Journal of Clinical and Translational Hepatology **2025** vol. 13(5) | 367–373
DOI: 10.14218/JCTH.2025.00030

Original Article

Analysis of the Disease Spectrum Characteristics of Inherited Metabolic Liver Diseases in Two Hepatology Specialist Hospitals in Beijing over the Past 20 Years

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Received: January 16, 2025 | **Revised:** February 24, 2025 | **Accepted:** March 07, 2025 | **Published online:** March 21, 2025

Abstract

Background and Aims: Inherited metabolic liver diseases (IMLDs) have complex etiologies and vary widely in clinical presentation, with a significant overall incidence. With the advancements in diagnostic and treatment technologies, an increasing number of children with inherited metabolic diseases are surviving into adolescence and adulthood. These advancements have improved our understanding of the IMLD disease spectrum and clinical outcomes. This study aimed to analyze changes in the disease spectrum and epidemiological characteristics of inherited metabolic liver diseases (IMLD) over the past 20 years in two specialized liver disease hospitals in northern China. ***Methods:*** A retrospective analysis was conducted on IMLD cases diagnosed between January 1, 2002, and December 31, 2023, at two liver disease specialty hospitals in Beijing. Data were obtained from inpatient and outpatient hospital information systems, with diagnoses based on national and international IMLD diagnosis and treatment guidelines. ***Results:*** A total of 2,103 IMLD patients were analyzed, including 1,213 adults and 890 children. IMLD accounted for 4.58‰ of hospitalized liver disease patients during this period. The most common IMLD was Wilson's disease, comprising 68% of all IMLD cases. The number of diagnosed IMLD types increased from 15 to 32 across two 11-year periods (2002–2012 and 2013–2023). Among pediatric patients, glycogen storage disease and Alagille syndrome were more prevalent in those under one year of age, while Wilson's disease was prevalent across all age groups. In adult IMLD patients, Wilson's disease, polycystic liver disease, and hereditary hyperbilirubinemia were more frequently observed. ***Conclusions:*** Over the past 20 years, both the number of diagnosed IMLD cases and disease diversity have significantly increased, with Wilson's disease remaining the most prevalent IMLD. These findings provide valuable insights for the long-term management of IMLD patients and the allocation of healthcare resources.

Citation of this article: Hou W, Huang Y, Shang T, Wang Z, Zhang W, Wang K, *et al*. Analysis of the Disease Spectrum Characteristics of Inherited Metabolic Liver Diseases in Two Hepatology Specialist Hospitals in Beijing over the Past 20 Years. J Clin Transl Hepatol 2025;13(5):367–373. doi: 10.14218/JCTH.2025.00030.

Introduction

Inherited metabolic liver diseases (IMLDs) comprise a diverse group of disorders characterized by liver dysfunction or structural abnormalities caused by genetic defects. These diseases have complex etiologies and vary widely in clinical presentation, with a significant overall incidence. Conservative estimates suggest that there are over 700 distinct types of IMLD,[1,2] most of which are considered rare diseases. While many of these conditions manifest in infancy or early childhood, some, such as Wilson's disease and hereditary hemochromatosis, may present during adolescence or even adulthood.[3,4]

With the expansion of newborn screening programs, advancements in diagnostic technologies, and the development of new treatments, an increasing number of children with inherited metabolic diseases are surviving into adolescence and adulthood. These advancements have improved our understanding of the IMLD disease spectrum and clinical outcomes. To explore how the IMLD spectrum has evolved over the past two decades, we conducted a retrospective analysis of IMLD cases at two hepatology specialist hospitals in Beijing. This study provides valuable insights for clinical practice and contributes important data to assist policymakers in planning and implementing newborn screening programs and optimizing resource allocation.

Methods

The cases included in this study were collected from January 1, 2002, to December 31, 2023, from inpatients and outpa-

Keywords: Inherited metabolic liver diseases; Disease spectrum; Epidemiology; Diagnosis; Wilson's disease; Hereditary hyperbilirubinemia.

