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CLINICAL CHARACTERISTICS OF AUTOIMMUNE LIVER DISEASES IN VIETNAMESE PATIENTS

By

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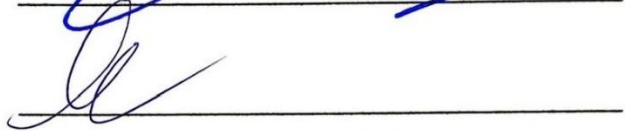Hanoi, 2024

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DECLARATION

I hereby declare that this thesis entitled "Clinical characteristics of autoimmune liver diseases in Vietnamese patients" is my own work, all information in the thesis is accurate and truthful, with full citations of the references, and does not violate the laws regarding intellectual property.

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List Of Abbreviations

Abbreviation	Definition
AIH	Autoimmune Hepatitis
ALD	Autoimmune Liver Diseases
AMA	Antimitochondrial Antibodies
AMA – M2	Anti-mitochondrial M2 antibody
AMA - M2 – 3E (BPO)	Anti-mitochondrial M2 antibodies with a mixture of bovine PDH and the recombinant fusion protein BPO, which encompasses the immunogenic domains of the E2 subunits of BCOADH, PDH, and OGDH (expression system: E. coli)
ANA	Antinuclear Antibody
ANCA	Anti-Neutrophil Cytoplasmic Antibody
ASMA or SMA	Anti-Smooth Muscle Antibodies
CENP A	Centromere protein A Antibodies
CENP B	Centromere protein B Antibodies
gp21	gp210 antibodies
HCC	Hepatocellular Carcinoma
HLA	Human Leukocyte Antigen
IAIHG	International Autoimmune Hepatitis Group
IgG	Immunoglobulin G
LC-1	Liver Cytosol Type 1
LKM	Liver-Kidney Microsomal Antibody
pANCA	perinuclear Anti-Neutrophil Cytoplasmic Antibodies
PBC	Primary Biliary Cholangitis
PGDH	15-hydroxyprostaglandin dehydrogenase Antibodies
PML	Promyelocytic Leukemia
PSC	Primary Sclerosing Cholangitis

Ro-52	Ro-52 Antibodies
Scl-70	Topoisomerase 1 Antibodies
SLA/LP	Soluble Liver Antigen/Liver-Pancreas
sp100	sp100 antibodies
SS-A	Sjogren's Antibodies

Abstract

Background: Autoimmune liver diseases (ALD) consist of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlapping syndrome. These are rare disorders that are assumed to belong to only Western countries; data from Eastern, particularly developing Asian countries, is currently lacking.

Aim: The purpose of this study is to describe the serologic spectrum, autoimmunologic profile, and clinical features of Vietnamese patients with ALD in Hanoi. The results are compared to data from previous research conducted in Western areas and other Asia-Pacific countries.

Methods: This cross-sectional study was conducted in two hospitals in Vietnam from 2021 to 2024. The following parameters were recorded when analyzing the medical records of all 32 patients: the patient's demographic data, clinical history at presentation, and findings of laboratory and serologic testing—not only the biochemistry but also the immunologic profile at the time of diagnosis.

Results: The total number of ALD patients in the study was 32, including 31.25% with AIH (n=10), 68.75% with PBC (n=22), and no patients with PSC and overlapping syndrome. Most were female and within middle age (51 years in the AIH group and 49 years in the PBC group). Fatigue, loss of appetite, and jaundice were the most reported symptoms in both groups. Depending on the pattern of ALD, the more serology antibodies were positive, the more accurately ALD was diagnosed in comparison to positive single antibody cases.

Conclusion: Our study found that most ALD cases in Vietnam were middle-aged females with PBC or AIH with nonspecific symptoms. Further long-term studies investigating the epidemiology and prognosis of ALD in Vietnam is needed.

Introduction

The liver disease could be acute or chronic; in contrast to the acute episode, the chronic stage of the liver could be variant, ranging from asymptomatic to mild or subtle, with constitutional manifestations that could lead to delayed diagnosis, such as decompensated cirrhosis and advanced malignancy. Two million deaths a year are caused by liver disease, which also accounts for 4% of all deaths (1 out of every 25 deaths globally) [1]. Based on the latest research on the global burden of liver disease updated in 2023 and published in the Journal of Hepatology, viral hepatitis (including viral hepatitis B and C), alcohol, and non-alcoholic fatty liver disease are the most frequent causes of chronic liver diseases globally [1, 2]. Autoimmune liver diseases (ALD), which include autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, are identified as the other, less common causes of liver burden. While the majority of studies conducted over the past few decades demonstrate that ALD is rare and is diagnosed in Western countries, a larger number of case series or multicenter retrospective observational studies from Eastern sites have been published in recent times, especially from developed countries such as Japan, South Korea, and China [3]. Unfortunately, depending on a variety of factors, such as the economy and healthcare mobility for facilities in a developing country such as Vietnam, the ALD is challenging to detect until the high-yield laboratory test or high-quality imaging technique allows for an accurate diagnosis after ruling out other common etiologies mentioned above. The diagnosis of ALD has gained attention as multidisciplinary healthcare systems have been supported or improved in recent years, and certain research studies on this specific type of liver disease have been published in Eastern populations. The January 2022 Liver International Journal published a paper comparing the differences in epidemiology, genetic predispositions, clinical features, diagnosis, and treatments between Eastern and Western countries [4]. The paper also noted the lack of data from the Vietnamese population in the context of publication resulting from misdiagnosis or underdiagnosis of chronically increased abnormal liver enzymes. In addition to providing a general overview of this rare disease from a Vietnamese perspective, this paper attempts to characterize the features of ALD patients in Vietnam. An adult patient with ALD who had chronic abnormal liver enzymes was recruited for this investigation from a tertiary hospital in Vietnam. Assess medical records to collect information on immunologic profiles, laboratory and imaging results, clinical manifestations, and epidemiology. Following the internationally published diagnosis criteria, generate the final diagnosis and then compare the research results to populations from Asia and the West to identify noteworthy, distinct characteristics.

Chapter 1
Background & Rationale

1.1. Global Liver Burden And Autoimmune Liver Diseases

Liver disease is the cause of two million deaths per year and 4% of all deaths worldwide (1 out of every 25 deaths) [1]. The majority of deaths are caused by complications from hepatocellular carcinoma and cirrhosis, with acute hepatitis contributing less to the deaths. According to the publication from 2023, viral hepatitis (including viral hepatitis B and C), alcohol, and non-alcoholic fatty liver disease are the most frequent causes of chronic liver diseases [1]. Apart from the most common causes mentioned above, autoimmune liver diseases (ALD) are rare, treatable, and frequently misdiagnosed in clinical settings since they have inconsistent as well as asymptomatic manifestations. ALD includes autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). AIH is a liver-inflammatory disease resulting from a defective immune system response directed against liver tissue. PBC and PSC, on the other hand, are biliary tract diseases resulting in cholestatic pattern abnormalities. The vast majority of the time, these conditions are associated with elevated tests for liver function with or without symptoms, and they further silently progress to end-stage liver disease, such as advanced malignancy or decompensated cirrhosis. Recognizing ALD is challenging, especially the seronegative type, which is known as the negative typical specific autoantibody. In a clinical setting, understanding the clinical spectrum and serological patterns of these diseases in different populations could be advantageous in enhancing patient management and preventing further complications from ALD.

1.2. Autoimmune Hepatitis

The term "autoimmune hepatitis" refers to a progressive, chronic liver inflammation that has no known cause and is marked by hypergammaglobulinemia, interface hepatitis, high levels of aminotransferases, and autoantibodies. When Waldenstrom first described AIH in 1950, it was known as chronic active hepatitis (CAH), and at the time it was considered a "new" disease. AIH was known as "lupoid" hepatitis, derived from associated lupus erythematosus (L.E.) cell test positivity, and emphasized accompanying multisystem features and immunological aberrations [5]. Systemic lupus erythematosus, which was thought to be its cause, was present in patients at the time of diagnosis. The development of serology tests such as an antinuclear antibody (ANA), anti-smooth muscle antibodies (SMA), serum immunoglobulin G (IgG) levels, and optimal safety liver biopsy performance significantly increased the diagnosis of AIH. The interaction of genetic predisposition, an environmental trigger, and native immune system dysfunction has been proposed as the mechanism for the development of autoimmune hepatitis, leading to chronic inflammation of hepatocytes and, eventually, liver fibrosis. Recent

epidemiological research has shown that the prevalence of AIH is rising globally; the prevalence and incidence of AIH were 3.1 and 2.8 times higher, respectively, than the rates recorded before the year 2000s [6]. AIH has a broad spectrum of clinical phenotypes, which makes it challenging to diagnose and manage. Typically, the International Autoimmune Hepatitis Group (IAIHG) diagnostic scoring system is utilized in combination with clinical, biochemical, serologic, and histological findings to establish the diagnosis. Diagnostic scores comprise mostly non-disease-specific findings. Although these criteria are available, often the diagnosis of AIH is made clinically. Compared to age- and sex-matched controls, AIH is linked to a 1.5-fold increased 10-year risk of any cancer, including hepatocellular carcinoma (HCC), colorectal cancer, lymphoma, and non-melanoma skin cancer. Patients with cirrhosis had a higher risk of developing any type of cancer among AIH patients, particularly when receiving immunosuppressive treatment for an extended period [1]. Given the increasing disease burden, several systematic reviews and meta-analyses were conducted to describe the characteristics of disease not only in the United States and Europe but also in developed Asian countries such as Japan, South Korea, and China.

In the latest publication in 2023 by Korean scientists, the incidence and prevalence of AIH have greatly increased and diverged significantly between global regions. The highest incidence and prevalence were recorded between 2015 and 2022. The global pooled incidence and prevalence of AIH were found to be 1.28 cases per 100,000 inhabitant-years and 15.65 cases per 100,000 inhabitants, respectively [6]. The incidence of AIH was highest in North America at 3.35 cases per 100,000 inhabitants per year and the lowest in Asia at 0.99 cases per 100,000 inhabitants per year. The highest prevalence was found in the United States (29.55 cases per 100,000 inhabitants), while the lowest prevalence was observed in Singapore (4.23 cases per 100,000 inhabitants). Subgroup analysis demonstrated a higher prevalence in European and American populations than in Asian populations; furthermore, a higher prevalence was observed in women and adults over 65.

Based on the immunologic profile, AIH is classified into two groups: seropositive, where antiantibodies are found during the evaluation process, and seronegative, where non-autoantibodies are observed in response to a corticosteroid treatment trial. The two standard types, referred to as type 1 and type 2, are grouped in the seropositive group. Type 1 AIH characteristic autoantibodies include antinuclear antibodies (ANAs), anti-smooth muscle antibodies (ASMAs), and anti-soluble liver antigen antibodies (anti-SLA), most common in adults. Type 2 AIH-characteristic autoantibodies include anti-liver-kidney microsomal-1 antibodies (anti-LKM-1) and anti-liver cytosol antibodies-1 (ALC-1), most common in children. While there may be a small number of young patients with type 2 AIH in South Asian

nations, the majority of patients in East and Southeast Asia are middle-aged women with type 1 AIH who benefit from steroid-based immunosuppressive therapy [7].

Although the precise etiology of AIH is unknown, environmental factors and an immunogenetic background may play a role in the disease's development. The current theory of pathogenesis is believed to be secondary to immune tolerance failure in a genetically susceptible individual, which results in T-cell-mediated inflammation triggered by different environmental stimuli. The common triggers are drug exposure and viral hepatitis, with the host's genetic predisposition in the background of the disease process. The main molecule involved in antigen presentation, the human leukocyte antigen (HLA), is acknowledged as the most significant genetic factor associated with the onset of AIH. The majority of individuals with HLA-DR4-positive AIH are middle- aged and older, and many of them respond well to immunosuppressive treatment. The significant proportion of HLA-DR4-positive cases (positivity rate ranging from 35% to 60%) among AIH patients in East Asia can fully explain the region's late onset and good therapeutic response [8, 9]. Conversely, younger adults with AIH who test positive for HLA-DR3 are more likely to experience treatment resistance [10]. These environmental factors have been assumed to be drug-induced cytotoxicity and immune tolerance failure caused by molecular mimicry between foreign and self-antigens. For drug-induced AIH, oral administration of statin drugs, antibiotics (nitrofurantoin and minocycline), Kampo medicines, non-steroidal anti-inflammatory drugs, uricosuric drugs, antituberculosis drugs, and dietary supplements could trigger insults [11–13]. Additionally, AIH has long been thought to be caused by a viral infection. It has been hypothesized that a viral infection triggers the activation of autoreactive T cells as a non-specific or antigen-specific reaction [14].

Thyroiditis (10–23%), ulcerative colitis (2–8%), celiac disease (1-2%), diabetes mellitus type 1 (7-9%), rheumatoid arthritis (2–5%), systemic lupus erythematosus (1-2%), vitiligo, and psoriasis are among the conditions that usually coexist with AIH. The greatest association has been encountered with Hashimoto thyroiditis [15, 16]. The clinical features are highly variable. In 26– 70% of patients, symptoms appear within two to 120 months (about 10 years). Anorexia, fatigue, nausea, amenorrhea, weight loss, fluctuating jaundice, arthralgia, and/or pruritus are among the most non-specific symptoms of AIH. Simultaneously, approximately 30% of patients with AIH have "acute hepatitis," which is defined by extremely elevated aminotransferase levels ($\geq$10 times the upper limit of normal); these patients typically have jaundice and require immediate medical attention [17]. A quarter or so of AIH patients have no symptoms [18]. In the absence of symptoms, distinctive hepatic biochemical and histologic abnormalities, including features of chronic hepatic failure, can be found.

