by typical liver disease countries such as China (Figure 2). Meanwhile, among the keywords of these articles, there were many liver diseases around the liver, for example, cancer, cirrhosis, fibrosis, and so on. Many graph methods have also appeared around the graph, for example, graph cut, 3D segmentation, graph matching, and so on (Figure 3). Figure 3 shows a literature visualization using VOSviewer software (<https://www.vosviewer.com/>) with the keywords liver and graph, which represents the bibliometric analysis of existing studies literature summary on the linguistic landscape from the database of Web of Science between 2000 and 2023 of “liver” and “graph.” The comprehensive search using the keywords “liver” and “graph” highlights a substantial presence of



**FIGURE 2** Publishing trends and publication ratios by country of liver relevant article numbers. (A) Numbers of articles on liver research by different graph methods from 2000 to 2022. (B) Numbers of papers for different countries. GNN, graph neural networks.



**FIGURE 3** Articles with liver and graph as keywords. Several categories of keywords are commonly used in the field, including graph cut, graph matching, probability map, and other methods. Additionally, there are various categories of image processing techniques, including liver segmentation, three-dimensional (3D) segmentation, and other image processing tools. Finally, several categories of medical scenarios are of interest to medical image analysts, including liver cirrhosis, cancer, fatty liver, and other diseases.

literature discussing various graph methods focused on liver diseases. These keywords and categories provide a framework for organizing and understanding the broad array of graph techniques and applications in liver research.

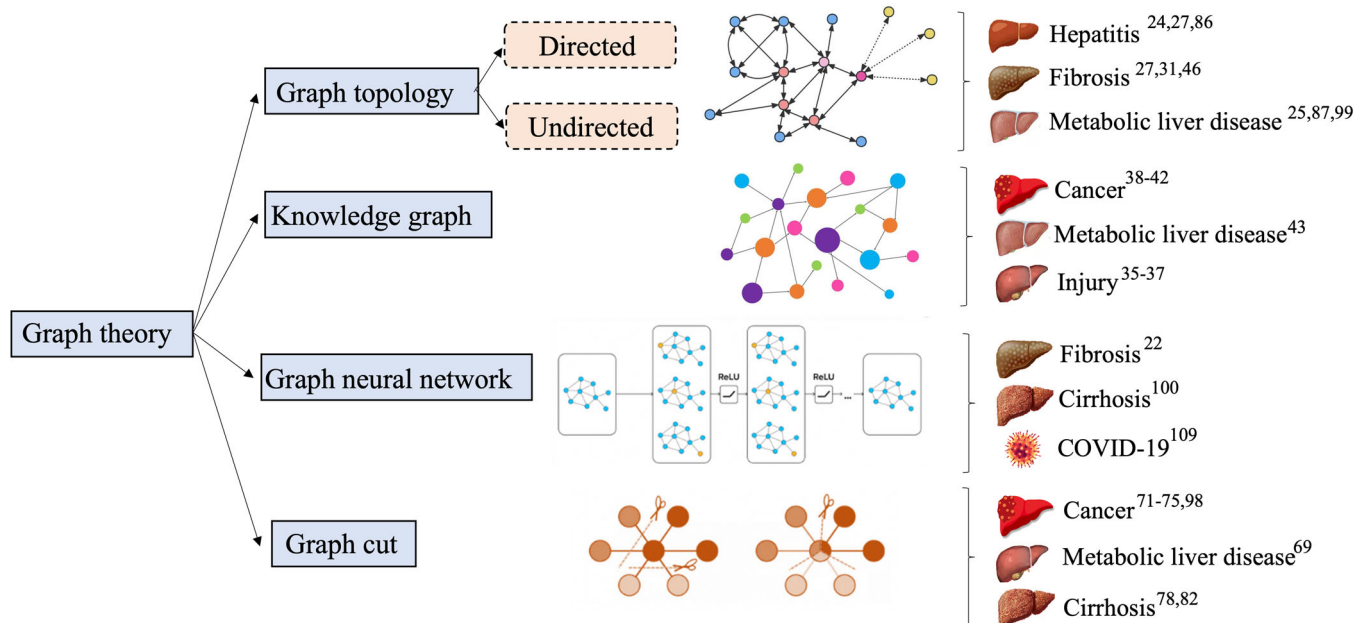
In summary, this chapter mainly introduces four types of graph theory methods and visualization data (Figure 4). Figure 4 shows the application and literature sources of liver diseases corresponding to different graph methods.