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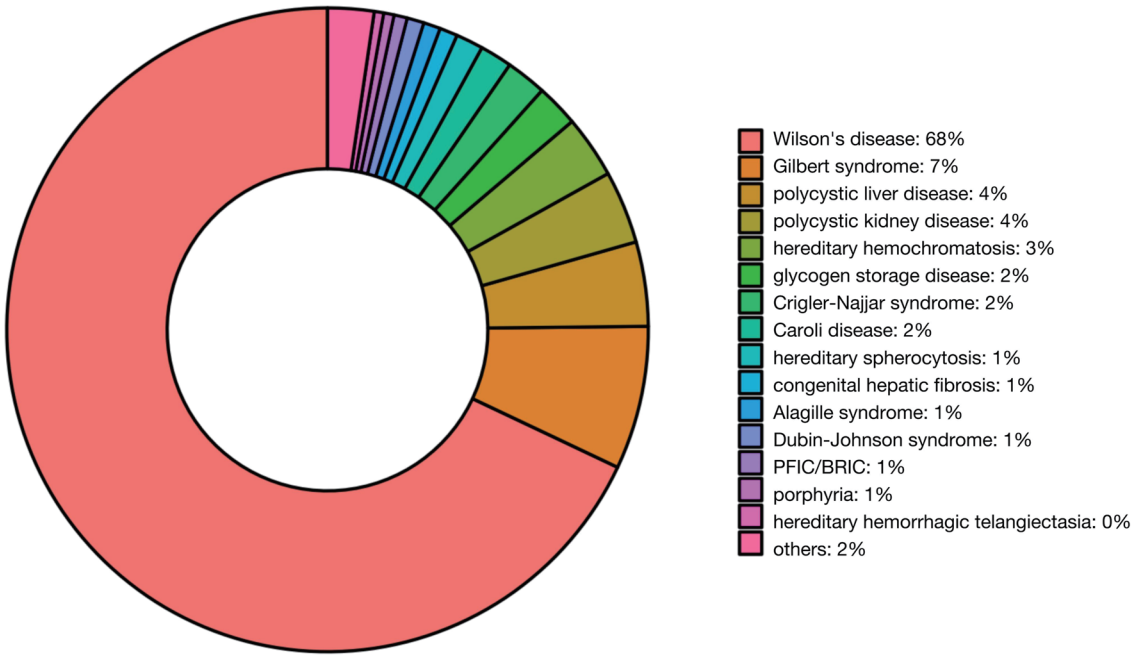

Fig. 1. Percentage composition of IMLD etiology for all visits from 2002 to 2023 (%). PFIC, progressive familial intrahepatic cholestasis; BRIC, benign recurrent intrahepatic cholestasis; IMLD, inherited metabolic liver disease.

tients at Beijing You'an Hospital, affiliated with Capital Medical University, and the Fifth Medical Center of the Chinese PLA General Hospital. Patient data were retrieved from the hospital information system for both inpatient and outpatient cases. The inclusion criteria encompassed all patients diagnosed with any of the following diseases: Wilson's disease, hereditary hemochromatosis, glycogen storage diseases, bile acid synthesis defects, familial intrahepatic cholestasis, Alagille syndrome, porphyria, Gilbert syndrome, Crigler-Najjar syndrome, Dubin-Johnson syndrome, Rotor syndrome, Gaucher disease, Niemann-Pick disease, congenital hepatic fibrosis, congenital intrahepatic bile duct dilatation, polycystic liver disease, polycystic kidney disease, cystic fibrosis, α1-antitrypsin deficiency, hereditary hemorrhagic telangiectasia, citrullinemia, tyrosinemia, hereditary spherocytosis, portal vein malformations, mucopolysaccharidosis, urea cycle disorders, glucose-6-phosphate dehydrogenase deficiency, glycosylation defects, and sitosterolemia. Clinical data for all identified IMLD patients were compiled and analyzed. The diagnosis for all cases conformed to the relevant national and international guidelines or diagnostic criteria for IMLD. The age of IMLD patients was recorded as their age at the first visit.

This study was approved by the Medical Ethics Committee of Beijing You'an Hospital, Capital Medical University (Approval No: Jing You Ke Lun Zi [2022] 048) and the Ethics Committee of the Fifth Medical Center, Chinese PLA General Hospital (Approval No: KY-2022-6-36-1).

Results

General information

A total of 2,103 patients diagnosed with IMLD were treated between January 2002 and December 2023, including 1,213 adults and 890 children. Among these, 1,829 were hospitalized, and 274 were outpatients. Among hospitalized patients, the proportion of IMLD cases among all liver disease admissions was 4.58‰ (1,829/399,098). Specifically, the proportion of adult IMLD patients was 2.98‰ (1,017/340,730), while in children, it was 13.9‰ (812/58,368).

