



# Prevalence of non-Alcoholic Fatty Liver Disease and Associated Factors in Patients with Moderate or Severe Hemophilia: A Multicenter-Based Study

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## Abstract

**Introduction:** Liver health is essential for persons with hemophilia (PWH) in order to maintain access to new therapies, such as gene therapy. Non-alcoholic fatty liver disease (NAFLD) is seldom reported in the hemophilia population. The study aimed to investigate the prevalence of NAFLD and associated factors in PWH. **Methods:** Data of this cross-sectional study were obtained from a multicenter collaborative registry database. **Results:** A total of 163 moderate or severe PWH with a complete data of liver examination were analyzed. There were 77 (47.2%) PWH diagnosed with NAFLD. The multivariate analysis showed that overweight/obesity was associated with NAFLD (OR, 4.31,  $P < .001$ ). In comparison with hemophilia B patients, hemophilia A patients showed a weaker correlation with NAFLD, (OR, 0.30,  $P = .009$ ). A total of 17 (25.8%) PWH with NAFLD had an elevated level of alanine transaminase (ALT). Both overweight/obesity and presence of inhibitor to clotting factor were independently associated with elevated ALT in PWH with NAFLD. **Conclusions:** The study indicated that a high prevalence of NAFLD existed in the hemophilia population. Overweight/obesity was an independent factor for NAFLD and elevated ALT.

## Keywords

hemophilia, non-alcoholic fatty liver disease, prevalence, overweight, obesity, alanine transaminase

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## Introduction

Hemophilia A (HA) and Hemophilia B (HB) are the most common congenital coagulation factor deficiencies caused by mutations in the genes encoding clotting factor VIII (FVIII) or factor IX, respectively.<sup>1</sup> Many studies have shown that high prevalence of HCV infection persists among persons with hemophilia (PWH) due to the use of contaminated blood components and clotting factor concentrate,<sup>2-5</sup> and it can lead to the development of chronic liver disease (CLD) and hepatocellular carcinoma (HCC).<sup>6-8</sup> Owing to improvements in the safety of replacement therapy and the introduction of direct-acting anti-viral therapy, which was approved in 2015, it has been possible to set targets to eliminate HCV infection by 2030.<sup>9</sup> At the population level, non-alcoholic fatty liver

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disease (NAFLD) affects approximately 30% of the global population, and cases of NAFLD continue to increase in the Asia-Pacific region.<sup>10,11</sup> NAFLD is known to be associated with obesity, diabetes, hyperlipidemia, metabolic syndrome, and hypertension. In addition, an elevated prevalence of obesity is observed in PWH,<sup>12-14</sup> and there may be an association of obesity with NAFLD in this population as well as in the general population. However, relevant studies on NAFLD are very scarce in the hemophilia population.<sup>15</sup> Importantly, a number of patients with NAFLD progress into CLD and HCC.<sup>16,17</sup> Therefore, it is essential to maintain liver health since it is the target organ for the future introduction of gene therapy and non-factor therapies.<sup>18,19</sup>

This study aimed to investigate the prevalence of NAFLD and associated factors in patients with moderate or severe hemophilia using a multicenter-based database in Taiwan.

## Methods

### Data Sources

The study was approved by the Institutional Review Board of all participating sites in Taiwan. Informed consent was obtained from all participants. Data were obtained from the collaborative registry database which was established in 2014 by six hemophilia comprehensive care centers from northern, central, and southern Taiwan in order to prospectively investigate the efficacy of prophylactic therapy and the comorbidities in PWH. The data analyzed in this cross-sectional study were collected between December 2021 and February 2022.

### Identification of Study Participants

All of 244 moderate or severe hemophilia, defined as a baseline level of clotting factor activity less than 1% and 1% to 5%, respectively with a regular annual check-up as part of their comprehensive hemophilia care were enrolled (Figure 1). We excluded 61 PWH with incomplete laboratory data and 20 PWH without imaging of liver sonography. A total of 163 PWH with complete liver examination data were classified into pediatric and adult groups. After excluding 5 patients with alcohol consumption, the remaining 158 PWH were classified into non-NAFLD and NAFLD groups for analysis and comparison.