As there is no disease-specific or definite diagnostic marker, the diagnosis of AIH is based on

positive autoantibodies (e.g., ANA, ASMA) and histological findings of interface hepatitis on biopsy. For the serology profile, elevated levels of AST and ALT are among the biochemical characteristics of AIH, while elevated serum IgG and positive autoantibody test results are key immunologic features. When histologically proven to be an active disease, both bilirubin and transaminase levels fluctuate over time and can spontaneously normalize. Thus, biochemical evidence of hepatitis cannot be used as an indicator of the disease's severity. In addition to being crucial for diagnosing AIH, a serological investigation usually (even though not necessarily) exhibits hypergammaglobulinemia with increased IgG and normal IgM and IgA levels. Serum IgG level tests are also essential for monitoring treatment outcomes and decreasing steroid dosage in AIH patients. From the immunologic features, the evaluation of autoantibodies is essential for the diagnosis of AIH. Eighty percent of cases are of type 1 AIH, which is mainly composed of antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and anti-actin antibodies. Type 2 AIH is predominantly composed of seronegativity for SMA and ANA, as well as anti-liver-kidney microsomal antibody 1 (anti-LKM1). Type 2 is considered a more aggressive course. The initial steps in diagnosing AIH are ANA, SMA, and anti-LKM1 serology. ANA is important for diagnosis among autoantibodies. ASMA measurement is of the utmost importance for AIH diagnosis, in addition to ANA. Most countries in the Asia-Pacific region have a percentage of ASMA-positive AIH patients ranging from 19% to 45% [8, 19–21]. About 70% of AIH patients in Europe have positive ANA results, while between 30% and 60% have positive ASMA results [22–25]. In America, ASMA-positive AIH patients are more common than any other population, ranging from 45% to 84% [26, 27]. Higher rates of recurrence, more severe histological alterations, and an increased risk of liver transplantation (LT) or liver failure mortality are all associated with antisoluble liver antigen/liver pancreatitis (anti-SLA/LP). Anti-SLA/LP, however, is not very common, particularly in Asia. Up to 20% of clinical scenarios suggest that AIH possesses seronegativity for ANA, SMA, or anti-LKM1 [28]. According to fluctuating serology throughout the diseases, seronegativity for ANA, SMA, and anti-LKM1 at the initial presentation with acute hepatitis should be reevaluated after three to six months [29]. In seronegative AIH, atypical autoantibodies can be evaluated. A variety of double-strand DNA (dsDNA) antibodies, anti-actin antibodies, anti-α -actinin antibodies, anti-liver cytosol 1 (anti-LC1) antibodies, anti-asialoglycoprotein receptor antibodies (anti-ASGPR), anti-liver kidney microsomal antibody 3 (LKM-3, anti-UDP-glucuronosyltransferase (UGT)), and atypical perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) could be positive beside the traditional typical autoantibodies in AIH. The seropositivity of atypical autoantibodies may increase diagnostic accuracy [30, 31]. Autoantibodies should be evaluated carefully, with atypical antibodies appearing after seronegativity for ANA, SMA, and anti-

LKM1. In circumstances where the immunologic profile is negative and AIH is still suspected in the non-diagnostic pre-treatment IAIHG revised diagnostic score, seronegative AIH is more likely to be established after other etiologies have been ruled out and the diagnosis is practically confirmed with an empirical three-month corticosteroid course [32]. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines both recommend liver biopsy as a means of supporting the diagnosis [31, 33]. As regards the previous versions of the simplified system for AIH diagnosis, liver histology is one of the parameters needed to validate the clinical diagnosis of AIH. The system consists of four parameters: AIH histology, which is coded as absent, typical, or compatible; autoantibodies; serum IgG; and the results of the viral hepatitis work-up. The results of histology could demonstrate overlapping characteristics of autoimmune biliary disorders and potentially coexisting disorders, particularly steatohepatitis of alcoholic or non- alcoholic disease, viral hepatitis, drug-induced liver injury (DILI), and other metabolic diseases (alpha1-antitrypsin deficiency, hemochromatosis, and Wilson disease, especially in young patients). Interface hepatitis (70–80% of patients), plasma cell infiltration (66%), emperipolesis (65%), lobular hepatitis (47%), hepatocytic rosettes (33%), and centrilobular necrosis (29%) are the most common features. The presence of interface hepatitis with emperipolesis, rosettes, and lobular lymphoplasmacytic invasion can be considered "typical" histologic pictures of AIH. In the histological spectrum of AIH, predominant or exclusive centrilobular injury is now recognized and may indicate an early stage of the disease [34]. There is no histological difference between AIH type

1 and type 2 clinical subtypes [35–37]. Additionally, the histology of seronegative AIH is not different from that of patients with a typical spectrum of autoantibodies [37]. The biopsy also allows the assessment of the response to therapy and provides information on the disease's severity and the stage of fibrosis. Since non-invasive tests for the assessment of fibrosis have not been fully validated in AIH and ALT values do not properly correlate with the severity of the disease, grading of the inflammatory activity and staging of the fibrosis under histology findings are necessary and have implications for prognosis and therapy. The EASL guidelines state that treatment withdrawal is considered after biochemical remission, but it also requires histological remission, which is characterized as normal histology or minimal hepatitis (HAI < 4 or equivalent) [33]. The persistence of inflammation to any extent, particularly interface hepatitis, and the presence of plasma cells in biopsy samples collected during treatment are strong indicators of AIH relapse if immunosuppression is discontinued.

Since there is currently no gold standard test to diagnose AIH, various published criteria based on specific situations, each with its advantages and disadvantages, are applied. A diagnostic

scoring system was proposed by the International Autoimmune Hepatitis Group (IAIHG) in 1993 to objectively identify patients as having "definite" or "probable" AIH. The scoring system's extremely high sensitivity (range, 97–100%) for diagnosing AIH in different populations was demonstrated by the validation studies [38, 39]. It was determined that across multiple validation studies, the overall diagnostic accuracy was 89.8% [40]. To improve the ability to rule out alternative types of autoimmune liver diseases and to improve diagnostic accuracy, the IAIHG revised the original diagnostic criteria in 1999. However, it is challenging to apply the updated original criteria in clinical practice since it contains 29 possible grades and 15 components. The IAIHG established simplified international diagnostic criteria in 2008. Additionally, the simplified version helps diagnose typical AIH cases and has excellent diagnostic specificity. The authors determined that a "definite" diagnosis of AIH required a score below 7 points, while a "probable" diagnosis required a score of 6. Out of an overall score of 8 points. In a validation set, the simplified criteria yielded 88% sensitivity and 97% specificity for probable AIH and 81% sensitivity and 99% specificity for definite AIH [41]. Nevertheless, in atypical cases—that is, cases with an acute onset or involving young patients, the elderly, or those coexisting with viral hepatitis—these criteria may contribute to a diagnosis being overlooked [42]. As previously mentioned, AIH varies by race in terms of genetic background, clinical features, and treatment responsiveness. Nevertheless, the IAIHG scoring system remains widely used as a diagnostic tool for AIH in the majority of Asian countries except Japan, which has a unique AIH diagnostic guideline.

The optimal management plan in AIH is to control the disease, prevent the acute episode, and prevent the progression to advanced cirrhosis, or HCC. AIH is linked to a 1.5-fold higher 10-year risk of any cancer (which comprises non-melanoma skin cancer, HCC, lymphoma, and colorectal cancer) when compared to age- and sex-matched controls. Patients with cirrhosis had a greater likelihood of developing any type of cancer than people with AIH, particularly when receiving immunosuppressive therapy for an extended period. It is recommended to exercise caution because patients with AIH who are male, elderly, or have cirrhosis have a higher risk of developing HCC. Older patients with AIH diagnoses probably already have cirrhosis and need to be closely monitored. Abdominal ultrasonography for HCC and serum tumor markers should be performed to continuously and closely monitor them. There have been published reports from Asia, Europe, and the USA on research studies on AIH in the elderly. The international diagnostic criteria did not show any difference in scoring between the younger and older groups. Conversely, cirrhosis was much more prevalent in older AIH patients compared to younger AIH patients. Elderly AIH patients, even in Europe, had a higher incidence of ascites, suggesting that their fibrosis may be more advanced [43]. The proportion

of cirrhosis is rising, presumably due to a decline in the proportion caused by viral hepatitis, such as HBV or HCV. However, AIH was responsible for 1.7%–11% of all cases of chronic hepatic disease in South Asia [44, 45]. The majority of cases in South Asia are identified as AIH after they have advanced to the cirrhosis stage [46]. Therefore, it is crucial to suspect and diagnose AIH at the earliest stage before it establishes cirrhosis. Besides invasive liver biopsy for the evaluation of liver inflammation and fibrosis, non-invasive assessment methods are repeatable, inexpensive, and well-accepted as alternative tools. The degree of fibrosis in chronic liver diseases, including AIH, is now possible to determine using a variety of non-invasive laboratory techniques and radiology-based methods. Potential laboratory markers of hepatic fibrosis in AIH include the FibroTest®, the serum AST/platelet ratio index (APRI), the Fibrosis-4 index (FIB-4), the enhanced liver fibrosis (ELF) test, angiotensin-converting enzyme levels, neutrophil-lymphocyte ratio, mean platelet volume, and red cell distribution width. AIH and other chronic liver diseases can be effectively and reliably monitored with transient elastography (FibroScan), which is gradually replacing liver biopsies. Transient elastography proved advantageous in the Asia-Pacific area for predicting notable liver fibrosis in AIH patients. FibroScan measurements of liver stiffness outperformed other non-invasive markers in assessing fibrosis in AIH patients. For routine noninvasive staging of hepatic fibrosis in AIH patients, transient elastography can be used during follow-up or at the time of diagnosis. In patients with AIH, a non-invasive technique called Acoustic Radiation Force Impulse (ARFI) elastography may be utilized to distinguish between significant and non-significant liver fibrosis. It can also be used to track the progression of fibrosis in AIH patients. The most recent non-invasive method is magnetic resonance elastography. In AIH, there was a strong correlation between the results of MRE and the advanced fibrosis stage. Unfortunately, in the simultaneous occurrence of aminotransferase flare- ups, particularly in patients with advanced cirrhosis and fibrosis who exhibit acute hepatitis as a clinical pattern, the liver stiffness can be impacted by hepatic inflammation, necrosis, and swelling, resulting in non-invasive assessment methods that are not reliable instruments.

In conclusion, there are many variations of AIH in Asia. Among these are the regional variations in ethnic background and genetic variations that contribute to the clinical characteristics and prognosis of AIH. Because hepatitis B and C are so common in Asia, AIH tends to be overlooked and underdiagnosed. Although type 1 AIH cases with a good treatment response are common in Asia, the overall percentage of cirrhosis observed in patients at the time of AIH diagnosis is high, and more severe disease progression has been observed. Early detection and treatment of AIH may be able to improve the current situation in Asia. There is currently no reliable information or research investigating the clinical spectrum, serological

profiles, and epidemiology of the Vietnamese population that compares the findings to pertinent literature.

1.3. Primary Biliary Cholangitis

Chronic cholestatic liver disease known as primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, can progress to cirrhosis and liver failure if left untreated [47]. In genetically susceptible hosts, environmental factors causing immunological dysfunction can result in autoimmunity against the interlobular bile ducts. Middle-aged women are usually affected by PBC, which often manifests as fatigue, pruritus, or an asymptomatic elevation of serum glutamyl transpeptidase (GGT) or alkaline phosphatase (ALP). The pathological characteristics include destructive, non- suppurative intrahepatic cholangitis that progresses and eventually results in cirrhosis and fibrosis. In clinical settings, antimitochondrial antibodies (AMAs), particularly the M2 subtype (AMA-M2), are very specific and sensitive to PBC. The most common treatment for this illness is ursodeoxycholic acid (UDCA).

PBC was thought to be primarily seen in Western countries and relatively rare in Eastern ones until recently. Although this was most likely correct, no epidemiological data from Eastern countries was available. Epidemiological studies conducted in North America and Europe during the first ten years of the twenty-first century showed a prevalence of 11.5 to 22.7 per 100,000 people. Epidemiological data on PBC have been emerging from Oceanian and Asian countries since 2010; published studies from developed countries such as Japan, New Zealand, and South Korea were investigated. Recent research has consistently indicated a rising trend in PBC prevalence worldwide. As with other autoimmune diseases, an increasing trend may be partially explained by a greater awareness of PBC among physicians, but it most likely represents a substantially increasing number of PBC cases. However, several studies showed that incidence remained constant over time, raising the possibility that better patient outcomes for PBC patients could be the cause of an increasing prevalence. In summary, the estimated worldwide incidence and prevalence were 17.6 million per year and 146 million per year, respectively [48]. In comparison to North America (27.5 and 218.1 per million, respectively) and Europe (18.6 and 145.9 per million, respectively), the Asia-Pacific region's reported incidence and prevalence of PBC (8.4 and 98.2–118.8 per million, respectively) were lower [47, 49].

PBC's etiology remains unknown. An important role is played by the interaction of genetic/epigenetic, environmental, and immune factors [50]. As autoreactive T cells and serum AMAs are present in most cases, it has been proposed that this is an autoimmune mechanism. For genetically susceptible people, exposure to toxins, smoking cigarettes, and infectious agents can all compromise their immune system's capacity. According to reports, microbes that are

infected may function as cross-antigens and induce molecular mimicry, which could compromise self-tolerance and trigger autoimmune reactions directed toward the intrahepatic bile ducts [51].

Familial and genetic studies highlight the importance of genetic susceptibility for PBC. Recently, genome-wide association studies (GWAS) have identified multiple genes in human leucocyte antigen (HLA) and non-HLA loci that confer PBC susceptibility. The immune abnormalities that were inherited were presented by the daughters of PBC patients, whose risk increased to 35 from the relative risk of 10 for siblings of PBC patients.

Middle-aged women (approximately 40–60 years old) are usually affected by PBC, with a female-to-male ratio as high as 10:1 [52, 53]. PBC is associated with several extrahepatic autoimmune diseases, including systemic sclerosis (1.4–12.3%), autoimmune thyroid disease (5.6–23.6%), Raynaud's phenomenon (1.8–5.6%), systemic lupus erythematosus (0–3.7%), and celiac disease (0.6–6%) [54]. Seventy-eight percent were female, and 46% had an extrahepatic autoimmune disorder. Certain autoantibodies related to rheumatologic disorders, such as those against centromere and SS-A/Ro-52kD, may correspond to the diagnosis and poorer outcome of PBC [55, 56].