Distribution of IMLD causes

Among the 2,103 patients diagnosed with IMLD, the distribution of cases, ranked by frequency from highest to lowest, was as follows: Wilson's disease (1,429 cases, 67.9%), hereditary hyperbilirubinemia (218 cases, 10.4%) (including Gilbert syndrome (151 cases, 7.5%), Crigler-Najjar syndrome (43 cases, 2.1%), Dubin-Johnson syndrome (18 cases, 0.8%), and Rotor syndrome (six cases, 0.3%)), polycystic liver disease (89 cases, 4.2%), polycystic kidney disease (including both autosomal recessive and autosomal dominant forms) (77 cases, 3.7%), hereditary hemochromatosis (66 cases, 3.1%), glycogen storage disease (45 cases, 2.1%), Caroli disease (34 cases, 1.6%), hereditary spherocytosis (29 cases, 1.4%), congenital hepatic fibrosis (19 cases, 0.9%), Alagille syndrome (18 cases, 0.8%), progressive familial intrahepatic cholestasis (PFIC) and benign recurrent intrahepatic cholestasis (BRIC) (14 cases, 0.7%), porphyria (11 cases, 0.5%), hereditary hemorrhagic telangiectasia (11 cases, 0.5%), portal vein malformations (six cases, 0.3%), cystic fibrosis (six cases, 0.3%), Niemann-Pick disease (five cases, 0.2%), and others (Fig. 1).

Distribution of IMLD causes in adults and children

Among the 1,213 adult patients with IMLD, the ten most common diagnoses, ranked by frequency, were as follows: Wilson's disease (720 cases, 59.4%), Gilbert syndrome (116 cases, 9.6%), polycystic liver disease (88 cases, 7.3%), autosomal dominant/recessive polycystic kidney disease (70 cases, 5.8%), hereditary hemochromatosis (63 cases, 5.2%), Crigler-Najjar syndrome (32 cases, 2.6%), Caroli disease (31 cases, 2.6%), hereditary spherocytosis (25 cases,

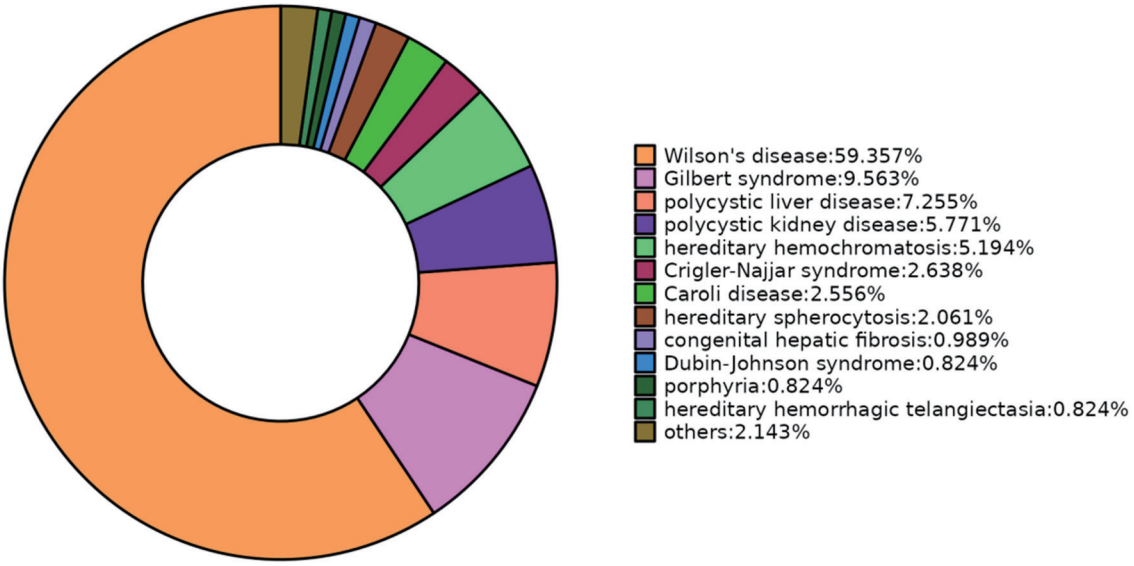

Fig. 2. Percentage distribution of IMLD causes in adults (%). IMLD, inherited metabolic liver disease.

2.1%), congenital hepatic fibrosis (12 cases, 1.0%), and Dubin-Johnson syndrome (10 cases, 0.8%) (Fig. 2).

Among the 890 pediatric patients diagnosed with IMLD, the ten most common causes were: Wilson's disease (709 cases, 79.7%), glycogen storage disease (44 cases, 4.9%), Gilbert syndrome (35 cases, 3.9%), Alagille syndrome (17 cases, 1.9%), PFIC/BRIC (12 cases, 1.3%), Crigler-Najjar syndrome (11 cases, 1.2%), Dubin-Johnson syndrome (eight cases, 0.9%), autosomal dominant/recessive polycystic kidney disease (seven cases, 0.8%), congenital hepatic fibrosis (seven cases, 0.8%), and Niemann-Pick disease (four cases, 0.4%) (Fig. 3).