Non-alcoholic steatohepatitis (NASH) diagnosis is often formally established using a liver biopsy. However, this invasive procedure can be risky for PWH. We used ALT level as a surrogate marker of risk classification for NAFLD.<sup>20</sup> In order to investigate the impact of NAFLD on liver function tests (LFTs), we further excluded PWH with autoimmune disease, inborn errors of metabolism, as well as active HCV and HBV infection which can cause abnormal LFTs. Autoimmune disease was screened by detecting antinuclear antibodies, anti-mitochondria antibody, and anti-smooth muscle antibody antibodies. With regard to the survey of inborn error of metabolism, we did tests including

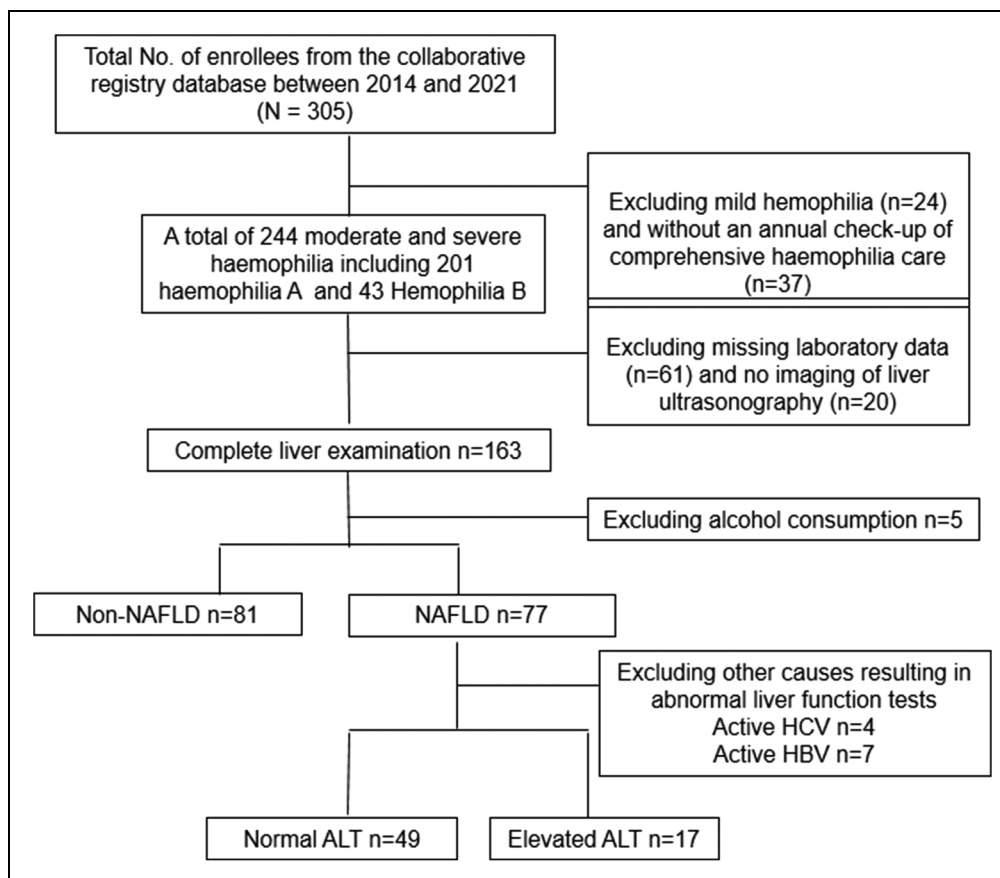
ammonia, blood gases, lactate, ketones, alpha-fetoprotein, urine copper, ceruloplasmin, alpha-1 antitrypsin level, blood amino acid, and urine organic acid. Finally, PWH with NAFLD who had two or more ALT values above the upper limit of the normal range (50 IU/L) more than 6 months apart were deemed to be the elevated ALT group; and the remaining PWH with NAFLD were classified as the normal ALT group.