PBC manifests clinically as pruritus, fatigue, and, less frequently, jaundice or cirrhosis-related problems. Nowadays, routine testing of liver biochemistry is mainly accountable for the early diagnosis of an increasing number of asymptomatic patients, particularly in East Asia. Nonetheless, within five years, two-thirds of the asymptomatic patients will progress into the symptomatic phase if they are not diagnosed or treated. Patients with symptomatic PBC typically exhibit jaundice, pruritus, or fatigue. Up to 80% of patients experience fatigue, which varies depending on the severity or course of the disease. Although the exact cause of fatigue is not known, abnormalities in the central nervous system caused by cholestasis and peripheral muscle dysfunction have been associated with autonomic dysfunction, daytime sleepiness, nighttime sleep disturbance, depression, and impaired concentration. Since 20–70% of patients experience pruritus, it's another common complaint among PBC patients. It may occur at any point—before, during, or after the onset of jaundice. Most PBC patients experience mild-tolerable pruritus, but some may experience severe and chronic pruritus.

Patients with PBC who have persistent cholestasis will ultimately progress to the advanced stage and experience complications related to cirrhosis and/or cholestasis if treatment is not received.

Patients with PBC may exhibit abnormal results in biochemical tests, including elevated immunoglobulins (primarily IgM), mildly elevated aminotransferases, and increased ALP and GGT. PBC can be diagnosed serologically using AMA, especially the AMA-M2 subtype,

which has a sensitivity and specificity of > 90–95% [57, 58]. Recombinant PDC-E2, BCOADC-E2, and OGDC-E2 proteins are the three main autoantigens of AMA, and AMA testing with ELISA (AMA-M2) uses these autoantigens to measure AMA specifically and sensitively compared to IIF. Given that Western blotting is highly specific for AMA detection, additional testing using a Western immunoblot against mitochondrial antigens may be useful for diagnosis in patients with a clinical suspicion of PBC but negative results from IIF and ELISAs. Up to 50% of PBC patients have detectable levels of anti-nuclear autoantibodies (ANAs), which are significant ancillary diagnostic markers of PBC. A few ANA patterns, such as the multiple nuclear dots pattern that targets multiple proteins, including sp100, and the rim-like membranous pattern that targets gp210 and p62, are highly specific for PBC. Anti-sp100 and anti-gp210 have a high specificity (both greater than 95%) but a low sensitivity (15 ~ 40%) for AMA-negative PBC.

People who have cholestasis should have routine ultrasonography examinations. A diagnosis of PBC is extremely unlikely in patients with extrahepatic or intrahepatic bile duct dilatation on ultrasonography. To rule out other biliary diseases, such as cholelithiasis, inflammation (such as primary sclerosing cholangitis, PSC), or malignancy, one should instead consider magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), or endoscopic ultrasound.

The diagnosis of PBC can be established when meeting two or more of the following three criteria: biochemical evidence of cholestasis based mainly on the elevation of ALP and GGT with the exclusion of extrahepatic biliary obstruction by imaging studies; the presence of AMA or other PBC-specific ANAs, including anti-sp100 and anti-gp210; or histologic evidence of non- suppurative destructive cholangitis mainly affecting the interlobular bile ducts. Although there are more and more reports of PBC in Eastern nations, PBC seems to be more prevalent in Western populations. Many Asian studies have been done, but none of them include people from Vietnam. The management's goal is to minimize the disease's symptoms and ultimately prevent the condition from becoming more severe. The majority of PBC cases respond to or are under good control with UCDA and maintain a high standard of living. Because of this, the purpose of this study is to determine the immunologic profile, clinical features, and epidemiology of PBC in Vietnam and then to compare the results with current literature.

1.4. Primary sclerosing cholangitis

The progressive chronic inflammation of the intrahepatic and extrahepatic bile ducts is known as primary sclerosing cholangitis (PSC). Although the precise cause is unknown, there is a strong correlation with autoimmune conditions, especially ulcerative colitis (UC). Consequently, most PSC epidemiological research comes from the West. Even though

population-based epidemiological studies are scarce, PSC, with or without ulcerative colitis, is less common in the Asia-Pacific and African regions [49, 59]. Based on results from MRCP, the overall prevalence of PSC in IBD is estimated to be 8%, and approximately 70% of PSC cases are associated with IBD; nearly 80% of IBD cases are related to ulcerative colitis [60, 61]. Young or middle-aged men with a history of IBD tend to have PSC. PSC has a prevalence of 0 to 31.7 per 100,000 persons and an incidence of 0.1 to 1.58 per 100,000 persons per year [62]. Increased use of higher-quality cross-sectional imaging modalities, such as contrast-enhanced computed tomography, MRCP, and endoscopic retrograde cholangiopancreatography (ERCP), and increased awareness of subclinical disease may all be contributing factors to higher observed rates. On the other hand, asymptomatic disease rates are high. In patients with PSC, 44% do not exhibit any symptoms, especially in the early stages [63]. Patients may experience pruritus, fatigue, weight loss, and abdominal pain in the right upper quadrant as the disease advances. Elevated levels of gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) are two indicators of cholestasis found in laboratory tests. Up to 80% of cases show positive pANCA results, although this test is not advised for diagnosis. For diagnostic confirmation, ERCP or magnetic resonance MRCP are utilized. Liver transplantation is only used for end-stage liver disease; other liver diseases are mainly managed symptomatically. PSC may increase the risk of premature mortality and is associated with cholangiocarcinoma (CCA), gallbladder cancer, and colorectal cancer. Patients with PSC have a fourfold greater risk of death compared to the general population, but they also have a 398-fold greater risk of developing CCA. After 39 years of the disease, the cumulative risk of developing CCA increases to an estimated 20%. In the first year following a PSC diagnosis, 27% of CCA cases are diagnosed, especially in younger patients, with nearly half of them diagnosed at index presentation. Additionally, PSC patients have a 10-fold higher risk of colorectal cancer, which manifests itself a median of 20 years earlier than in ulcerative colitis controls (median age 39 vs. 59 years) [60].

PSC seems to be more prevalent in Western populations, even though reports of PBC in Eastern nations are rising—exactly like what researchers aim for in PBC. The majority of cases go undiagnosed, and if treatment is put off, it may even progress to advanced decompensated liver cirrhosis or colorectal cancer (CCA). The ultimate goal of this research is to investigate the immunologic profiles, clinical spectrum, and epidemiological characteristics of PSC in the Vietnamese patients.

In conclusion, even chronic liver disease from viral hepatitis, alcohol-related disorders, NASH/NALFD, and autoimmune liver diseases from the liver parenchymal and biliary tracts have been a burden for the healthcare system in the last several years. Since most reports from

Western sites and developed Asian countries are based on increased awareness of these diseases, information from developing countries—particularly Vietnam—is lacking, we conducted an observational, descriptive, cross-sectional study as this retrospective study which aims to two specific objectives as:

- Characterize the clinical characteristics, serology, and autoimmunology spectrum of ALD in Vietnam patients in suspected ALD patients.

- Determine the sensitivity and specificity of the autoimmune EUROLINE trip test of ALD in suspected ALD patients.

Chapter 2
Research Design And Methodology

2.1. Research Aim

- Characterize the clinical characteristics, serology, and autoimmunology spectrum of ALD in Vietnam patients in suspected ALD patients.

- Determine the sensitivity and specificity of the autoimmune EUROLINE trip test of ALD in suspected ALD patients.

2.2. Type Of Research: a cross-sectional study.

2.3. Research Population: suspected ALD Vietnamese adult patients.

2.4. Research Duration: from January 2021 to April 2024.

2.5. Sampling Design And Method

2.5.1. Sampling Frame

- Frame list: listed in the Appendix A

- Area frames: the Vinmec International Hospital and 108 Military Center Hospital

2.5.2. Inclusion And Exclusion Criteria

- **Inclusion criteria:**

    o Age $\geq$ 18 years.

    o AST, ALT, or ALP $\geq$ 2 times of upper normal limit.

    o GGT $\geq$ 5 times of upper normal limit.

    o No preexisting liver disease was detected.

    o Serology negative for viral hepatitis (HBV, HCV, HAV, HEV), HSV, CMV, EBV.

- **Exclusion criteria:**

    o Age < 18 years.

    o AST, ALT, or ALP < 2 times of upper normal limit.

    o GGT < 5 times of upper normal limit.

    o Preexisting liver disease detected.

    o Incomplete medical records.

    o Confirmed acute liver failure with liver injury (abnormal liver tests), INR >1.5, and hepatic encephalopathy within 26 weeks.

    o Fulfill the criteria for non-alcoholic fatty liver disease, alcohol-associated liver disease with alcohol consumption > 25 g/day, Wilson's disease, or hereditary hemochromatosis.

    o Using any drug-induced liver injury.

2.5.3. Sample Size: 458 patients

2.5.4. Sampling Method: Convenience sampling

2.6. Data collection method

2.6.1. Operationalization

- AIH diagnosis criteria from 2008 IAHG simplified criteria for the diagnosis of autoimmune hepatitis: patient score of more than 6 was probable AIH, and more than 7 was definite AIH.

  o ANA or SMA positive [titers ≥ 1:40] (1 point), ANA or SMA positive [titers ≥ 1:80] or LKM positive [titers ≥ 1:40] (2 points)

  o IgG titers over the UNL (1 point), or over 10% above the upper normal limit (2 points)

  o Histology compatible with AIH (1 point), or typical of AIH (interface hepatitis) (2 points)

  o Absence of viral hepatitis (2 points)

- AIH subtype:

  o Type 1 AIH: AIH with ANA, ASMA, or SLA/LP was positive

  o Type 2 AIH: AIH with LKM-1, or LC-1 was positive

  o Seronegative AIH: diagnosis AIH without positivity of antibodies (with typical histology finding).

- PBC diagnosis criteria from Practice Guidance from the American Association for the Study of Liver Diseases in 2018: more than 2 of 3 of the following criteria were met:

  o ALP ≥ 2 times of upper normal limit and/or GGT ≥ 5 times of upper normal limit.

  o AMA positive or sp100 or gp210 positive

  o Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts.

- PSC diagnosis criteria from the American Association for the Study of Liver Diseases in 2022:

  o Exclusion of secondary sclerosing cholangitis

  o Elevated serum cholestatic pattern tests

  o Multifocal strictures of the intrahepatic and extrahepatic bile ducts on MRCP

  o Histology in case the highly considered

- Overlapping AIH – PBC syndrome - Paris criteria:

  o ≥ 2 of 3 features associated with AIH:

    ▪ Serum alanine aminotransferase level ≥ 5 times of upper normal limit

    ▪ IgG level ≥ 2 times of upper normal limit or SMA positive

- Interface hepatitis on histological examination
  - ≥ 2 of 3 features associated with PBC:
    - Serum ALP ≥ 2 times of upper normal limit; or GGT level ≥ 5 times of upper normal limit
    - AMA positive
    - Florid duct lesions or destructive cholangitis on histological examination

2.6.2. Research Variables

- Demographic data: age, gender, weight, height, body mass index, comorbidities, other autoimmune diseases.

- Clinical manifestations: asymptomatic and symptomatic which include fatigue, jaundice, pruritis, loss of appetite, abdominal discomfort, cirrhosis

- Serologic biochemistry profile: AST (reference range for individuals: 14 - 20 international units per liter (IU/L) for male and 10 - 36 UI/L for females), ALT (reference range for individuals: 29 - 33 IU/L for males and 19 - 25 IU/L for females), ALP (reference range for individuals: 44 to 147 IU/L), GGT (reference range for individuals: below 50 IU/L), IgG (reference range for individuals: 700–1600 mg/dL).

- Autoimmune profile: ANA, LKM, AMA, SMA, SLA/LP, ASMA, AMA – M2, M2 – 3E, sp100, PML, gp210, LKM-1, LC-1, SLA/LP, SS-A, Ro-52, Scl-70, CENP A, CENP B, PGDH.

2.6.3. Research Sources, Tools, And Modalities

- **Research sources:**

  o Demographic data and clinical manifestations data: collected from electric medical records available, and accessible in the medical network system in both hospitals.

  o Serologic biochemistry profile: collected from the laboratory network system in both hospitals.

  o Autoimmune profile: collected from the laboratory network system in the Vinmec International Hospital.

- **Research tools and modalities:**

  o Demographic data and clinical manifestations data: collected from electric medical records.

  o Serologic biochemistry profile: using Roche module Cobas 6000 (C-501, Roche Diagnostics International AG, Rotkreuz ZG, Switzerland)

  o Autoimmune profile: Screening test: ANA, LKM, AMA, and SMA by indirect immunofluorescence testing using HEp2 cells and rodent substrate including kidney, liver, and stomach cells. SLA/LP by indirect immunofluorescence testing using transfected cells. ASMA
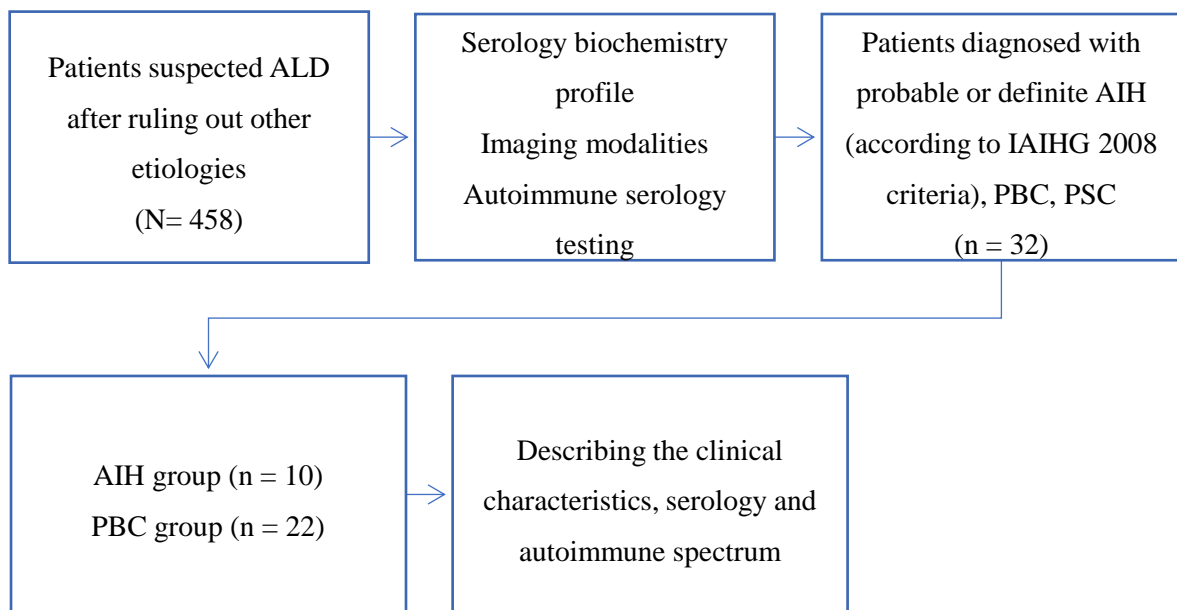
against F – actin using VSM47 cells. The determination of the total immunoglobulin G (IgG) titer is performed using a COBAS INTEGRA 400 plus analyzer — (Roche Diagnostics International AG, Rotkreuz ZG, Switzerland). The determination of ANCA is by indirect immunofluorescence testing. Confirmation test as Multiparametric EUROLINE Autoimmune Liver Diseases 14 Ag test: AMA – M2, M2 – 3E, sp100, PML, gp210, LKM-1, LC-1, SLA/LP, SS-A, Ro-52, Scl-70, CENP A, CENP B, PGDH using antigen – coasted test trips.