When analyzing pediatric patients by age group, the distribution of diseases was as follows: under one year old (111 cases): The top three diseases were glycogen storage disease (33.3%, including type I: 10.8%; type III: 6.3%; type IV: 5.4%; type IX: 10.8%), Wilson's disease (30.6%), and Alagille syndrome (15.3%). Children aged one to six years (175 cases): The top three diseases were Wilson's disease (83.1%), PFIC/BRIC (4.9%), and hereditary hyperbilirubinemia (3.8%). Children aged six to sixteen years (497 cases): The most common cause was Wilson's disease (90.6%), followed by hereditary hyperbilirubinemia (4.9%). Other IMLDs, such as glycogen storage disease, hereditary spherocy-

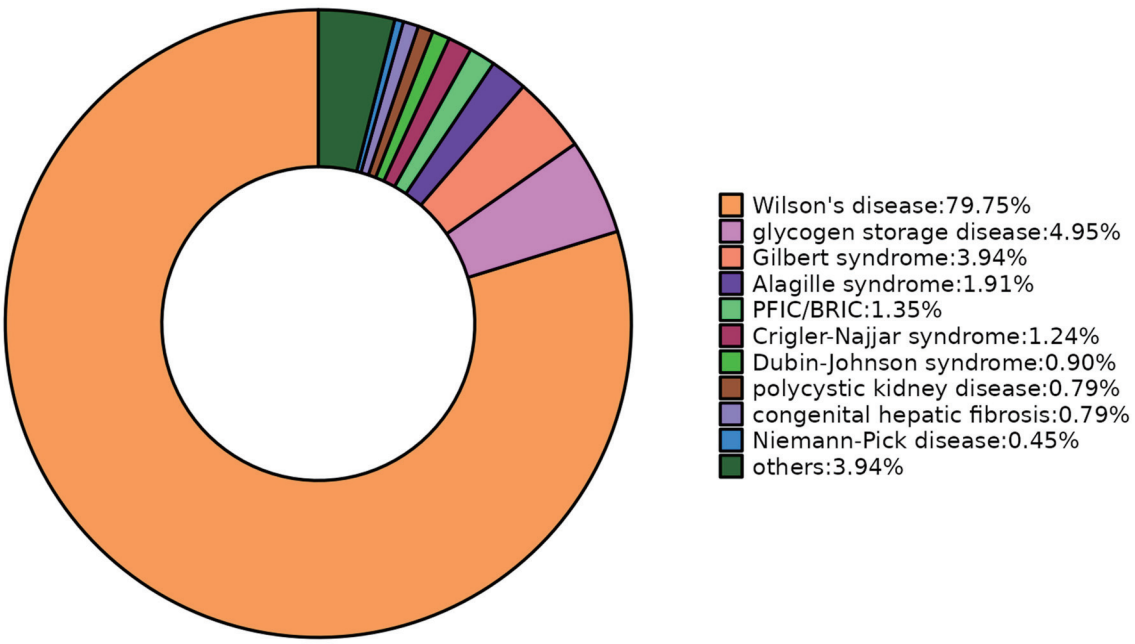

Fig. 3. Percentage distribution of IMLD causes in children (%). PFIC, progressive familial intrahepatic cholestasis; BRIC, benign recurrent intrahepatic cholestasis; IMLD, inherited metabolic liver disease.