### Data Collection and Definition

The demographic data and characteristics of the patients included in the analysis were as follows: birth date, treatment regimens, presence of inhibitor to clotting factor, body mass index (BMI), alcohol consumption, and smoking. Data related to transfusion transmitted infection, such as HBV, HCV, and HIV infection, including HBsAg, HBeAg, anti-HBs, anti-HCV, HCV virus load, and HIV-enzyme-linked immunosorbent assay, were collected. Comorbidities including hyperlipidemia, cardiovascular disease, hypertension, and diabetes mellitus (DM) were investigated. Hyperlipidemia was defined as one or more of the following: total cholesterol greater than 200 mg/dl, low-density lipoprotein greater than 130 mg/dl and triglycerides greater than 150 mg/dl. Cardiovascular diseases included arrhythmia, acute coronary syndrome, heart failure, peripheral artery occlusive disease, and cerebral infarction. Overweight was defined as a BMI of 25.0 to less than 30.0 kg/m<sup>2</sup>. Obesity was defined as a BMI of 30.0 kg/m<sup>2</sup> or greater.

Blood test data for LFTs including aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase, total bilirubin and direct bilirubin were collected. Elevated LFTs were defined as levels above the upper limit of the normal range.

The definition of NAFLD encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption defined as alcohol consumption of less than 210 g per week. It ranges from fatty liver to hepatic steatosis (HS) to cirrhosis. There must be evidence of HS by liver ultrasonography and lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long-term use of a steatogenic medication, or monogenic hereditary disorders.<sup>21</sup> The severity of fatty liver was divided into mild, moderate, and severe degree based on the examination of liver ultrasonography (Figure 2). Mild fatty liver was defined as mild increase of liver parenchyma echogenicity compared to kidney or spleen with normal visualization of the wall of portal vein and diaphragm. Moderate fatty liver was defined as moderate increase of liver parenchyma echogenicity compared to kidney or spleen with mild dimness of the portal vein wall and diaphragm. Severe fatty liver was defined as severe increase of liver parenchyma echogenicity compared to kidney or spleen with poor visualization of the portal wall and diaphragm due to elevation of echogenicity.<sup>22</sup> The images of liver ultrasonography were reviewed by radiologists or hepatologists at the participating sites.



**Figure 1.** Study design flowchart. NAFLD, non-alcoholic fatty liver disease; ALT, alanine transaminase.

## Statistical Analyses

Frequencies were calculated by direct counting. The prevalence rates of patients' demographic variables, characteristics, and comorbidities were calculated as the proportion of individuals with variables relative to the study group. Categorical data were calculated using the chi-square test. Continuous variables were expressed as mean with 95% confidence intervals (CIs), and were compared using t-test analysis. A two-tailed *P*-value of less than .05 was considered significant. For the multivariate analysis, the odds ratios (OR) for comparisons of variables between the two groups were calculated using a logistic regression model. Accompanying 95% CIs were calculated, and a two-tailed *P*-value of less than .05 was considered significant. All statistical analyses were conducted using SAS software (version 9.2; SAS Institute Inc., Cary, NC).