- **Data collection procedures:** All patients who met the inclusion criteria listed above who were tracked at the International Vinmec Times City hospital and the 108 Military Center hospital in Hanoi, Vietnam, from January 2021 to April 2024, were the subjects of a retrospective analysis that we conducted. Before any data collection, the proposal will be approved by both the IRB at Vinmec Times City Hospital and VinUniversity. Additionally extracted were the patient's demographic information, clinical history at presentation, and the outcomes of laboratory and serologic testing at diagnosis. When available, liver biopsy results were collected. Several chemistry and serologic profiles (listed above) are collected by the same standardized laboratory unit, and the liver biopsy is obtained and evaluated by histopathologists. The researcher entered all the data into the established electronic case report form (eCRF). The researcher underwent repeated education based on the original and updated data guidelines, and data cleaning, in addition to a bimonthly correction of detected errors and subsequent monitoring, was performed by an independent professional data manager to manage the quality of data provided by multiple centers.

2.7. Data Analysis Method

Statistical analysis of all data was conducted using the statistical package for social sciences (SPSS) 22.0 (SPSS Inc., Chicago, IL, USA). Continuous data were reported as means, median, and range, while categorical data were reported as frequencies [n (%)]. Associations between categorical variables were assessed using the chi-squared test (χ2). Two-tailed Mann–Whitney U test (M–W), and Kruskal–Wallis test (K–W) were used to investigate possible associations between scale variables and categorical variables. p values < 0.050 were considered statistically significant.

2.8. Research Framework

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┌─────────────────────┐      ┌─────────────────────┐      ┌─────────────────────┐
│ Patients suspected  │      │ Serology biochemistry│     │ Patients diagnosed  │
│ ALD                 │      │ profile             │      │ with                │
│ after ruling out    │ ──→  │ Imaging modalities  │ ──→  │ probable or definite│
│ other               │      │ Autoimmune serology │      │ AIH                 │
│ etiologies          │      │ testing             │      │ (according to IAIHG │
│ (N= 458)            │      │                     │      │ 2008 criteria), PBC,│
│                     │      │                     │      │ PSC (n = 32)        │
└─────────────────────┘      └─────────────────────┘      └─────────────────────┘

┌─────────────────────┐      ┌─────────────────────┐
│                     │      │ Describing the      │
│ AIH group (n = 10)  │      │ clinical            │
│ PBC group (n = 22)  │ ──→  │ characteristics,    │
│                     │      │ serology and        │
│                     │      │ autoimmune spectrum │
└─────────────────────┘      └─────────────────────┘
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2.9. Ethical Approval

This study was approved by the Institutional Review Board of International Vinmec Times City Hospital **and** VinUniversity. Without facing any discrimination, participants are liberated to withdraw at any moment and decline to respond to any research questions. The computerized data collection process encrypts all personally identifiable information, which is kept private and accessible only to researchers for study requirements. The study's findings are disclosed anonymously.

Chapter 3
Thesis Results

3.1. Demographics Of Suspected Autoimmune Liver Diseases Patients

Table 3.1.1: Characteristics of the epidemiology of suspected autoimmune liver diseases patients in Vietnam.

	ALD (N = 458)
Age (years)*	50.00, 49.76 (23.00 – 73.00)
Female (%)	56.33
Overweight/obese (%)	39.45

*Data were presented as mean, median, minimum, maximum.

Comment: The proportion of female patients was 56.33% with a male-to-female ratio of 1:1.3. The mean age was 49.76 years (ranging from 23 to 73 years). No patient was underweight, and 39.45% of patients were in the overweight or obese category.

Table 3.1.2: Characteristics of co-morbidities in suspected ALD patients.

Underlying diseases	
No co-morbidity detected (%)	72.28
Co-morbidities (%)	27.72

Comment: 331 patients, or 72.28% of the 458 patients, were in the group where no comorbidity had been identified. The group with detected comorbidities had a minor proportion.
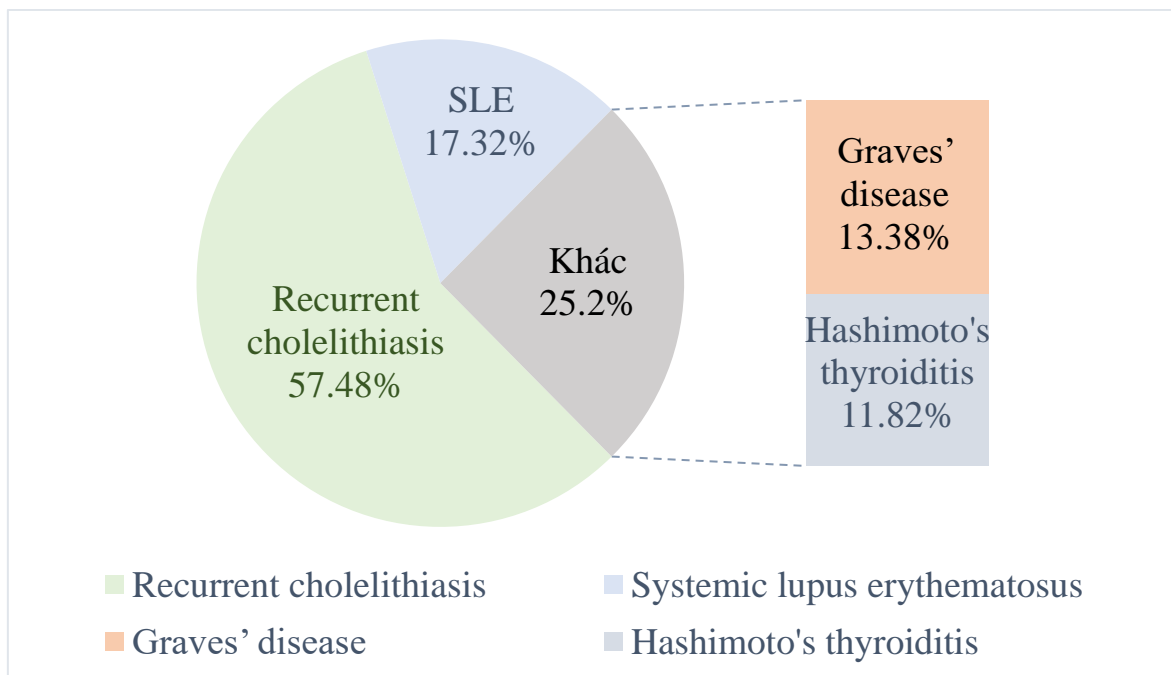

Figure 3.1.1: Distribution of comorbidities of the suspected ALD patients in the study cohort

Comment: The majority (57.48%) of the co-morbidities identified in the group had cholelithiasis. Graves' disease was more common than Hashimoto's thyroiditis among the autoimmune diseases in the study cohort, with a thyroid-autoimmune disease proportion of 25.20 percent.
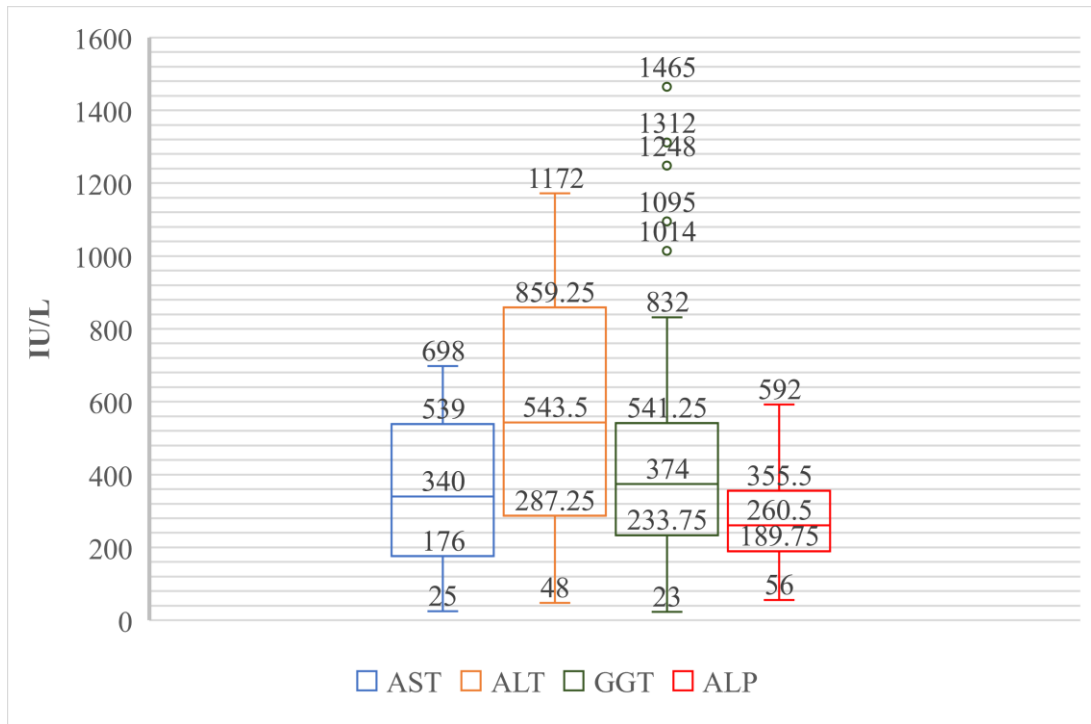

Figure 3.1.2: Distribution of liver enzymes of the suspected ALD patients in the study cohort.

Comment: The mean and range of the liver parenchymal injury pattern were 345.83 IU/L (from 25 IU/L to 698 IU/L) for AST and 574.94 IU/L (from 48 IU/L to 1172 IU/L) for ALT. The mean and range of the cholestasis pattern were 275.92 IU/L (from 56 IU/L to 582 IU/L) for ALP and 411.53 IU/L (from 23 IU/L to 1465 IU/L) for GGT. The AST-to-ALT ratio was 0.601, which suggested the destruction of the liver in general. The liver injury R factor (R factor) was 6.3, which suggested a hepatocellular injury.

3.2. Demographics Of Autoimmune Liver Diseases

Table 3.2.1: Number of cases diagnosed with ALD from in study cohort per year.

Date	Suspected ALD	AIH	PBC
	Number (N)	number (n)	number (n)
2021	117	1	1
2022	158	8	7
2023	183	1	14
Total	458	10	22

Comment: 458 patients underwent screening and confirmation for autoimmune liver disease;

however, only 32 cases were found to fulfill the diagnostic criteria. The final study population consisted of thirty-two ALD-diagnosed patients, of whom 10 (31.25%) patients had AIH and 22 (68.75%) patients had PBC; no case of PSC or overlapping syndrome was diagnosed during that specific time.

Table 3.2.2: Characteristics of the epidemiology in AIH and PBC

	AIH (n = 10)	PBC (n=22)
Age (years)*	51 (23 – 73)	49 (19 – 84)
Female n(%)	8(80)	17 (77.3)
Overweight/obese n(%)	6 (60)	12 (54.5)
Other autoimmune	None	None
Recurrent cholelithiasis n(%)	None	10 (45.45)

*Data were presented as mean, minimum and maximum.

Comment: For the AIH group, the proportion of female patients was 8 (80.00%) and male was 2 (20.00%), with a male-to-female ratio of 1:4. The mean age was 51 years (range from 23 to 73 years). No patient was underweight, and 60.00% of patients fell into the overweight or obese category. For the PBC group, the proportion of female patients was 17 (77.30%) and males were 5 (22.70%), with a male-to-female ratio of 1:3.4. The mean age was 49 years (range from 19 to 84 years). No patient was underweight, 45.50% of patients fell into the normal range, and 54.50% of patients fell into the overweight or obese category. Co-morbidities in seven out of twenty-two PBC patients were identified as recurrent cholelithiasis (ten out of twenty-two, 45.45%). Among the comorbidities detected, female patients were predominant (six out of seven, 85.71%). No other autoimmune disease was found at the time of diagnosis in both groups.

Table 3.2.3: Distribution of AIH subtypes in the study cohort.

AIH subtypes	n (%)
AIH type 1	8 (80)
AIH type 2	1 (10)
Seronegative AIH	1 (10)

Comment: Seven of the ten patients had probable AIH (70.00%), two had definite AIH (20.00%), and one had seronegative AIH (10.00%) at the time of diagnosis without any information on the histology. Seven of the nine patients in the group with seropositive AIH are type 1 (77.78%), and two are type 2 (33.32%).