### 3 | APPLICATION OF GRAPH METHODS IN LIVER RESEARCH

### 3.1 | Image processing

### 3.1.1 | Image registration

Image registration is a well-established technique in medical imaging, commonly employed to align images from different modalities or time points. In a recent



**FIGURE 4** Graph methods in different references. Schematic representation of the four graph theory methods (graph topology, knowledge graph, graph neural network, and graph cut) in this study.

study by Charnoz et al.,<sup>98</sup> a method was proposed to compute the vascular skeleton from medical images, convert it into a graphical representation, and perform computational graph registration to estimate liver deformation. This approach may facilitate comparative analysis and help diagnose cancer progression by matching the deformed liver to the cancer. The proposed technique has potential applications in the field of medical imaging for improved diagnosis and treatment planning. Hassenpflug et al.<sup>27</sup> proposed a procedure for the intraoperative generation of attributed relational vessel graphs, which constitutes a prerequisite for vessel-based registration of a virtual, patient-individual, preoperative, 3D liver model with the intraoperatively deformed liver by graph matching.

### 3.1.2 | Image synthesis

Image synthesis techniques are crucial for medical imaging, and advances in this field have enabled the generation of high-quality images that may help clinicians reach accurate diagnoses. Xu et al.<sup>53</sup> proposed a novel pixel-level graph reinforcement synthesis learning method, which directly takes regular nonenhanced liver images as input and output artificial intelligence (AI)-enhanced liver tumor images.

### 3.1.3 | Image segmentation

Graph theory methods have demonstrated remarkable success in improving the performance of image segmentation methods. This is due to the ability of graph-based approaches to model and capture the complex relationships among image pixels or regions. By representing an image as a graph, the nodes correspond

to image elements, while the edges reflect the relationships between them. This enables the incorporation of both local and global contextual data, which is crucial for accurate segmentation. Moreover, graph-based approaches provide a powerful framework for exploring and exploiting the structural features of images, including their scale-invariance and symmetry, resulting in more robust and accurate segmentation data.

#### Liver segmentation

GNNs have demonstrated significant potential in various medical image analysis tasks, including liver segmentation. GNNs leverage structural data in medical images and effectively capture the spatial relationships among liver structures. By learning discriminative features from the graph representation of liver structures, GNNs yield accurate segmentation of the liver. The use of GNNs in liver segmentation has the potential to improve the accuracy and efficiency of liver image analysis, which may ultimately improve diagnostic assessment and treatment planning for liver diseases.

Chen et al.<sup>99</sup> utilized K-means clustering and prior knowledge to identify liver and nonliver index pixels and then employed a graph cut-based technique for liver segmentation from low-contrast open magnetic resonance (MR) images. Chen et al. segmented the liver in a sequence of CT images with an augmented masked region-based convolutional neural network (CNN).<sup>66</sup> Additionally, model-based 3D automatic segmentation methods are also commonly utilized.<sup>100</sup> Kim et al.<sup>101</sup> developed a graph U-Net model for 3D liver segmentation from CT scans, incorporating a GCN to learn spatial features and a U-Net architecture for segmentation. Lei et al.<sup>102</sup> proposed a spatial GCN for liver segmentation in CT images, incorporating a graph convolutional layer



and a spatial attention mechanism to learn discriminative features and improve segmentation accuracy. Chen et al.<sup>66</sup> presented a graph-regularized region-based CNN for liver segmentation in CT scans, which integrates a graph Laplacian regularization term to improve the smoothness of segmentation data and accuracy. GNNs inherently understand and utilize the spatial relationships within the liver, leading to more precise segmentation. Methods like the graph U-Net and spatial GCNs have been shown to improve segmentation accuracy significantly by integrating graph convolutional layers and spatial attention mechanisms. However, the complex nature of GNNs often requires substantial computational resources and time for training and inference. High-quality annotated datasets are crucial for training effective GNN models, which may not always be readily available.

#### *Focal liver lesion segmentation*

GNNs have also been employed for liver lesion segmentation, a challenging task requiring the delineation of lesions with varying shapes and appearances. The application of GNNs in liver lesion segmentation leverages the graph representation of liver structures and may effectively capture spatial relationships among lesions and the surrounding tissues.