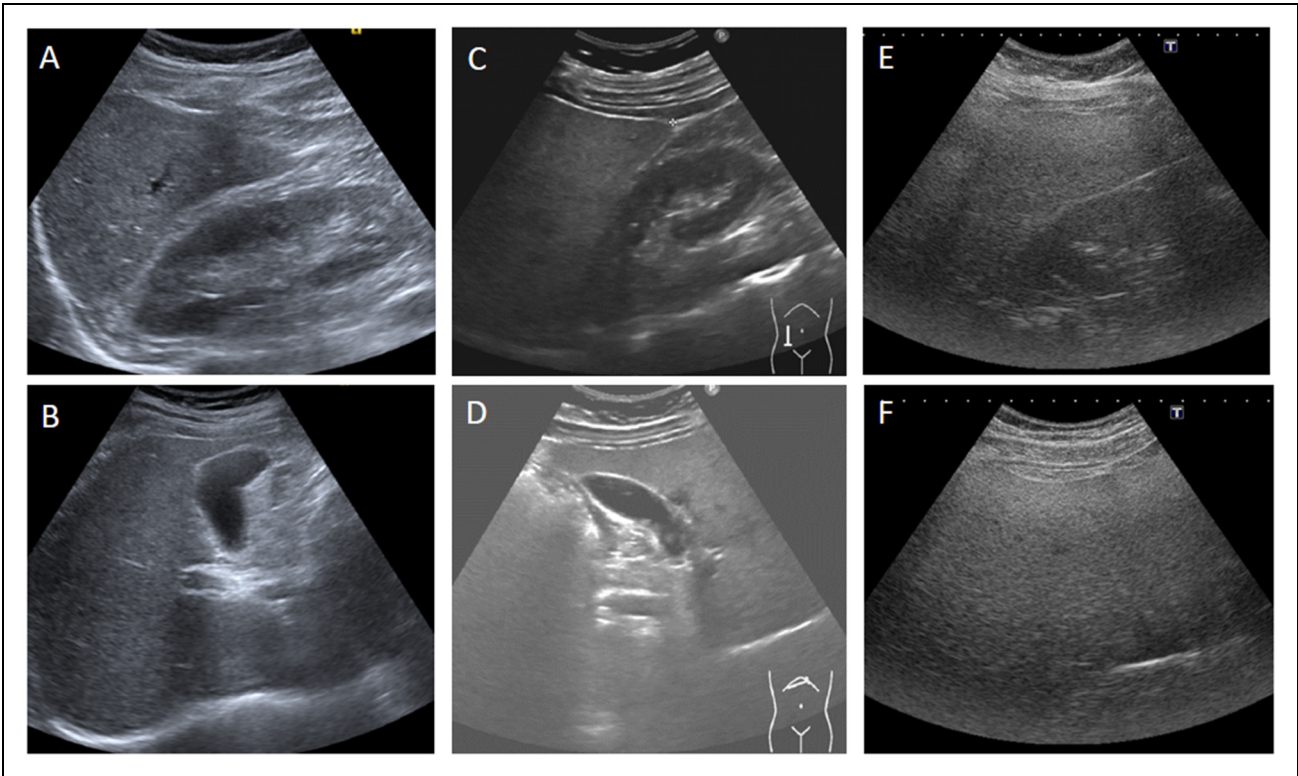
## Results

### Demographics, Characteristics and Comorbidities of 163 Patients with Moderate or Severe Hemophilia

Data from the Taiwan Society of Thrombosis and Hemostasis (TSTH) registry were available for further analysis of 163 males with moderate or severe PWH (Table 1). Of these, 32

(19.6%) PWH below the age of 18 years old were classified into the pediatric group, while the remaining 151 (80.4%) PWH were assigned to the adult group. The percentage of HA and HB were 77.9% and 22.1%, respectively. Disease severity of hemophilia was predominantly (87.7%) the severe type. The total rate of PWH on a prophylactic therapy was 81.6%. The rate of presence of inhibitor to clotting factors was 18.8% and 9.2% in the pediatric and adult groups, respectively.