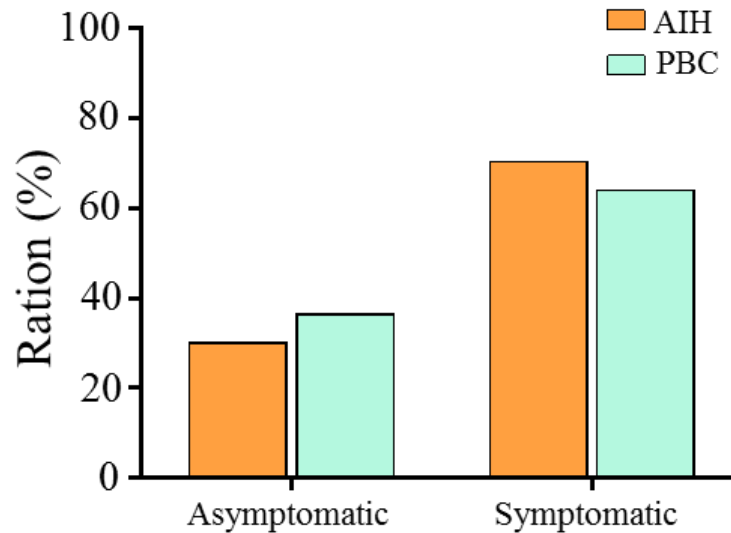## 3.3. Clinical Manifestations Of Autoimmune Liver Diseases

Figure 3.3.1 Characteristics of the clinical manifestations in AIH and PBC in the study cohort.

Comment: The symptomatic group predominated in both diseases by a significant percentage (70.00% in the AIH group and 63.60% in the PBC group). None of the patients in the study cohort displayed acute liver injury or signs or symptoms of cirrhosis, which include splenomegaly, ascites, caput medusae, hepatic encephalopathy, or palmar erythema.
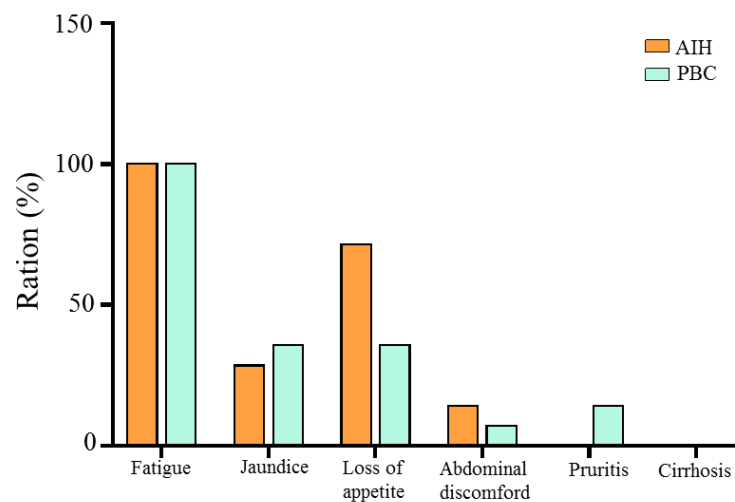

Figure 3.3.2: Characteristics of the clinical symptoms in AIH and PBC in the study cohort.

Comment: Generalized fatigue was the most common chief complaint across the entire patient group (100.00%). Loss of appetite (71.42% in the AIH group and 4.14% in the PBC group), mild to moderate jaundice (28.57% in the AIH group and 35.71% in the PBC group), and abdominal discomfort (14.28% in the AIH group and 4.14% in the PBC group). 14.28% of PBC cases of pruritus were reported, and the AIH study group did not have any data on this symptom.

3.4. Biochemistry Serology Characteristics Of Autoimmune Liver Diseases

Table 3.4.1: Characteristics of the biochemistry laboratory results in AIH and PBC in the study cohort.

Variable	AIH	PBC
IgG (mg/dL)	2007.82, 1718.70 (1597.70 – 3465.50)	No data available
AST (IU/L)	444.07, 479.60 (25.00 - 698.00)	84.09, 80.00 (34.00 – 165.00)
ALT (IU/L)	561.82, 147.51 (84.00 – 1172.90)	105.73, 97.00 (37.00 – 201.00)
GGT (IU/L)	224.66, 154.46 (44.00 – 591.00)	387.06, 270.50 (23.00 – 1465.00)
ALP (IU/L)	175.24, 147.52 (56.40 – 327.10)	213.67, 190.08 (56.10 – 514.70)

Data were presented as mean, median, and range. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma- glutamyl transpeptidase; IgG, immunoglobulin G; IU/L, International Units Per Liter; mg/dL, Milligrams Per Deciliter

Comment: For the AIH group, the mean AST and ALT were 444.07 IU/L and 561.82 IU/L, respectively. More than ten times the upper normal limit was exceeded by both of these liver parenchymal injury enzymes. The AST-to-ALT ratio was 0.791. The mean GGT and ALP were 224.66 IU/L and 175.24 IU/L, respectively. The liver injury R factor (R factor) was 9.5. The liver injury pattern in AIH was predominant. All patients had IgG levels that were greater than 1.1 times the upper normal limit, both at the mean and median levels (2007.82 mg/dL and 1718.70 mg/dL). For the PBC, as mentioned above, no available data was collected from total Ig, IgM, or IgG. The mean AST and ALT were 84.09 IU/L and 105.73 IU/L, respectively. Both of these liver parenchymal injury enzymes were mildly elevated, more than two times the upper normal limit in some circumstances; the maximum levels were moderately increased, five times the upper normal limit (165.00 IU/L and 201.00 IU/L). The AST-to-ALT ratio was 0.795. On the other hand, the mean GGT and ALP were 387.06 IU/L and 213.67 IU/L, respectively. The R factor was 1.5, which pointed toward cholestatic injury.

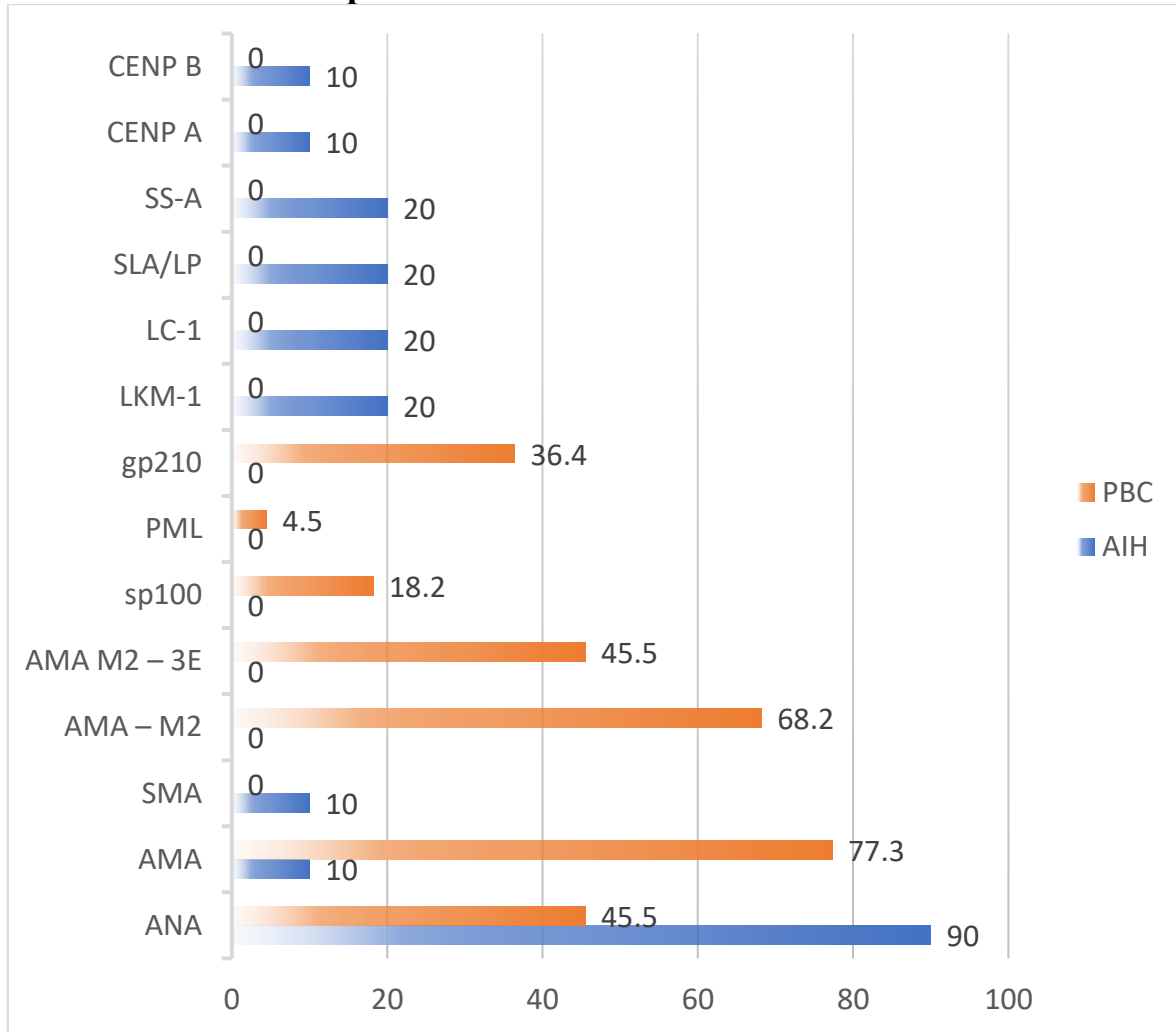## 3.5. Autoantibodies Spectrum Of Autoimmune Liver Diseases

Figure 3.5.1: Autoantibodies spectrum of AIH and PBC at the time of diagnosis

Comment: In the AIH group, one case of seronegative for all typical auto-antibodies. Nine patients tested positive for autoantibody of ANA, which was also the most frequently detected antibody in the group. Anti-LC-1, anti-LKM-1, and anti-SLA/LP auto-antibodies were also frequently detected positively for AIH subtypes (20.00% for each antibody). 10.00% (for each antibody) of the atypical auto-antibodies, which are prognosis predictors such as CENP A-B, and SS-A, were also positive. No antibodies for the cholestatic disorder were positive. In the PBC group, the most common auto-antibody identified in the PBC group was AMA (77.30%). The AMA-M2 (68.20%), AMA-M2 3E (45.50%), and ANA (45.50%). The results of these tests appear in decreasing order of frequency. Antibodies against sp100, gp210, and PML were only 18.20%, 36.40%, and 4.50%, respectively.
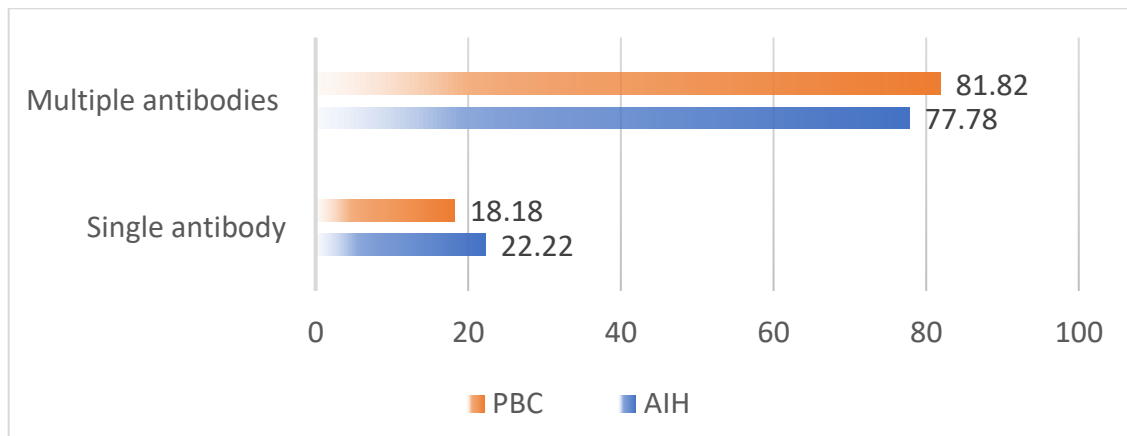
Figure 3.5.2: Proportion of single antibody compared with multiple antibodies in AIH and PBC at the time of diagnosis

Comment: In the AIH group, two (22.22%) were positive for only one antibody (ANA). The remaining seven cases (77.78%) tested positive for multiple antibodies, one of which was always ANA and the others could be typical, atypical, or prognostic autoantibodies. A single antibody-positive PBC was found in a small percentage of the study group (18.18%). In the remaining eighteen cases, multiple antibodies were detected (81.82%), regardless of either the AMA and its subtype or the specific cholestatic ANA (sp100 and gp210).

3.6. The Calculated Hospital-Based Prevalence Of Autoimmune Liver Diseases

Table 3.6.1: The sensitivity and specificity of the EUROLINE 14 Ag test in AIH and PBC

AIH			
EUROLINE 14 Ag test	**Confirm diagnosis**	**Absence of disease**	**Total**
Positive	9	26	35
Negative	1	422	423
Total	10	448	458
PBC			
EUROLINE 14 Ag test	**Confirm diagnosis**	**Absence of disease**	**Total**
Positive	22	37	59
Negative	0	399	399
Total	22	436	458

Comment: In the AIH group, the calculated hospital-based sensitivity was 90.00% (95%CI

[55.50 – 99.75]) and the calculated hospital-based specificity was 94.20% (95%CI [91.61 - 96.17]). In the PBC group, the calculated hospital-based sensitivity was 100.00% (95%CI [84.56 -100.00]) and the calculated hospital-based specificity was 91.51% (95%CI [88.49 - 93.95]). The calculated hospital-based prevalence was 2.18% (95% CI [1.05–3.98]) in the AIH group and 4.80% (95% CI [3.03–7.18]) in the PBC group.