For liver cancer segmentation, Wu et al.<sup>103</sup> developed a multiscale U-Net-based feature recalibration method for automatic segmentation of the liver and cancer in CT images. Ali et al.<sup>104</sup> reported an efficient semi-automatic CT liver cancer segmentation method based on fuzzy C-means and graph-cut approaches. After the initial liver segmentation, an optimized graph cut can be utilized to segment liver cancer samples using shape and augmentation constraints.<sup>105</sup> Li et al.<sup>106</sup> proposed a novel hybrid densely connected U-Net, comprising a 2D Dense U-Net for efficiently extracting intra-slice features and a 3D counterpart for hierarchically aggregating volumetric contexts using the auto-context algorithm for liver and tumor segmentation. This reveals a spatial relationship among voxels and learns discriminative features for cancer segmentation. Zhang et al.<sup>107</sup> reported a GNN for automatic liver cancer segmentation on CT images, which incorporates a graph convolutional layer and a region-based attention mechanism to improve the accuracy and robustness of cancer segmentation. GNNs effectively model the spatial relationships between lesions and adjacent tissues, improving segmentation accuracy. Techniques like multiscale U-Net-based feature recalibration help in capturing detailed features at various scales, enhancing the segmentation of both the liver and lesions. The use of attention mechanisms and graph convolutions improves the robustness of the segmentation process, making it less susceptible to variations in lesion appearance. However, similar to liver segmentation, the complexity of GNNs necessitates significant computational power and efficient algorithms to handle large datasets. Semi-automatic methods still require manual input, which can be time-consuming and prone to human error.

#### *Hepatic vascular segmentation*

GNNs have also been applied for liver vessel segmentation, a critical task in various clinical applications, including liver surgery planning and liver disease diagnosis. The use of GNNs in liver vessel segmentation enables the modeling of complex vessel structures and effectively captures spatial relationships among vessels and the surrounding tissues. Accurate segmentation of liver vessels is essential for preoperative planning and intraoperative navigation during liver surgery. Furthermore, vessel segmentation may help diagnose liver diseases such as liver cirrhosis and portal hypertension. The application of GNNs in liver vessel segmentation has significant potential to increase the accuracy and efficiency of liver image analysis, ultimately improving patient outcomes.

In terms of vessel segmentation, Li et al.<sup>58</sup> proposed a plug-in tool to integrate GNNs into CNNs and utilized connectivity data to improve 3D liver vessel segmentation. Wu et al. developed a new method for automatically delineating the liver and vessels in CT volume images based on supervoxel image segmentation. Chen et al.<sup>108</sup> proposed a protocol for generating a 3D skeletal graph for liver vessels using a thinning algorithm and graph theory based on skeletonization and graph-based techniques.

## 3.2 | Disease diagnosis

### 3.2.1 | Diffuse liver disease

#### *Liver necrosis*

Cell-location-based modeling and evaluation of histopathological data provide important information. Serin et al. utilized the circular neighborhood cell graph to extract features from liver pathology images and used the obtained features for the classification of hepatic necrosis based on liver histopathology images.<sup>109</sup>

Lv et al. evaluated the abnormal topological organization of the structural network in individuals with hepatitis B virus-induced cirrhosis without overt hepatic encephalopathy (OHE) by structural magnetic resonance imaging (MRI) and graph topology analysis.<sup>15</sup> Similarly, Indhumathy et al. employed the weighted association rule mining technology in a bipartite graph to predict potential novel interactions between hepatitis C virus and human proteins.<sup>24</sup> Hellard et al. utilized a network-based approach and parameterized an exponential random graph model in graph topology to examine the clinical effects of injected direct-acting antivirals on the prevalence of hepatitis C virus.<sup>90</sup> These studies demonstrate the utility of graph theory and associated analytical techniques in understanding liver disease and developing potential treatment strategies.

#### *Fibrosis and cirrhosis*

Dwivedi et al.<sup>110</sup> reported a novel tool using a multimodal CNN-GNN-based graph fusion approach that leverages complementary information from multiple nonregistered histopathology images to predict pathologic scores. This tool was utilized to identify basic

fibrosis ratings from F0 to F4 (METAVIR scoring system). Baldissera et al. employed directed acyclic graphs (DAGs) and other modeling methods to assess the impact of liver disease and its severity on survival in children with cystic fibrosis.<sup>26</sup> Feng et al. used bipartite graph attention networks to integrate disease-microbe and metabolite-microbe bipartite graphs, developing biomarkers for liver cirrhosis and other disorders.<sup>14</sup> Long et al. developed a computational model, termed Weighted Meta-Graph Human Microbe-Disease Association, to predict potential associations between human microbes and diseases, for example, Crohn's disease, liver cirrhosis, and type-1 diabetes.<sup>111</sup> Shi et al. proposed a deep learning framework applying a graph convolutional attention network to identify potential microbe-disease associations and predict high-risk microorganisms for human diseases such as cirrhosis and epilepsy.<sup>10</sup> Taken together, these studies exemplify the utilization of graph theory and machine learning techniques for understanding and forecasting liver diseases.