In the adult group, the mean BMI was 25 (95% CI, 24.6-26.1); 63 (48.1%) PWH were overweight and 19 (14.5%) PWH were obese. Moreover, the mean BMI was 20 (95% CI, 18.4-21.8) in the pediatric group; 4 (12.5%) were overweight and 1 (3.1%) was obese. Alcohol consumption was reported by 5 (3.1%) adult PWH. The amount of alcohol consumed per week ranged from 297 to 693 g. In total, 43% of adult PWH had a history of HCV infection, including only one below 18 of age. Twenty (15.3%) of the 131 adult PWH had elevated LFT, and 3 (2.3%) had an elevated level of ALT more than twice the normal upper limit. Hyperlipidemia, hypertension and DM all occurred in adult PWH except for one pediatric PWH with hyperlipidemia. A total of 79 (49.1%) PWH, comprising 5 pediatric and 74 adult PWH, had fatty liver as determined by ultrasonography. Thirty-eight percent of PWH with fatty liver were classified as moderate or severe.



**Figure 2.** Liver ultrasonography. A 42-Year-old severe hemophilia A with mild fatty liver showing mild increase of liver parenchyma echogenicity compared to kidney (A) and normal visualization of the wall of portal vein(B). A 57-Year-old severe hemophilia B with moderate fatty liver showing moderate increase of liver parenchyma echogenicity compared to kidney (C) and mild dimness of the portal vein wall (D). A 50-Year-old severe hemophilia A with high titer inhibitor and severe fatty liver showing severe increase of liver parenchyma echogenicity compared to kidney (E) and poor visualization of the portal wall due to elevation of echogenicity (F).

### Prevalence of NAFLD and Associated Factors

In the crude analysis, the age of PWH in the NAFLD group was older than that in the non-NAFLD group, 39.7 versus 27.5 ( $P < .001$ ) (Table 2). The ratio of HA to HB in the non-NAFLD group (5.8:1) was significantly higher than that in the NAFLD group (2.2:1), (OR=0.30,  $P = .009$ ). Overweight/obesity, HCV infection, hyperlipidemia and hypertension were all associated with NAFLD.

In the multivariate analysis, overweight/obesity was independently associated with NAFLD, (OR=4.31, CI 1.87-9.93,  $P < .001$ ). In comparison with HB, HA showed a weaker association with NAFLD (OR=0.30, CI 0.12-0.75,  $P = .009$ ).

### Factors Associated with Elevated Level of ALT in PWH with NAFLD

A total of 17 (25.8%) PWH with NAFLD had an elevated level of ALT (Table 3). The mean age of PWH with an elevated level of ALT was not different compared with that of PWH with a normal level of ALT, 39.6 versus 37.8 years ( $P = .642$ ). PWH in the elevated ALT group had a higher rate of overweight/obesity than that in the normal ALT group. All of the PWH in the elevated ALT group were overweight or obese. In addition, PWH in the elevated ALT group had a higher rate of

inhibitor to clotting factors compared with that of PWH in the normal ALT group, OR=14.77, 1.52-143.73,  $P = .004$ . In addition, all of 4 PWH with NAFLD and elevated ALT had high-titer inhibitor. There was no association between overweight/obesity and presence of inhibitor to clotting factors ( $P > .05$ ).

### Discussion

The study demonstrated a high prevalence (47.2%) of NAFLD among moderate or severe PWH. Although a number of studies showed that NAFLD affects approximately 30% of the global population and an increasing prevalence has been observed both in children and adults,<sup>10,11,23,24</sup> there are few data on NAFLD in the hemophilia population. In the literature, only one study on the prevalence of NAFLD in hemophiliacs has been conducted by Revel-Vilk *et al* in 2011 and the results indicated that 3 (1.8%) of 170 hemophiliac boys had clinical and imaging findings compatible with a diagnosis of NAFLD which was considered as a common cause of liver disease in the study population. In contrast, our study reported that 5 (15.3%) of 32 hemophiliac boys had NAFLD, and 1 in 5 had elevated ALT. In comparison with the general population, a recent systematic review and a meta-analysis of 33 studies,

**Table 1.** Demographics, Characteristics, Comorbidities and Liver Examination in 163 Moderate or Severe Hemophilia Patients.