Chapter 4
Discussion

4.1. Demographics Of Autoimmune Liver Diseases

4.1.1. About Gender, Age, BMI Distributions

This study showed females were predominant in both diseases (80.00% in AIH and 77.30% for PBC), with a male-to-female ratio of AIH and PBC of 1:4 and 1:3.4, respectively. Compared with available published data from Asia-Pacific regions, the male-to-female ratios from Japan, South Korea, and China were 1:43, 1:5.9, and 1:6.8; the highest ratio was 1:1.5 in Pakistan and the lowest ratio was 1:20 in South Israel. In the United States and Europe, the male-to-female ratio ranged from 1:2.6 (in Denmark) to 1:9 (in Alaska) [3]. Females in this study were also predominant in ALD, even in the AIH or PBC, as in other publications. The gender difference that is more vulnerable to the disease could be explained by specific immunogenetic factors and sex hormones [64]. The average age for AIH and PBC was 51 years (range from 23 to 73 years) and 49 years (range from 19 to 84 years). These results were comparable to the published research from around the world recently. Even though in the last several researchers noticed the Asia cohort might be more likely to be diagnosed later and older than patients from Western countries, the reality showed that most of the average age from Europe and the developing countries from Asia were around middle age, 51.08 years (ranging from 36.00 years to 59.90 years; the median was 52.80 years) [4]. From the body mass index factor in patients with ALD, there was no patient underweight, and surprisingly enough, more than half of the patients belonged to the overweight or obese range (60.00% in AIH and 54.50% in PBC). In comparison to Western countries, the population of Vietnam had a lower percentage of overweight and obese patients due to traditional or cultural nutrition behaviors, differences in sedative lifestyles, and other environmental factors. Even though the population with a BMI greater than 23 was modest, this group was diagnosed with ALD more frequently than patients with a BMI less than 23. As a literature review, most of the previous studies showed obesity may be a significant factor in the development of autoimmune disease because the immune system could work inappropriately. Overactivation of intracellular nutrient and energy-sensing pathways in overweight or obese people causes metabolic overload in peripheral tissues involved in immune responses. Additionally, inflammatory cytokines secreted by adipose tissue include leptin, interleukin-1 (IL-1), IL-6, IL-17, tumor necrosis factor-alpha, and interferon-gamma. These cytokines could enhance the risk of autoimmunity and damage to peripheral tissues. [65– 67]. Fortunately, despite experiencing a higher risk of developing an autoimmune disease, patients with a BMI of greater than 23 had better outcomes with ALD, including a lower likelihood of portal hypertension, ascites, variceal hemorrhage, and spontaneous bacterial peritonitis. [68]. Furthermore, the higher weight in this group may suggest a less severe case of ALD. Due to

this, there was no evidence of cirrhosis in the obese patients in this study, and their baseline liver enzyme values showed chronic abnormalities rather than acute liver disease or any decompensated liver end-stage disease.

4.1.2. About The Definite AIH Diagnosis Based On Scoring Systems And The Subtype Of AIH Distributions

For the AIH group, at the time of diagnosis, the probable AIH, which scored more than six points, was higher than the group of definite AIH, which scored more than seven points, according to the simplified criteria in 2008. As with the other research for AIH, the probability of a probable group was higher as compared to non-invasive methods to meet the criteria of biochemistry and

immunology without evidence of histology [69–71].

Seronegative AIH was detected at 10.00% in the study cohort, and compared to the updated research, seronegative AIH was underdiagnosed and delayed treatment. Even the published research demonstrated that this atypical presentation proportion ranged from 7 to 34%, with an average of 10% of diagnosed AIH [32,72,73].

The diagnosis of the AIH subtypes was based on the immunologic profile. The study showed 77.78% of type 1. This result was more similar to the percentage in the Europe and North America group, where the average number was 74.2% with a range from 72% to 76.7%. Even though there was a lack of data on human leukocyte antigen in the Vietnamese population, the percentage of type 1 was suitable to the result published from previous research, which noticed that the HLA-DR4 is associated with the characteristics of type 1 AIH in East Asia and the HLA-DR3 occurs in AIH patients from South Asia with characteristics of type 2 [3]

4.1.3. About The Comorbidities And Concurrent Autoimmune Diseases

There was insufficient data from both groups in the area of concurrent auto-immune disorders for the comorbidities in the study cohort. This is because most common diseases in the general healthcare burden, like focusing on dyslipidemia, type 2 diabetes, and hypertension, were automatically recorded during the history-taking process as a daily basic requirement so that concurrent autoimmune diseases could be misdiagnosed. Furthermore, the majority of patients included in the research came from general medicine outpatient wards or gastrointestinal surgery clinics, where they are not seen by immunologists. As a result, there may be a higher rate of underdiagnosis of other autoimmune disorders.

In the PBC, recurrent cholelithiasis was detected in almost half of the group (45.45%) which is related to chronic cholestasis condition in the biliary tract. Bacterial translocation and biliary infection are caused by decreased bile acid secretion and altered gut microbiota, which ultimately contribute to the development of various types of gallstones [74]. Even though the diagnosis of PBC was fulfilled after ruling out other cholestasis disorders, in patients with non-

cirrhotic PBC, concurrent cholelithiasis was a common and independent risk factor linked to a worse prognosis [75]. The percentage of cholelithiasis in this study was higher than in the previous research (45.45% as opposed to 22.90%) and could be explained by the BMI (more than 23), age (more than 40s), and gender (female predominance) of the study group were favorable for the development of the stones within the gallbladder.

4.2. Clinical Manifestations Of Autoimmune Liver Diseases

The symptomatic manifestations predominated the clinical manifestations of both diseases (70.00% for AIH and 63.60% for PBC). The proportion of asymptomatic individuals was small, consistent with previous research on ALD.

The most common complaint in the AIH symptomatic group was fatigue (100.00%), followed by a loss of appetite (71.42%). When compared to earlier studies, fatigue came in second (49.69%), with jaundice coming in first (59.01%). The degree of abnormalities in biochemical serology could be responsible for the differences in the frequency of clinical manifestations between the two studies. The elevation of the cholestatic enzyme ALP was at the same levels (the mean value of this study and the previous one were 174.24 IU/L and 196 IU/L). Otherwise, the elevated liver parenchymal injury was significantly higher in this study when compared to previous data. AST and ALT were 444.07 IU/L and 561.82 IU/L in this study, respectively, in contrast with 166 IU/L and 129 IU/L [76]. Loss of appetite and fatigue were reported more frequently than cholestatic symptoms such as pruritis and jaundice considering there was a significant increase in liver injury compared to cholestasis (R factor was 9.5).

According to the PBC clinical manifestation spectrum, the frequency of jaundice and pruritis was higher in the AIH group even though the mean level of ALP in this study was less than half that of the previous research (213.67 IU/L versus 432 IU/L) [76]. This resulted in an injury pattern from cholestasis that was greater than the injury from liver parenchyma (R factor was 1.5).

4.3. Biochemistry Serology Characteristics Of Autoimmune Liver Diseases

In the AIH group, the liver injury pattern was higher when compared to the cholestatic pattern. On the other hand, in the PBC group, the cholestatic pattern was predominantly higher. As a literature review, these elevated liver enzymes in each group have no difference among the research [76].

4.4. Autoantibodies Spectrum Of Autoimmune Liver Diseases

The standard serological assortment for AIH diagnosis encompasses ANA, SMA, and anti-LKM1. In this study, ANA was still the one auto-antibody that had the highest frequency. The anti-SMA was 10.00% and the anti-LKM1 was 20.00%. Twenty-two percent of AIH patients had ANA, SMA, or LKM1 as an isolated serological finding at presentation, while seventy-

seven percent had multiple autoantibodies. These percentages were not consistent with the other data; in earlier studies, the proportion of a single autoantibody to multiple autoantibodies was roughly approximately fifty percent (49.00% and 51.00%). Numerous studies have shown that if two ANA and SMA were detected together at presentation, the diagnostic accuracy in the case of multiple autoantibodies increased from 58.00% to 74.00%. In autoimmune hepatitis, ANA and SMA were the most common serological combinations (43.000%), whereas AMA, LKM1, SMA, and ANA were only detected in 8.00% of cases [77]. The most frequent combination in this study was ANA and LKM1 (two of the nine seropositive AIH cases), followed by ANA and SMA (one of the nine seropositive AIH cases). Furthermore, this investigation found that only one case had baseline positive results for ANA, AMA, and LKM1, the three conventional auto-antibodies. Although the sensitivity of each combination in the autoimmune spectrum was low, the specificity for establishing AIH ranged from 94.00% to 100.00% [77]. Apart from the standard typical autoantibodies of AIH, prognostic factors accompanying the typical autoantibody, as well as SLA/LP, LC-1, SS-A, and CENP A/B, were detected positive in cases of minority [55,78]. In the PBC group, the AMA, AMA-M2, AMA-M2 3E, and ANA were the common autoantibodies detected in the study cohort. A single autoantibody-positive PBC was found in three out of the twenty-two cases, and these belonged to the only anti-sp100 or only anti-gp210. Multiple seropositivity antibodies were detected; 36.36% of cases were two-marker presented, and 45.46% of cases were more than three-marker presented. Antibodies against the centromere (CENP-A and CENP-B), anti-sp100, and anti-gp210 exhibited promise as prognostic markers in addition to the standard diagnostic antibodies for PBC diagnosis. Twenty-seven percent of PBC patients have anti-sp100, 16–25% have anti-gp210, and 16% have anti-centromere antibodies, respectively [78]. In this study, the proportion of anti-gp210 was 36.40%, anti-sp100 was 18.20%, and no case was noted as positive for anti-centromere. As mentioned above in the AIH autoantibodies spectrum, the more antibodies detected in the trip test, the more accurate the PBC diagnosis.

4.5. The Calculated Hospital-Based Prevalence Of Autoimmune Liver Diseases

Taking into consideration the rarity of the disease worldwide, the global pooled prevalence of AIH was found to be 15.65 cases per 100,000 people, and the prevalence of AIH in Asia was 4.23 cases per 100,000 people. This recent study showed a calculated hospital-based AIH prevalence of 2.18% (95% CI [1.05–3.98]), which was higher than other results from previous studies. In the same situation, the estimated worldwide prevalence was 146 million per year and 118.75 cases per million in the Asia-Pacific region, respectively. The study result reported that the calculated hospital-based PBC prevalence was 4.80% (95% CI [3.03–7.18]), which is also

higher than other published research. ALDs such as AIH and PBC have increased significantly and exhibit substantial variation across regions worldwide. Especially, several studies from Asia have noted an increase in concern for these rare disorders recently. Despite the increased prevalence, the number of other studies from Asia was still lower than those published in Western countries. The explanation for this misappropriated result was based on the inclusion criteria, which included confirmed-diagnosed cases and suspected ALD patients. On the other hand, the high ALD prevalence reported by this study was conducted on people who came to a hospital health checkup, which means the patients suspected of ALD, including the asymptomatic groups and mildly symptomatic patients, were able to reach a tertiary hospital. This may not be the same as the general healthy population and overestimate the ALD prevalence. With these factors, the calculated prevalence in this study was only represented for the suspected group of ALD and not for the whole population in Vietnam, which made the number of cases of both diseases quite high.

4.6. Research Limitations

This study had several limitations that with the essential cautions in the study of rare diseases, should be taken into account when interpreting results, including the retrospective design. Because the current study's data was obtained from medical records, there is the potential that certain of the information is of poor quality or incorporates a few missing variables. Additionally, the fact that the current study was conducted at a tertiary care teaching hospital in Hanoi, Vietnam and that the majority of its patients came from the country's central region, suggests that the sample may not be entirely representative of the nation. Due to the relative rarity of ALD, we were unable to recruit a large number of patients for this study. There was a probability that a small sample size would affect how accurate the analysis's conclusions were.

Conclusions

To sum up, this research highlights the immunological and clinical features of ALD in Vietnam. 10 AIH patients and 22 PBC patients were detected among the suspected ALD population, and there is no data for PSC or any overlapping syndrome. The characteristics of epidemiology, clinical features, and autoimmune profile are compatible with those of the other Asia-Pacific cohort. The predominant gender detected was female in both groups (80.00% and 77.30%) and within middle age (around 50 years). The majority of patients had nonspecific symptoms and fatigue was reported the most in both groups. Depending on the pattern of ALD, the more serology antibodies were positive, the more accurately ALD was diagnosed in comparison to positive single antibody cases. The ANA and AMA were the most detected antibodies regardless of the single or multiple antibody-positive situations.

Recommendations

Beforehand, most suspected ALD cases were underdiagnosed or misdiagnosed not only because of the lack of awareness from general medicine clinical physicians but also the required invasive modalities to establish the diagnosis. The utility of an autoimmune profile as a non-invasive test in diagnosing and prognosis is proven to be more advantageous, and the more positive multiple antibodies presented, the more accurate the ALD diagnosis, as per the perspective of this study.

Overdiagnosis may result from antibodies identified during the confirmation trip test and screening tests in the general population. Otherwise, in the exceptional case of the suspected ALD group, the advantage of detectable or available autoantibodies assists in the scoring system's scoring before utilizing the biopsy in a significant number of cases, thus minimizing the risk of procedure-related complications and reducing the cost of invasive methods.

Consequently, we propose building on the findings of the current pilot study and establishing a national database for Vietnam to further investigate this rare disease in the future.

Appendices

Appendix A

Research data summary and results

Table 3.1.1: Characteristics of the epidemiology of suspected autoimmune liver diseases patients in Vietnam.

	ALD (N = 458)
Age (years)	50.00, 49.76 (23.00 – 73.00)
Female (%)	56.33
Overweight/obese (%)	39.45

Data were presented as mean, median, and range.

Table 3.1.2: Characteristics of co-morbidities in suspected ALD patients.