Liver cirrhosis also causes multiple complications, for example, muscle atrophy and hepatic encephalopathy. Manian et al.<sup>13</sup> developed an integrative graph-theoretic network-based drug repurposing method to examine the interplay of key regulated genes and protein-protein interactions in muscle atrophy conditions. A gene-disease KG was constructed with a scalable precision medicine knowledge engine, and a disease-drug KG was generated for predicting new drugs using a GNN.<sup>18</sup> Chen et al. employed graph topology analysis to predict alterations in brain structural connectomes in cirrhosis cases with OHE.<sup>32</sup> Another study also utilized graph topology to predict the impact of previous OHE episodes on the topological structure of functional brain networks in cirrhotic individuals and examined its association with cognitive impairment.<sup>34</sup> Gou et al. applied graph topology to assess the global, modular, and local topological organization of the brain structural network in cirrhotic individuals with minimal hepatic encephalopathy and investigated the multilevel damage to the network.<sup>33</sup> Zou et al. predicted the topological changes of the brain structural covariance network in individuals with mild hepatic encephalopathy induced by cirrhosis using graph topology.<sup>35</sup> Finally, Wu et al. used graph topological parameters to assess the dynamic score of module connectivity for multiple differential modules, with the aim of identifying genes and pathways associated with hepatic encephalopathy in alcoholics.<sup>112</sup>

#### *Metabolic liver diseases*

Takamura et al. utilized DAGs in graph topology to examine the effect of metabolism-associated fatty liver disease in psoriasis patients, as well as the role of interleukin-17 inhibitors in liver fibrosis and the associated influencing factors.<sup>25</sup> Similarly, Zhang et al. employed the DAG method in graph topology to evaluate the relationship between honey consumption frequency and NAFLD in the general population.<sup>113</sup>

Khan et al.<sup>114</sup> developed a research framework based on network theory to understand the comorbidity

pattern of type-2 diabetes and associated chronic disorders occurring over time. They proposed the "comorbidity network" concept that effectively models chronic disease comorbidities and their transition patterns, thereby representing the progression of chronic diseases. They found that the diabetic cohort exhibited more comorbidity prevalence and denser network properties. For example, in the diabetic cohort, heart and liver-related disorders, and so on, were more prevalent.<sup>14</sup> Campos et al. carried out a case-control study to investigate risk factors for hospital-acquired venous thromboembolism in children. The authors utilized DAGs to identify confounders, thereby reducing bias and improving the accuracy of the analysis. The DAG model involved liver failure as a variable in the initial conventional univariable model, and DAG-informed conditional logistic regression was employed to establish the final model.<sup>28</sup>

### 3.2.2 | Focal liver lesions

#### *Drug-induced liver injury (DILI)*

Bresso et al. utilized KG region mining features to train a classifier for the detection of adverse drug reactions, which was successfully applied in clinical settings for detecting DILI and severe skin adverse reactions.<sup>42</sup> Lim et al. developed a supervised subgraph mining method, which progressively refines a single graph transition to extract explicit subgraph features to enhance detection accuracy in DILI.<sup>52</sup> Fan et al. constructed a network-based KG using a sepsis study and performed liver and other organ damage-related research, providing substantial insights into DILI.<sup>43</sup> Hwang et al. employed a graph attention network to learn embedding vectors of drug structure and drug-induced gene expression profiles, enabling the prediction of DILI with high accuracy.<sup>115</sup> Finally, Ma et al. proposed a deep graph learning neural network considering attribute enhancement for the prediction of DILI with high precision.<sup>63</sup> These tools have significantly contributed to the development of effective DILI predictive models for increased patient safety and improved healthcare outcomes.

Graph theory methods have also been applied in coronavirus disease 2019 (COVID-19) research. Joshi et al. designed and trained a KG deep neural network to predict adverse drug reactions employing KG embedding.<sup>44</sup> Case studies were conducted on drugs that cause liver damage and those recommended for COVID-19. Marhl et al. adopted a KG approach to identify three pathophysiological pathways by which diabetics are more susceptible to COVID-19, including liver dysfunction.<sup>50</sup> Toor et al. used a graph network to analyze the associations of COVID-19, type-2 diabetes, NAFLD, and diet to predict their unknown correlation.<sup>57</sup>