	Total		Pediatrics		Adult	
	n = 163	%	n = 32	%	n = 131	%
Age (years)	33.7	31.2-36.1	12.9	11.6-14.2	38.7	36.4-41.0
Hemophilia type						
HA	127	77.9	28	87.5	99	75.6
HB	36	22.1	4	12.5	32	24.4
Severity of hemophilia						
Severe	143	87.7	27	84.4	116	88.6
Moderate	20	12.3	5	15.6	15	11.5
On prophylactic therapy	133	81.6	27	84.4	106	80.9
Presence of inhibitor	18	11.0	6	18.8	12	9.2
Body mass index	24	23.6-25.0	20	18.4-21.8	25	24.6-26.1
Alcohol consumption	5	3.1	0	0.0	5	3.8
Smoking	24	14.7	0	0.0	24	18.3
HIV infection	1	0.0	0	0.0	1	0.8
HBV infection	11	6.8	0	0.0	11	8.4
Positivity of anti-HCV	58	35.6	1	3.1	57	43.5
Elevated LFTs	21	12.9	1	3.1	20	15.3
Hyperlipidemia	34	20.9	1	3.1	33	25.2
Hypertension	18	11.0	0	0.0	18	13.7
Diabetes mellitus	6	3.7	0	0.0	6	4.6
Cardiovascular disease	3	1.8	0	0.0	3	2.3
Fatty liver by ultrasonography	79	49.1	5	15.6	74	57.4
severity of fatty liver						
severe	8	10.1	1	20.0	7	9.5
moderate	22	27.9	0	0.0	22	29.7
mild	49	62.0	4	80.0	45	60.8

Abbreviations: HA, hemophilia A; HB, hemophilia B; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; LFT, liver function test. Age and body mass index expressed as mean and 95% confidence interval

comprising a total population of 20 595 children in Asia, showed an overall NAFLD prevalence of 5.5%, of which 36.6% of NAFLD subjects had elevated levels of ALT.<sup>24</sup> A trend of male predominance was also observed in NAFLD (boys: 8.1% vs girls: 3.6%). Our study showed the prevalence of NAFLD in pediatric PWH was higher than that in the general population. Additionally, the prevalence of pediatric NAFLD in the hemophilia population increased from 1.8% in 2011 to 15.3% in 2021. Although the two studies were conducted in different countries and different methods were used, it is abundantly clear that more attention needs to be paid to the prevention and treatment of NAFLD in hemophiliacs.

This study also demonstrated that an association of NAFLD in PWH with overweight/obesity, which has been well-established as the largest risk factor for NAFLD in the general population. Despite increasing awareness of this trend, several studies have shown the prevalence of overweight/obesity remains high in the hemophilia population.<sup>12,14,25,26</sup> In line with these reports, our study showed a high prevalence of overweight/obesity in the adult and pediatric groups, with rates of 62.6% and 15.4%, respectively. Importantly, NAFLD has been recognized as the most common cause of CLD in the pediatric population and is strongly associated with obesity.<sup>27-29</sup> In addition, children with NAFLD are at elevated risk of developing cirrhosis and

HCC.<sup>30</sup> This should serve as a wake-up call to increase awareness of pediatric NAFLD.

With regard to the relationship between hemophilia type and NAFLD, our study findings showed that HA had a weaker association with NAFLD in comparison with HB. Although both HA and HB have many similarities, several differences between HA and HB have been observed from both the clinical and molecular perspectives.<sup>31,32</sup> Beyond hemostasis, differences in thrombin generation between HA and HB have been observed, which may be attributed to the role of platelets in the assembly of the tenase complex on their surface. One study also suggests that HA has a protective effect against liver fibrosis development in a murine model.<sup>33</sup> It could be attributed to reduced thrombin generation, resulting in a lowered ability to activate hepatic stellate cells and platelets via the protease-activated receptor pathway. Emerging evidence also shows that FVIII is involved in multiple biological systems, including bone, vascular, and immune systems.<sup>34</sup> A dysregulation of the inflammatory processes has been observed in FVIII deficiency.<sup>35</sup> In patients with NAFLD, inflammation can be observed over liver lobules, even in the portal system which is associated with more advanced disease.<sup>36</sup> It is unknown whether FVIII deficiency attenuates development of NAFLD, and more studies are needed to elucidate the relationship.