Underlying diseases	
No co-morbidity detected (%)	72.28
Co-morbidities (%)	27.72
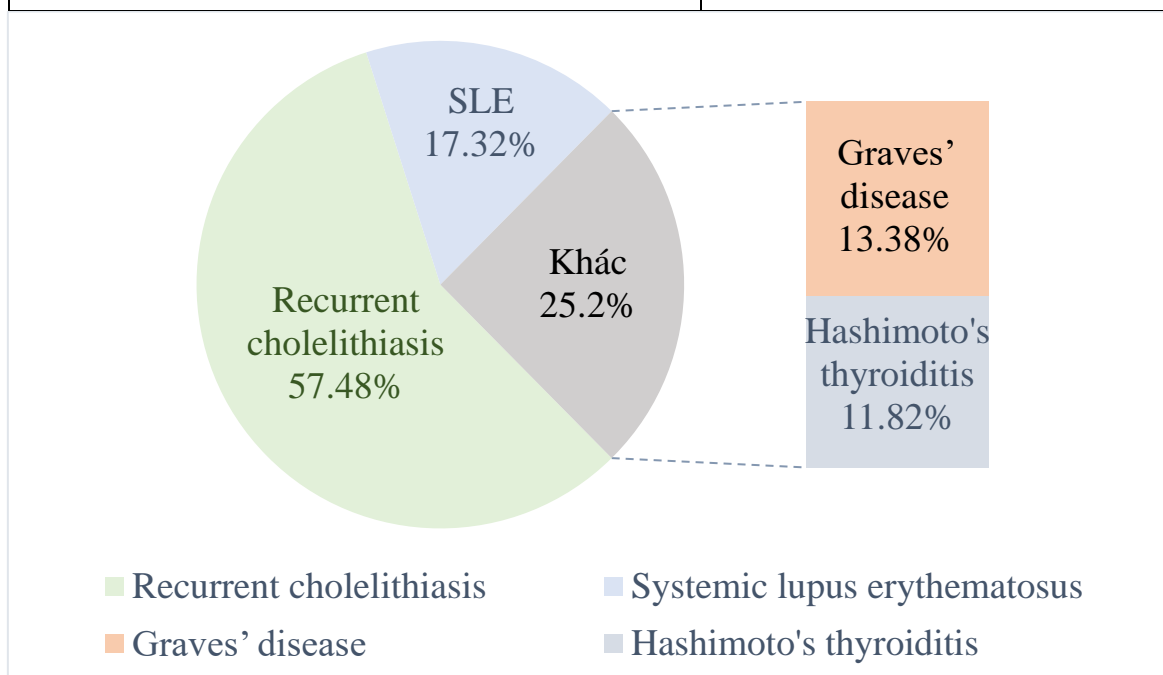
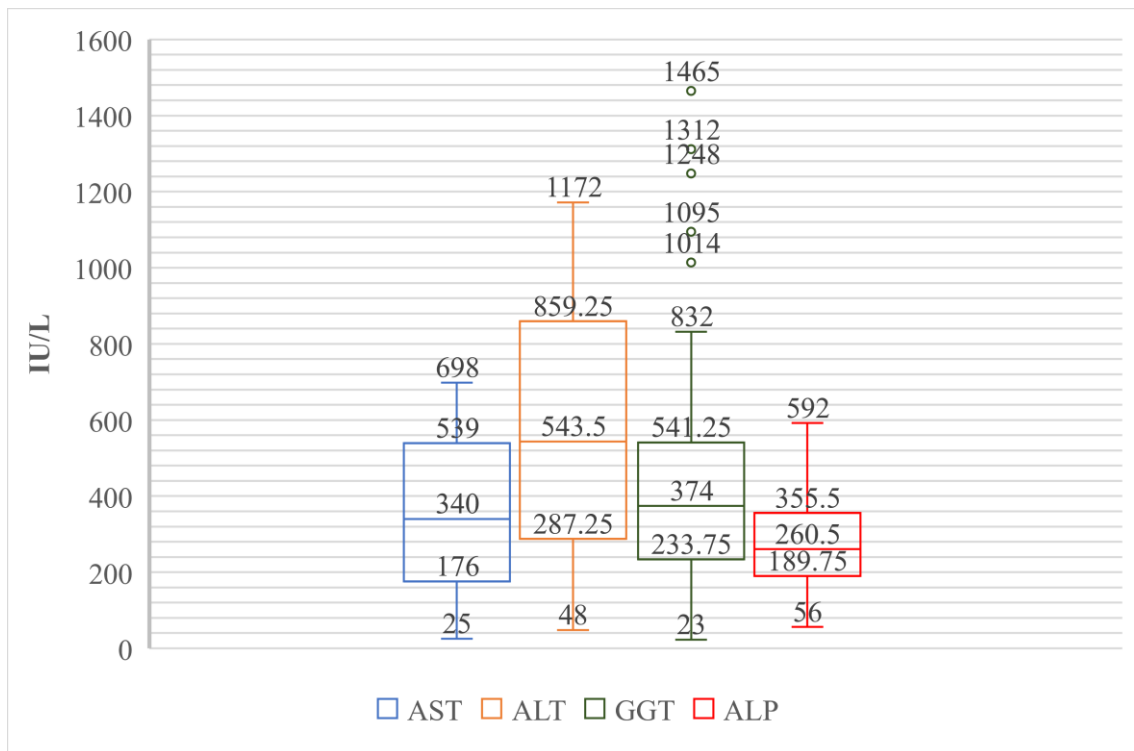Figure 3.1.1: Distribution of comorbidities of the suspected ALD patients in the study cohort

Figure 3.1.2: Distribution of liver enzymes of the suspected ALD patients in the study cohort.

Table 3.2.1: Number of cases diagnosed ALD from in study cohort per year.

Date	Suspected ALD	AIH	PBC
	Number (N)	number (n)	number (n)
2021	117	1	1
2022	158	8	7
2023	183	1	14
Total	458	10	22

Table 3.2.2: Characteristics of the epidemiology in AIH and PBC

	AIH (n = 10)	PBC (n=22)
Age (years)	51 (23 – 73)	49 (19 – 84)
Female (%)	8(80)	17 (77.3)
Overweight/obese (%)	6 (60)	12 (54.5)
Other autoimmune	None	None
Recurrent cholelithiasis (%)	None	45.45

Data were presented as mean and range.

46

Table 3.2.3: Distribution of AIH subtypes in the study cohort.

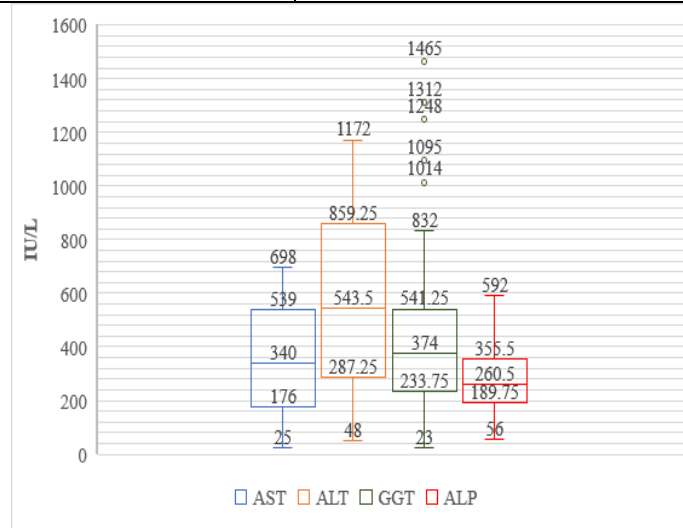| AIH subtypes	n (%)
AIH type 1	8 (80)
AIH type 2	1 (10)
Seronegative AIH	1 (10)

Figure 3.3.1 Characteristics of the clinical manifestations in AIH and PBC in the study cohort.
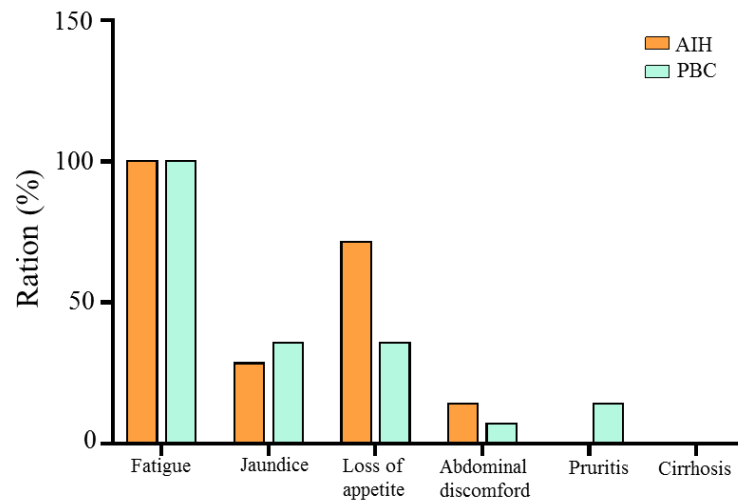

Figure 3.3.2: Characteristics of the clinical symptoms in AIH and PBC in the study cohort.

Table 3.4.1: Characteristics of the biochemistry laboratory results in AIH and PBC in the study cohort.

Variable	AIH	PBC
IgG (mg/dL)	2007.82, 1718.70 (1597.70 – 3465.50)	No data available
AST (IU/L)	444.07, 479.60 (25.00 - 698.00)	84.09, 80.00 (34.00 – 165.00)
ALT (IU/L)	561.82, 147.51 (84.00 – 1172.90)	105.73, 97.00 (37.00 – 201.00)
GGT (IU/L)	224.66, 154.46 (44.00 – 591.00)	387.06, 270.50 (23.00 – 1465.00)
ALP (IU/L)	175.24, 147.52 (56.40 – 327.10)	213.67, 190.08 (56.10 – 514.70)

Data were presented as mean, median, and range. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma- glutamyl transpeptidase; IgG, immunoglobulin G; IU/L, International Units Per Liter; mg/dL, Milligrams Per Deciliter
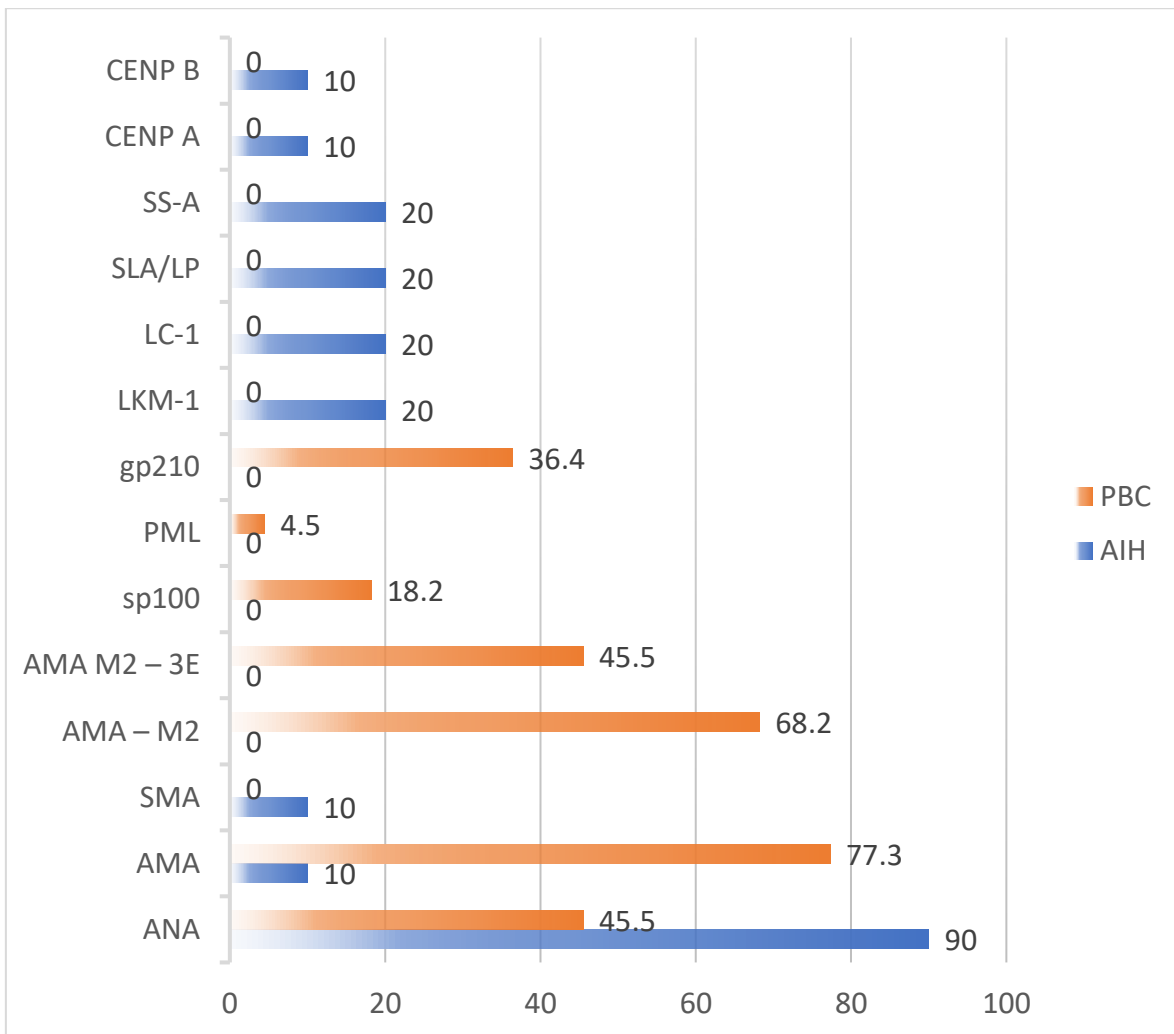
Figure 3.5.1: Autoantibodies spectrum of AIH and PBC at the time of diagnosis
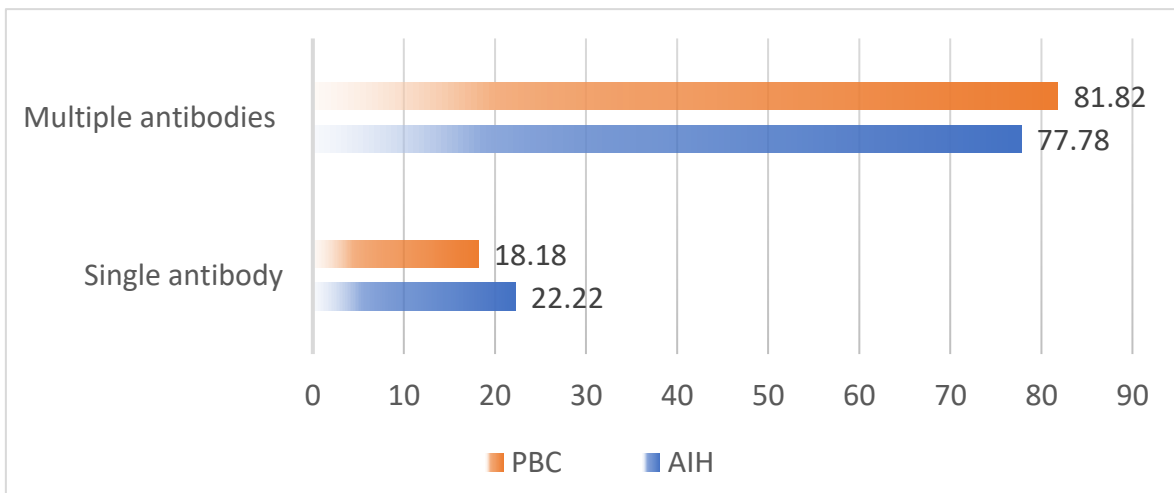