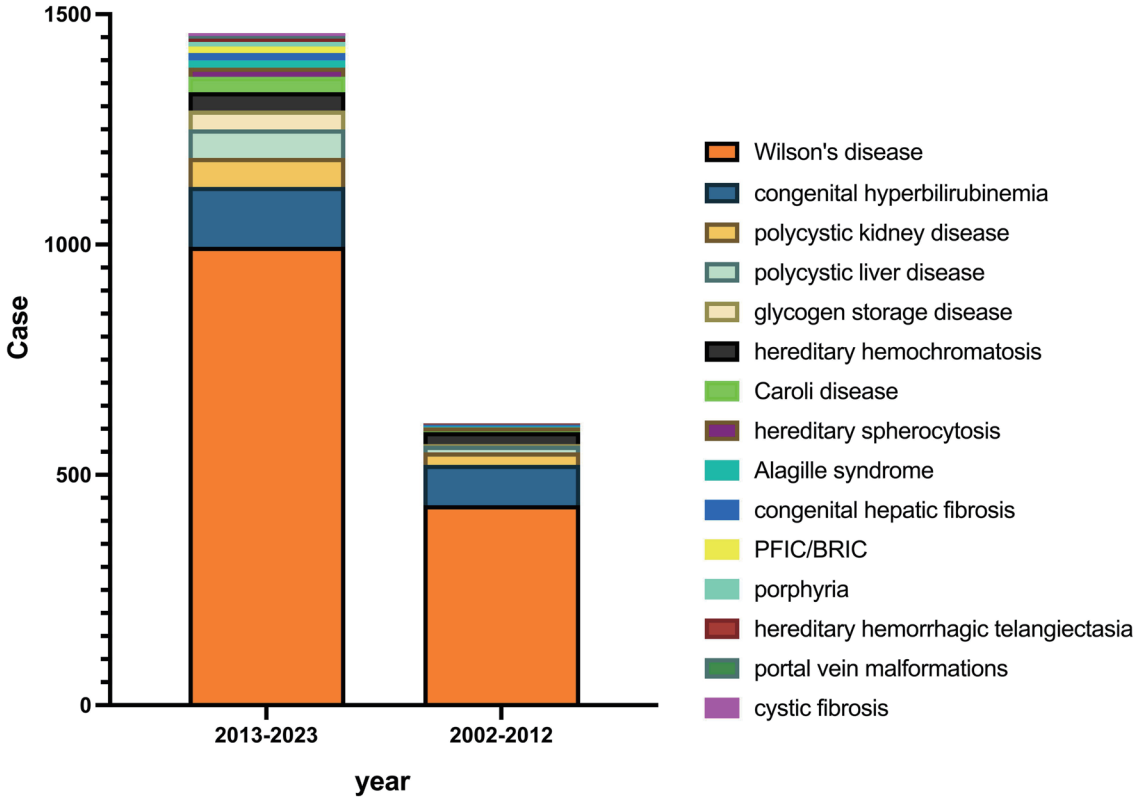

Fig. 4. Comparison of the top 15 IMLD causes between 2002–2012 and 2013–2023. PFIC, progressive familial intrahepatic cholestasis; BRIC, benign recurrent intrahepatic cholestasis; IMLD, inherited metabolic liver disease.

tosis, Caroli disease, and cystic fibrosis, each accounted for less than 0.6%.

Changes in IMLD disease types over the past 20 years

We compared the distribution of IMLD cases over two 11-year periods: 2002–2012 and 2013–2023. During 2002–2012, a total of 15 types of IMLD were diagnosed, ranked in descending order of frequency: Wilson's disease, hereditary hyperbilirubinemia, autosomal dominant/recessive polycystic kidney disease, hereditary hemochromatosis, polycystic liver disease, hereditary spherocytosis, glycogen storage disease, congenital hepatic fibrosis, hereditary hemorrhagic telangiectasia, Alagille syndrome, Caroli disease, porphyria, glucose-6-phosphate dehydrogenase deficiency, Gaucher disease, and tyrosinemia.

Between 2013–2023, a total of 32 types of IMLD were diagnosed. In addition to the 15 types identified in the earlier period, newly diagnosed conditions included PFIC, portal vein malformations, cystic fibrosis, Niemann-Pick disease, mucopolysaccharidosis, urea cycle disorders, Duchenne muscular dystrophy, glycosylation defects, transient infantile hypertriglyceridemia, Aicardi-Goutières syndrome, α1-antitrypsin deficiency, citrullinemia, familial hypercholesterolemia, sitosterolemia, congenital hypothyroidism, mitochondrial diabetes, and platelet glycoprotein IV deficiency.

In both periods, Wilson's disease remained the most frequently diagnosed condition, accounting for over 60% of all IMLD cases. The proportion of hereditary hyperbilirubinemia cases decreased (14.3% vs. 8.7%), while the proportion of other IMLDs increased (Fig. 4).

Among the top ten most common IMLDs, over 60% of cases were diagnosed in the past 11 years. Notably, Caroli disease, Alagille syndrome, and glycogen storage disease were predominantly diagnosed in the latter period, with over 90% of cases identified between 2013 and 2023 (Fig. 5).

The diagnostic situation of two common types of IMLD patients over the past 20 years

Among all IMLD patients, Wilson's disease had the highest prevalence, accounting for over 60% of cases. The number of Wilson's disease diagnoses increased significantly after 2008, whereas before 2008, diagnoses were relatively low (Fig. 6A). Regarding age at onset, the majority of Wilson's disease patients were in the 0–20 years age group, which accounted for 54.4% of all Wilson's disease cases (777/1,429) (Fig. 6B).

Hereditary hyperbilirubinemia was also relatively common. Among these cases, Gilbert syndrome, Crigler-Najjar syndrome, Dubin-Johnson syndrome, and Rotor syndrome accounted for 69.3%, 19.7%, 8.3%, and 2.8%, respectively (Fig. 7A). Similarly, the majority of these cases were diagnosed after 2008 (Fig. 7B).