**Table 2.** Associated Factors of non-Alcoholic Fatty Liver Disease in Patients with Moderate or Severe Hemophilia.

	non-NAFLD		NAFLD		Odds ratio (crude)	95% CI	P-value†	Odds ratio (adjusted)	95% CI	P-value‡
	n = 81	%	n = 77	%						
Age (years)	27.5	24.1-31.0	39.7	36.6-42.8			<.0001*§	1.03	(0.999-1.07)	.060
Hemophilia type										
HA	69	85.2	53	68.8	0.38	(0.18-0.834)	.014*	0.30	(0.12-0.75)	.009*
HB	12	14.8	24	31.2						
Severity of hemophilia										
Severe	71	87.7	69	89.6	1.21	(0.45-3.26)	.698	–	–	–
Moderate	10	12.4	8	10.4						
On prophylactic therapy	64	79.0	66	85.7	1.59	(0.69-3.66)	.27	–	–	–
Presence of inhibitor	11	13.6	7	9.1	0.64	(0.23-1.74)	.374	–	–	–
Overweight/obesity	17	21.0	47	61.0	5.90	(2.92-11.93)	<.0001*	4.31	(1.87-9.93)	.000*
Smoking	6	7.4	14	18.2	2.78	(1.01-7.65)	.041*	2.08	(0.63-6.83)	.228
HIV infection	0	0.0	1	1.3	3.20	(0.13-79.66)	.303	–	–	–
HBV infection	4	4.9	7	9.1	1.93	(0.54-6.86)	.305	–	–	–
Positivity of anti-HCV	17	21.0	39	50.7	3.86	(1.92-7.76)	<.0001*	1.85	(0.69-4.97)	.221
Hyperlipidemia	6	7.4	27	35.1	6.75	(2.6-17.53)	<.0001*	2.94	(0.94-9.19)	.064
Hypertension	4	4.9	14	18.2	4.28	(1.34-13.65)	.008*	0.86	(0.21-3.57)	.835
Diabetes mellitus	1	1.2	5	6.5	5.56	(0.63-48.68)	.083	–	–	–

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HA, hemophilia A; HB, hemophilia B; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

Age expressed as mean and 95% confidence interval.

\*P-value < .05; †P-value for chi-square test; ‡P-value for logistic regression mode; §P-value for t test.

**Table 3.** Associated Factors of Elevated Alanine Transaminase in 66 Hemophilia Patients with non-Alcoholic Fatty Liver Disease.

	Normal ALT		Elevated ALT		Odds ratio	95% CI	P-value†
	n = 49	%	n = 17	%			
Age (years)	37.8	33.7-41.9	39.6	33.0-46.3	–	–	.642‡
Hemophilia type							
HA	35	71.4	10	58.8	1.75	(0.56-5.51)	.336
HB	14	28.6	7	41.2			
Hemophilia severity							
Severe	44	89.8	15	88.2	0.85	(0.15-4.86)	.857
Moderate	5	10.2	2	11.8			
On prophylactic therapy	44	89.8	12	70.6	0.27	(0.07-1.10)	.057
Presence of inhibitor	1	2.0	4	23.5	14.77	(1.52-143.73)	.004*
Overweight/obesity	24	49.0	17	100.0	–	–	–
Smoking	9	18.4	3	17.7	0.95	(0.23-4.03)	.947
HIV infection	0	0.0	0	0.0	–	–	–
Prior HCV infection	23	46.9	7	41.2	0.79	(0.26-2.42)	.681
Hyperlipidemia	17	34.7	6	35.3	1.03	(0.32-3.26)	.964
Hypertension	10	20.4	3	17.7	0.84	(0.20-3.48)	.805
Diabetes mellitus	3	6.1	2	11.8	2.04	(0.31-13.42)	.449

Abbreviations: ALT, alanine transaminase; HA, hemophilia A; HB, hemophilia B; HIV, human immunodeficiency virus; HCV, hepatitis C virus.