Figure 3.5.2: Proportion of single antibody compared with multiple antibodies in AIH and PBC at the time of diagnosis

Table 3.6.1: The sensitivity and specificity of the EUROLINE 14 Ag test in AIH and PBC

AIH			
EUROLINE 14 Ag test	**Confirm diagnosis**	**Absence of disease**	**Total**
Positive	9	26	35
Negative	1	422	423
Total	10	448	458
PBC			
EUROLINE 14 Ag test	**Confirm diagnosis**	**Absence of disease**	**Total**
Positive	22	37	59
Negative	0	399	399
Total	22	436	458

Appendix B
Participant list

No.	Name of participant	Medical record number
1	Nguyen Thi N.	20026332
2	Luu Thi Ngoc A.	20056754
3	Bui Thi H.	201027659
4	Doctora Griegggy M.	200989025
5	Ha Thi Thu N.	200911698
6	Hoang Thi Quynh H.	814014925
7	Hoang Thi T.	817012330
8	Lam Huong G.	821019539
9	Le Thi Phuong L.	201090389
10	Le Thi Thanh T.	200904812
11	Nguyen Hong H.	201060182
12	Nguyen Thi H.	200896093
13	Nguyen Thi Ngoc H.	201085494
14	Nguyen Van D.	200888640
15	Oinuma H.	820051814
16	Vu Thi T.	200905579
17	Vu Thi T.	200543312
18	Bui Hoang N.	200385378
19	Do Thanh C.	200818775
20	Hoang Thi T.	201264226
21	Luong Thi B.	201279316
22	Nguyen Duc M.	201227722
23	Nguyen Thi C.	201120198
24	Nguyen Thi L.	201102491
25	Nguyen Thi Ngoc H.	201085494

26	Nguyen Thi N.	201171664
27	Nguyen Thi Thi H.	815059443
28	Nguyen Thu H.	200213336
29	Nguyen Trong H.	201196498
30	Pham Thi H.	815028819
31	Joe S.	201225587
32	Dao Thi S.	200816009

TS.BS. *Nguyễn Văn Đính*

Confirmation from the thesis
supervisor

Confirmation from the
primary institution

Appendix C

Research survey

RESEARCH MEDICAL RECORD – INTERNAL MEDICINE			
PATIENT INFORMATION	Fullname		
	PID		
	Gender	Male	Female
	DOB		
	Age		
	Occupation		
	Address		
SUBJECTIVE DATA	Chief complain		
	History of present illness	Fatigue Jaundice Itching Skin rashes Joint pain Abdominal discomfort Diarrhea Loss of appetite Dark/ yellow urine Weight loss		
	Allergies		
	Past medical history	Internal medicine history	Hypertension Diabetes Mellitus Dyslipidemia Cirrhosis Autoimmune liver disease: Primary biliary cholangitis Primary sclerosing cholangitis

			Overlap syndromes
			Hepatitis:
			Drug-induced liver injury Nonalcoholic steatohepatitis
			Systemic lupus erythematosus (SLE)-associated liver disease
			Acute liver failure Viral hepatitis
			Associated extrahepatic disorders:
			Asthma
			Autoimmune thyroiditis: Grave's disease
			Hashimoto's disease
			DM type 1 IBD Celiac disease
			Systemic lupus erythematosus MCTD
			Rheumatoid arthritis Sjogen's syndrome
			Psoriasis Virtiligo
			Others:
			Wilson's disease Hemochromatosis
			Emphysema Budd – Chiari syndrome
		Surgery history	
		Social history	

		OBGYN history			
		Family history	Cirrhosis HCC Celiac disease		
			Other autoimmune diseases		

	Current medications	Prescription drugs:			
		Clometacin Diclofenac Fenofibrate Methyldopa Minocycline			
		Nitrofurantoin Papaverine Phenytoin Propylthiouracil Statins			
		Others:			
		Herbal medications:			
		Nonprescription drugs: Acetaminophen			
		Others:			

	Review of systems	Constitutional:	☐ weight loss/gain	☐ fatigue	☐ fever
	▪ Head–to–toe symptom detection		☐ loss of appetite	☐ heat/cold intolerance	
			☐ increased/decreased sweating		
	▪ Associated extrahepatic disorders	Eyes:	☐ eye pain/drainage	☐ visual change	☐ dry/irritated eye
		HENNT:	☐ ear pain/drainage	☐ sinus infection	☐ hearing loss/change
			☐ hoarse voice		
		Cardiovascular:	☐ chest pain ☐ palpitation ☐ fainting		☐ swelling feet/legs
		Respiratory:	☐ sputum ☐ wheezing ☐ cough		☐ shortness of breath

		GI:	☐ heartburn ☐ dysphagia ☐ odynophagia		☐ N/V
			☐ bloating ☐ abdominal pain		☐ ab. Distension
			☐ pale stools ☐ steatorrhea ☐ melena		☐ constipation
			☐ diarrhea		
		Genitourinary:	☐ hematuria ☐ yellow urine ☐ dysuria		☐ urinary urgency
			☐ urinary frequency	☐ oligo/amenorrhea	
			☐ menorrhagia	☐ decreased libido	
			☐ erectile dysfunction	☐ delayed ejaculation ☐ infertility	
		Integument:	☐ rash ☐ itching, ☐ jaundice		☐ hair loss
			☐ brittle nails ☐ cold/dry skin		
		Musculoskeletal:	☐ stiffness ☐ cramps		☐ joint pain
			☐ proximal muscle weakness		
		Neuropsychiatric:	☐ anxiety ☐ depression		☐ restlessness
			☐ emotional instability	☐ insomnia	☐ somnolence
			☐ impaired cognition	☐ heat/cold intolerance	

OBJECTIVE DATA	Vital Signs	▪ HR bpm ▪ BP mmHg ▪ RR bpm ▪ Temp oC ▪ SpO2 % (room air)	Height – Weight BMI	▪ Height ▪ Weight ▪ BMI
	Physical examination	General Appearance		
		CV system		
		Respiratory		
		Abdominal		
		Specific organ PE		
	Diagnosis	Initial Diagnosis		
		Differential Diagnosis		

ASSESSMENT	Laboratory studies	CBC	Within normal limit						
			Anemia: ☐ Microcytic ☐ Normocytic ☐ Macrocytic					
			Thrombocytopenia					
			Others:					
		BMP	Within normal limit					
			Others:					
		Thyroid function	TSH			Anti TPO	☐(+)ve	☐ (-)ve	
			fT4			Anti Tg	☐(+)ve	☐ (-)ve	
		Celiac disease	Ig A total			*Associated extrahepatic disorders*		
			Ig A tTG					
		Liver function	Parameters of hepatocyte damage	AST	ALT		AST/ALT	
				ALP	GGT		ALP/AST	
			Parameters of impaired	PT					
				INR					
				Albumin					

			hepatic synthesis						
		Initial diagnosis studies	Gamma globulins	IgG or gamma globulin level					
			Autoantibodies	ANA	☐ Positive	☐ Negative			
				ASMA	☐ Positive	☐ Negative			
				Anti – LKM – 1	☐ Positive	☐ Negative			
				AMA	☐ Positive	☐ Negative			
		Differential diagnosis studies	Hepatitis:					
			Viral hepatitis: ☐ HBsAg ☐ Anti-HBs ☐ Anti-HBc					
			☐ Anti-HCV ☐ HCV RNA					
			☐ IgM HAV ☐ IgM HEV					
			NASH: ☐ Cholesterol ☐ Triglyceride ☐ LDL ☐HDL					
			α1 antitrypsin deficiency: ☐ Serum α1-antitrypsin					
			Hemochromatosis: ☐ Serum iron ☐ Ferritin ☐ TIBC/ TfS					
			Wilson disease: ☐ Serum copper ☐ Urine copper ☐ Serum ceruloplasmin					

			☐ Coombs test					
			PBC: ☐ AMA/ AMA-M2					
			PSC: ☐ pANCA					
			SLE -associated liver disease: ☐ ANA ☐Anti ds DNA					
			☐Anti-SM					
	Imaging	US	Abdomen:					
			Thyroid gland and cervical lymphonodes					
		CT scan						
		MRCP						
		Transient elastography						
		Endoscopy						
	Biopsy							

PLAN	Additional lab studies	If all the above autoantibodies are negative then order these tests:

		If all the above autoantibodies are negative then order these tests:		
		▪ ALC – 1	☐ Positive	☐ Negative
		▪ Anti – SLA/LP	☐ Positive	☐ Negative
		▪ p – ANCA	☐ Positive	☐ Negative

Disease classification based on autoantibodies results:

Type 1 AIH:		Type 2 AIH:	
▪ ANA	☐(+)ve ☐ (-)ve	▪ Anti - LKM – 1	☐(+)ve☐ (-)ve
▪ ASMA (65% pt)	☐(+)ve ☐ (-)ve	▪ ALC -1	☐(+)ve☐ (-)ve
▪ AAA	☐(+)ve ☐ (-)ve	▪ Anti – SLA/LP	☐(+)ve☐ (-)ve
▪ AMA	☐(+)ve ☐ (-)ve	▪ Anti ds DNA	☐(+)ve☐ (-)ve
▪ Anti – SLA/LP (10 – 30% pt) ☐(+)ve ☐ (-)ve		▪ Anti – LKM – 3 (rare) ☐(+)ve☐ (-)ve	
▪ Anti ds DNA (25 – 35% pt) ☐(+)ve ☐ (-)ve			
▪ p – ANCA	☐(+)ve ☐ (-)ve		

	Additional lab results	

	Definitive diagnosis	☐ AIH ☐ PBC ☐ PSC
		☐ Complication (if any)

Appendix D
Thesis permission approvement

SỞ Y TẾ HÀ NỘI
BỆNH VIỆN ĐA KHOA QUỐC TẾ
VINMEC TIMES CITY

Số: 242/QĐ-KHTH/VMTC

CỘNG HÒA XÃ HỘI CHỦ NGHĨA VIỆT NAM
Độc lập – Tự do – Hạnh phúc

Hà Nội, ngày 21 tháng 12 năm 2023

QUYẾT ĐỊNH
Về việc thông qua đề tài nghiên cứu và cho phép thu thập số liệu

Căn cứ vào Quy định quản lý nghiên cứu khoa học và công nghệ ngày 21 tháng 03 năm 2022 của Công ty cổ phần Bệnh viện đa khoa Quốc tế Vinmec;

Căn cứ Quyết định số 48/2023/QĐ-VMTC ngày 18 tháng 02 năm 2023 về việc kiện toàn hội đồng chuyên môn khoa học Bệnh viện ĐKQT Vinmec Times City;

Căn cứ theo biên bản họp Hội đồng chuyên môn khoa học Bệnh viện ĐKQT Vinmec Times City ngày 13 tháng 4 năm 2023,

QUYẾT ĐỊNH

Điều 1: Thông qua Đề tài nghiên cứu khoa học của TS.BS. Nguyễn Văn Đĩnh và BSNT. Trần Võ Thùy Nhi

Tên đề tài: Đặc điểm lâm sàng bệnh lý viêm gan tự miễn ở Việt Nam.

Tiếng Anh: : Clinical characteristics of autoimmune liver diseases in Vietnamse population

Điều 2: TS.BS. Nguyễn Văn Đĩnh và BSNT. Trần Võ Thùy Nhi có trách nhiệm triển khai thực hiện đề tài nghiên cứu khoa học này.

Điều 3: Quyết định có hiệu lực kể từ ngày ký.

Nơi nhận:
- Phòng KHTH;
- Chủ nhiệm đề tài;
- Lưu: KHTH.

GIÁM ĐỐC CHUYÊN MÔN

NGUYỄN NGỌC QUANG

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Abstract/Summary

Background: Autoimmune liver diseases (ALD) consist of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlapping syndrome. These are rare disorders that are assumed to belong to only Western countries; data from Eastern, particularly developing Asian countries, is currently lacking.

Aim: The purpose of this study is to describe the serologic spectrum, autoimmunologic profile, and clinical features of Vietnamese patients with ALD in Hanoi. The results are compared to data from previous research conducted in Western areas and other Asia-Pacific countries.

Methods: This cross-sectional study was conducted in two hospitals in Vietnam from 2021

to 2024. The following parameters were recorded when analyzing the medical records of all 32 patients: the patient's demographic data, clinical history at presentation, and findings of laboratory and serologic testing—not only the biochemistry but also the immunologic profile at the time of diagnosis.

Results: The total number of ALD patients in the study was 32, including 31.25% with AIH (n=10), 68.75% with PBC (n=22), and no patients with PSC and overlapping syndrome. Most were female and within middle age (51 years in the AIH group and 49 years in the PBC group). Fatigue, loss of appetite, and jaundice were the most reported symptoms in both groups. Depending on the pattern of ALD, the more serology antibodies were positive, the more accurately ALD was diagnosed in comparison to positive single antibody cases.

Conclusion: Our study found that most ALD cases in Vietnam were middle-aged females with PBC or AIH with nonspecific symptoms. Further long-term studies investigating the epidemiology and prognosis of ALD in Vietnam is needed.

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