#### *Liver cancer*

Cetin-Atalay et al. utilized KG to promote the evaluation of potential therapeutics for hepatocellular carcinoma within the context of AI-assisted drug discovery or re-utilization.<sup>48</sup> Folschette et al. developed a method to

automatically extract regulatory knowledge from KG to generate new knowledge associated with the expression or activity status of biomolecules, specifically in the context of hepatocellular carcinoma progression, and assessed the accuracy and stability of these computational predictions.<sup>47</sup> Svecic et al. developed a new spatiotemporal discriminative GNN based on GCNs, which could predict future dynamic contrast-enhanced (DCE)-MRI examinations after transcatheter arterial chemoembolization for clinical hepatocellular carcinoma.<sup>116</sup> Mo et al. performed a trajectory analysis using a partition-based graph abstraction method to determine significant interactions between immune cells and their targeted drugs in liver carcinoma, using single-cell and bulk transcriptomic data.<sup>54</sup>

Liver cancer comprises several subtypes. Pancoska et al. developed a network phenotyping strategy employing graph theory data transformation to identify two main subtypes of hepatocellular carcinoma, including small and large cancers.<sup>30</sup> Zhang et al. explored the potential of web-based machine learning and graph theory algorithms in the integrated analysis of personal genomic data and biomedical databases to identify molecular mechanisms, candidate targets, and retargeted drugs for liver cancer, to facilitate personalized therapy.<sup>117</sup>

## 4 | DISCUSSION

Graph theory approaches have shown significant promise in addressing various prediction and image-processing challenges in liver diseases, offering valuable insights into both scientific research and clinical applications. However, several challenges and open questions remain, necessitating further investigation to effectively leverage these approaches in this context. By addressing these issues, significant improvements in medical image analysis and the development of more accurate diagnostic and therapeutic strategies for liver diseases can be achieved.

Compared with traditional deep learning methods, graph network techniques hold the potential to better capture the spatial structure and associations of liver diseases, facilitating the direct input of structured data into learning models. Efforts to integrate data from multiple sources, such as genomics and proteomics, can enhance our understanding of liver disease development and progression. Nonetheless, graph network methods face challenges such as computation and memory constraints when handling large and complex graphs. Moreover, the complex pathological mechanisms of liver diseases may limit the ability of graph theory to fully describe disease pathogenesis, necessitating further investigation and improvement of models. Future research should focus on developing more comprehensive and accurate models that incorporate a broader range of factors, ultimately leading to more effective diagnostic and treatment strategies for liver diseases and improved patient outcomes.

A significant barrier to the widespread adoption of graph theory approaches in clinical practice is the lack

of transparency, which undermines trust in AI models. The opacity of AI model decisions may make physicians hesitant to rely on their predictions. Therefore, the development of explainable AI tools is crucial for providing insights into the reasoning behind AI model predictions. Additionally, open platforms and datasets are essential to enable transparency and reproducibility of results. Addressing these issues can lead to the development of more reliable and effective AI models, fostering greater adoption in clinical practice and ultimately benefiting patient care.

As machine learning techniques continue to evolve, the potential of graph network methods in liver disease applications will expand further. Future research efforts should focus on optimizing the performance and efficiency of graph network methods through data preprocessing optimization, integration with other machine learning techniques, and validation in clinical settings. These approaches have the potential to advance diagnostic and therapeutic strategies for liver diseases, ultimately improving patient outcomes.

While graph theory approaches hold promise for liver disease analysis, several challenges must be addressed before their widespread application in clinical practice. Future research endeavors should aim to develop more comprehensive and accurate models while also addressing issues of transparency and interpretability. By overcoming these challenges, confidence in AI predictions can be increased, facilitating their integration into clinical practice and contributing to better patient outcomes.

## 5 | CONCLUSION

This review provides a comprehensive overview of the current state of graph theory in liver disease analysis, highlighting its potential for imaging analysis. Recent studies have demonstrated the promising application of graph theory in various liver diseases, including staging liver fibrosis, detecting portal hypertension, characterizing focal hepatic lesions, predicting the prognosis of malignant hepatic cancers, and segmenting the liver and liver cancers. While the technical feasibility of graph theory in liver research has been established, its applicability and generalizability in actual clinical practice require further investigation. To become a valid clinical tool, the performance of graph theory methods should be evaluated through well-designed clinical trials. Additionally, future research should focus on determining the clinical impact of graph theory and related techniques that can be effectively incorporated into real-world clinical practice.

## AUTHOR CONTRIBUTIONS

Xumei Hu and Longyu Sun were responsible for the conception and writing of this paper. Rencheng Zheng and Xueqin Xia handled the proofreading. Meng Liu was in charge of data collection, while Weibo Chen took care of the language refinement. Xinyu Zhang provided technical support. Chengyan Wang served as the overall project leader.



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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Not applicable.

## ETHICS STATEMENT

Not applicable.

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