Discussion

IMLDs are a group of disorders caused by genetic defects that lead to metabolic abnormalities. These diseases have complex etiologies, a wide range of clinical presentations, and a high overall incidence. This study analyzed data from IMLD patients at two hepatology specialist hospitals in Beijing between 2002 and 2023. The results showed that IMLDs accounted for 4.58‰ of all liver disease hospitalizations during this period, with Wilson's disease being the most common IMLD, consti-

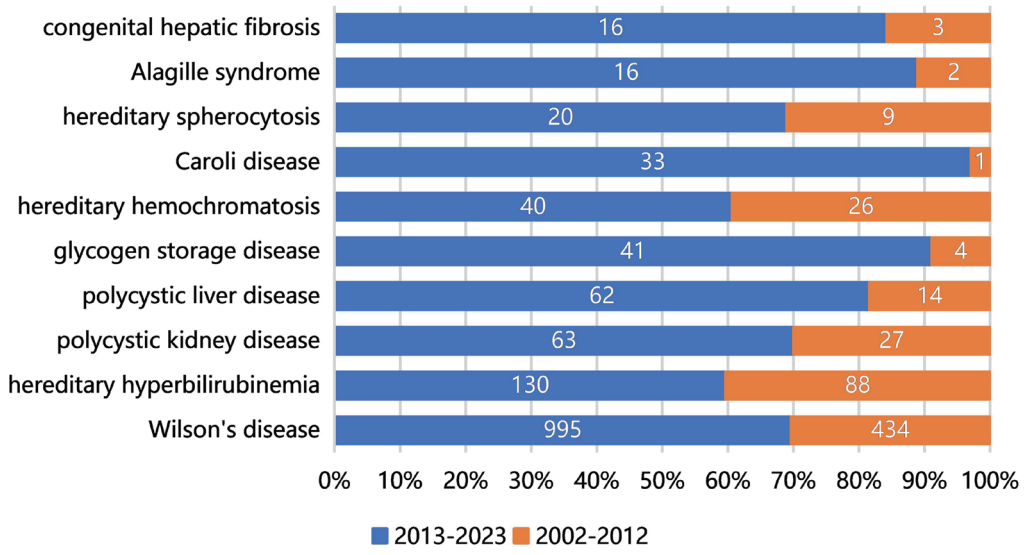

Fig. 5. Changes in the number of diagnoses for the top 10 IMLDs between 2002–2012 and 2013–2023. IMLD, inherited metabolic liver disease.

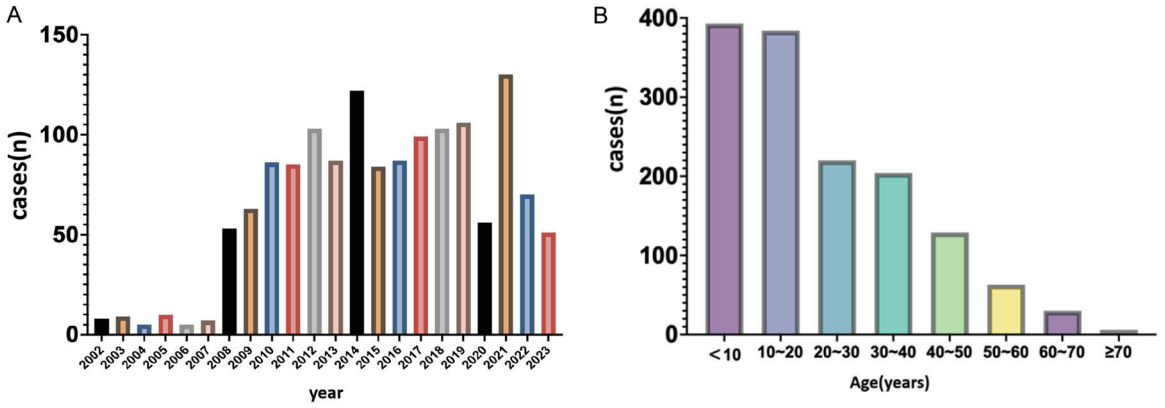

Fig. 6. (A) Number of diagnoses per year in patients with Wilson's disease, (B) Age of onset in patients with Wilson's disease. 10–20: ≥10 and <20; 20–30: ≥20 and <30; 30–40: ≥30 and <40; 40–50: ≥40 and <50; 50–60: ≥50 and <60; 60–70: ≥60 and <70.

tuting 68% of all cases. A comparison of the disease spectrum between two 11-year periods (2002–2012 and 2013–2023) revealed significant changes, with both the number of diagnoses and the variety of diseases increasing substantially.