Age expressed as mean and 95% confidence interval.

\*P-value < .05; †P-value for chi-square test; ‡P-value for t test.

NASH is the progressive form of NAFLD, defined as the presence of  $\geq 5\%$  hepatic steatosis with inflammation and ballooning of hepatocytes, regardless of hepatic fibrosis.<sup>21</sup>

Although liver biopsy is still essential for the diagnosis, it is risky for PWH. The NASH biomarkers and the performance of imaging modalities such as magnetic resonance spectroscopy

are still under investigation, and are not yet universally used in clinical practice.<sup>37</sup> Moreover, serum ALT is widely used to screen for NAFLD in obesity and provides a good diagnostic accuracy for determining the presence of NAFLD.<sup>29</sup> Additionally, a large cohort study showed patients with NAFLD and elevated ALT were at higher risk for cirrhosis than those with NAFLD and normal ALT.<sup>20</sup> In this study, we used the upper normal limit of ALT level as the cut-off point to classify NAFLD into the two groups in order to investigate factors associated with elevated ALT in NAFLD patients.

The study showed that both overweight/obesity and presence of inhibitor to clotting factor were associated with elevated ALT in NAFLD patients. All PWH with NAFLD and elevated ALT were overweight or obese. Previously, most PWH with presence of inhibitor were severely affected until the introduction of emicizumab.<sup>38</sup> It has been postulated that the disease severity of hemophilia is associated with known or potential risk factors for weight gain, and PWH are more likely to be sedentary due to the fear of traumatic bleeding. However, some prevalence studies have examined the relationship between hemophilia disease severity and obesity, and the findings were inconsistent.<sup>14,15,39</sup> Our results support previous findings showing that the association between NAFLD and presence of inhibitor to clotting factor was not confounded by overweight/obesity. With regard to the presence of inhibitor and its association with elevated ALT in PWH with NAFLD, we conducted a further analysis to determine whether there was a correlation with annual bleeding rate (ABR). However, the result showed no difference in ABR between the two groups ( $P = .728$ ). Therefore, further studies are needed to elucidate the relationship between presence of inhibitor and elevated ALT in PWH with NAFLD.

Some limitations in this study could have affected the results and interpretations. The studied population was not compared with an age-matched normal population. In addition, mild hemophilia was not included in this study because of the enrollment limitation of the collaborative registry database. It resulted in selection of more severe cases requiring replacement therapy. We also used the images of liver ultrasonography instead of histology to diagnose and determine the severity of fatty liver. Lastly, due to the rare nature of hemophilia, the number of enrolled subjects might not be large enough, in particular for the pediatric group to reach statistical power, and further data collection may lead to more findings.

## Conclusions

This study found that a high prevalence of NAFLD existed in the hemophilia population. Overweight/obesity was strongly associated with NAFLD and elevated ALT. Current therapeutic approaches prolong the life expectancies of PWH, resulting in an elevated demand for liver examination in hemophilia comprehensive care.

## Acknowledgment

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Medical University Chung-Ho Memorial Hospital, Chung Shan Medical University Hospital, Taichung Veterans General Hospital, and China Medical University Children's Hospital in Taiwan. We also thank Mr. Wei-Cheng Chan for assisting with the statistical analysis.

## Authors' Contributions

M. C. Shen and J. D. Wang designed the study, wrote the paper, and did the critical revision; C. Y. Lin, S. S. Chiou, S. C. Chou, T. F. Weng, and C. T. Peng collected and analyzed the data. S. W. Lee designed the study.

## Data Availability

The datasets used and analyzed during the current study are available from corresponding author on reasonable request.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


## Ethics Approval


The study was approved by the Institutional Review Board of all participating sites in Taiwan. (IRB TCVGH No.: CF14354A)

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