Over the past 11 years, both the diversity and incidence of IMLDs have risen. Between 2002 and 2012, 15 types of

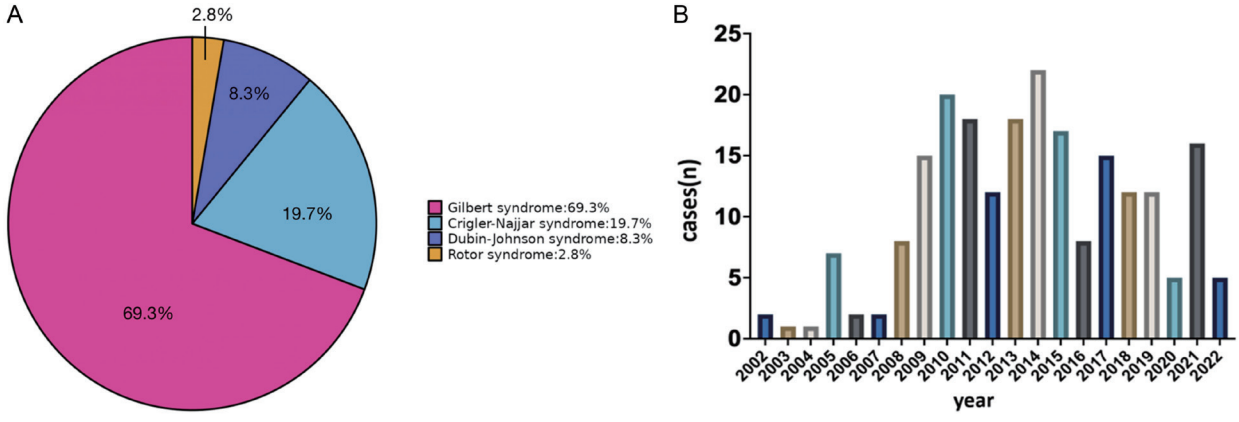

Fig. 7. (A) Distribution of hereditary hyperbilirubinemia causes, (B) Number of cases diagnosed annually with hereditary hyperbilirubinemia.

IMLDs were diagnosed, whereas the number increased to 32 between 2013 and 2023. In terms of case numbers, more than 60% of the top 10 most common IMLDs were diagnosed in the last 11 years, with Caroli disease, Alagille syndrome, and glycogen storage disease, in particular, having over 90% of cases identified during this period. These epidemiological changes in IMLDs may be attributed to several factors. First, advances in diagnostic technologies have played a key role. The widespread adoption and refinement of genetic testing techniques, particularly whole-exome sequencing, have enabled the diagnosis of an increasing number of inherited metabolic diseases at earlier stages.[5,6] Second, the expansion of newborn screening programs has contributed to this trend. As screening programs now cover a broader range of diseases, many inherited metabolic disorders are being detected in infancy, allowing for earlier intervention and treatment, which can slow disease progression and reduce complications.[7] Additionally, public health policies have influenced the shifting disease spectrum. The widespread use of hepatitis B vaccination and antiviral treatments has led to a yearly decline in viral hepatitis incidence, while non-infectious liver diseases, such as IMLDs, have become a more prominent component of liver disease cases.[2] A Chinese single-center study showed that the proportion of non-viral liver diseases in pediatric cases increased from 17.53% during 2001–2010 to 23.3% during 2011–2017.

Our study also analyzed the characteristics and distribution of IMLDs across different age groups. Among the 2,103 IMLD patients, 1,213 were adults and 890 were children, with a higher proportion of adults. This finding contrasts with the general perception that IMLDs primarily occur in children. Further analysis revealed that Wilson's disease accounted for a significant proportion of adult cases, with 59.4% of the 1,213 adult patients diagnosed with this condition. This suggests that Wilson's disease affects both childhood and adulthood, requiring management across the entire lifespan. Moreover, 45.6% of all Wilson's disease patients were diagnosed after the age of 20. The delay in diagnosis may be related to the diversity of manifestations and the subtlety of symptoms. Wilson's disease can mimic various conditions, including hepatitis, cirrhosis, splenomegaly, hepatomegaly, encephalitis, encephalopathy, peripheral neuropathy, psychiatric disorders, osteoarthritis, kidney disease, and anemia, leading to frequent misdiagnosis. One study found that the misdiagnosis rate of Wilson's disease within the first three months of symptom onset could be as high as 72.1%.[8] Additionally, up to 60% of Wilson's disease patients across all age groups initially present with liver disease, which can be asymptomatic and only detected through routine physical examinations. This often results in long-term misdiagnosis or unclear diagnosis. These findings highlight the need to strengthen public health education, raise awareness among physicians across disciplines, and reduce diagnostic delays.

In pediatric IMLD cases, among children under one year of age, the most common diseases were glycogen storage disease (33.3%), Wilson's disease (30.6%), and Alagille syndrome (15.3%). Among children aged one to six years, the prevalence of PFIC (4.9%) and hereditary hyperbilirubinemia (3.8%) gradually increased, with these diseases often persisting into adulthood. This distribution reflects the heterogeneity and complexity of IMLDs and highlights the need for clinical diagnosis and treatment strategies tailored to age-specific characteristics. For diseases such as Wilson's disease and glycogen storage disease, which are more common in childhood, early diagnosis and intervention are critical. For adolescents and adults, it is important not only to manage patients diagnosed in childhood but also to remain vigilant for conditions that may manifest later in life, such as hemochromatosis, hereditary hyperbilirubinemia, and Caroli disease.

Furthermore, our study found that hereditary hyperbilirubinemia, particularly Gilbert syndrome, is relatively common among adult patients. However, its diagnosis rate is significantly lower than reported in the literature. The prevalence of Gilbert syndrome in the general population is estimated to be between 3% and 12%.[9] The highest prevalence has been observed in African populations, ranging from 15% to 25%, while in regions such as India, South Asia, and the Middle East, it can reach up to 20%.[10,11] However, our data revealed only 151 cases of Gilbert syndrome recorded in the past 20 years, which is significantly lower than the figures reported in previous studies. A similar phenomenon has been noted in the literature. A large cohort study on Gilbert syndrome in the European population found that while the incidence rate of the rs887829-T homozygous variant of Gilbert syndrome was approximately 10%, only 3% of cases were formally diagnosed.[12] This lower diagnosis rate may be attributed to several factors. First, most patients have minimal or no symptoms and may not seek medical attention. Second, those who do seek care are typically seen in outpatient settings and are not hospitalized for this condition. Third, many patients inquire about Gilbert syndrome during consultations for other health issues rather than seeking a specific diagnosis or treatment. Fourth, the diagnosis of Gilbert syndrome is exclusionary, and although molecular genetic testing can now confirm it, physicians rarely recommend genetic testing for patients with mild bilirubin elevation.[13] Additionally, mild hyperbilirubinemia may be misinterpreted as a latent or chronic liver disease or masked by other conditions.[14] As a result, clinicians often provide explanations and educational guidance during outpatient visits but do not formally diagnose the condition in the hospital information system, making it difficult to extract accurate diagnostic data. However, this does not mean that the prevalence is low. Further large-scale studies are needed to more accurately assess the actual prevalence of Gilbert syndrome and the relationship between genotype and phenotype in the population.

The limitations of this study include its reliance on data from only two hospitals in Beijing, which may introduce regional bias. Future research should expand the sample size by incorporating data from additional regions and hospitals. Moreover, further investigation is needed to explore disease progression and treatment outcomes for different IMLDs across various age groups, providing stronger evidence to support clinical practice. For example, multi-center, large-scale prospective studies could be conducted to validate our findings further and explore new diagnostic and therapeutic approaches.

Conclusions

This study analyzed the trends and epidemiological characteristics of IMLDs in two hepatology specialist hospitals in Beijing over the past 20 years. The results indicate a significant increase in both the number of diagnoses and the variety of IMLD types, with Wilson's disease remaining the most prevalent. Key driving factors behind these epidemiological changes include advances in genetic testing and the expansion of newborn screening programs. These findings offer valuable insights for the long-term management of IMLD patients and can inform resource allocation strategies in clinical practice.

Funding

This study was supported by Capital Health Development Research Project (2022-1-2182), Beijing Hospitals Authority's

Ascent Plan (DFL20241701), and high-level public health technical talents of the Beijing Municipal Health Commission (Academic Leader -02-14).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (WH, SZ, MZ), drafting of the manuscript (WH, YH, TS), data collection (ZW, WZ, KW), critical revision of the manuscript for important intellectual content (SJZ, MZ, YG), administrative support (SZ, MZ), and study supervision (SZ). All authors have made significant contributions to this study and have approved the final manuscript.

Ethical statement

This study was approved by the Medical Ethics Committee of Beijing You'an Hospital, Capital Medical University (Approval No: Jing You Ke Lun Zi [2022] 048) and the Ethics Committee of the Fifth Medical Center, Chinese PLA General Hospital (Approval No: KY-2022-6-36-1). The informed consent was waived.

Data sharing statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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