

UNIWERSYTET JANA KOCHANOWSKIEGO W KIELCACH
COLLEGIUM MEDICUM

Jakub Janczura

**Stłuszczeniowa choroba wątroby u chorych z przewlekłym wirusowym
zapaleniem wątroby**

Rozprawa doktorska napisana pod kierunkiem
prof. dr hab. n. med. Doroty Zarębskiej – Michaluk

Promotor pomocniczy
dr n. med. Krystyna Dobrowolska

Praca przyjęta pod względem
merytorycznym i formalnym
w formie papierowej i elektronicznej

.....
/data i podpis promotora/

Kielce 2026

Dziękuję Pani Profesor za nieustanne wsparcie, życzliwość oraz nieocenioną relację uczeń-mentor, która miała i nadal ma ogromny wpływ na mój rozwój naukowy i zawodowy.

Pracę dedykuję Ewie.

Spis treści

Wykaz użytych skrótów.....	5
Analiza bibliometryczna publikacji wchodzących w skład cyklu publikacji stanowiących rozprawę doktorską	7
Wstęp	10
Publikacje stanowiące rozprawę doktorską	13
Podsumowanie i wnioski	45
Bibliografia	53
Streszczenie w języku polskim	56
Streszczenie w języku angielskim.....	58
Informacje o charakterze udziału współautorów w publikacjach wraz z szacunkowym określeniem procentowego wkładu.....	60
Oświadczenia współautorów.....	67
Analiza całego dorobku naukowego	94

Wykaz użytych skrótów

ALT - Alanine Aminotransferase (aminotransferaza alaninowa)

APRI - AST to Platelet Ratio Index (wskaźnik stosunku aktywności AST do liczby płytek krwi)

AST - Aspartate Aminotransferase (aminotransferaza asparaginianowa)

BMI - Body Mass Index (wskaźnik masy ciała)

CHB - Chronic Hepatitis B (przewlekłe wirusowe zapalenie wątroby typu B)

CHC - Chronic Hepatitis C (przewlekłe wirusowe zapalenie wątroby typu C)

DAA - Direct-Acting Antiviral(s) (lek(i) o bezpośrednim działaniu przeciwwirusowym)

DNA - Deoxyribonucleic Acid (kwas deoksyrybonukleinowy)

FIB-4 - Fibrosis-4 Index (wskaźnik włóknienia FIB-4)

GGTP - Gamma-Glutamyl Transpeptidase (gamma-glutamylotranspeptydaza)

HBeAg - Hepatitis B e Antigen (antygen e wirusa zapalenia wątroby typu B)

HBsAg - Hepatitis B Surface Antigen (antygen powierzchniowy wirusa HBV)

HBV - Hepatitis B Virus (wirus zapalenia wątroby typu B)

HCC - Hepatocellular Carcinoma (rak wątrobowokomórkowy)

HCV - Hepatitis C Virus (wirus zapalenia wątroby typu C)

HIV - Human Immunodeficiency Virus (ludzki wirus niedoboru odporności)

IF - Impact Factor (wskaźnik cytowań czasopisma)

INR - International Normalized Ratio (międzynarodowy współczynnik znormalizowany)

ITT - Intention-To-Treat (analiza według zamiaru leczenia)

MASLD - Metabolic Dysfunction-Associated Steatotic Liver Disease (metabolicznie uwarunkowana stłuszczeniowa choroba wątroby)

MNiSW - Ministerstwo Nauki i Szkolnictwa Wyższego

MTTP - Microsomal Triglyceride Transfer Protein (mikrosomalne białko przenoszące trójglicerydy)

NA - Nucleos(t)ide Analog(s) (analogi nukleozydów/nukleotydów)

NAFLD - Nonalcoholic Fatty Liver Disease (niealkoholowa stłuszczeniowa choroba wątroby)

PZWB - Przewlekłe Zapalenie Wątroby typu B

PZWC - Przewlekłe Zapalenie Wątroby typu C

PP - Per-Protocol (analiza wśród pacjentów, którzy zakończyli terapię zgodnie z protokołem)

PPAR- α - Peroxisome Proliferator-Activated Receptor Alpha (receptor aktywowany przez proliferatory peroksysomów alfa)

RBV - Ribavirin (rybawiryna)

SLD - Steatotic Liver Disease (stłuszczeniowa choroba wątroby)

SOF/VEL - Sofosbuvir/Velpatasvir (lek przeciwwirusowy)

SVR - Sustained Virologic Response (trwała odpowiedź wirusologiczna)

T2DM - Type 2 Diabetes Mellitus (cukrzyca typu 2)

VLDL - Very-Low Density Lipoprotein (lipoproteina o bardzo małej gęstości)

WHO - World Health Organization (Światowa Organizacja Zdrowia)

WZW - Wirusowe Zapalenie Wątroby

Analiza bibliometryczna publikacji wchodzących w skład cyklu publikacji stanowiących rozprawę doktorską

Prace oryginalne

Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michaluk

Steatotic liver disease in patients treated for chronic hepatitis B

Polish Archives of Internal Medicine 2025

DOI: 10.20452/pamw.16942

IF 4.7, 200 MNiSW

Jakub Janczura, Michał Brzdęk, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdęk, Piotr Rzymski, Dorota Zarębska-Michaluk

Steatotic liver disease in patients with chronic hepatitis C

World Journal of Hepatology 2025

DOI: 10.4254/wjh.v17.i12.113639

IF 2.5, 100 MNiSW

Prace przeglądowe

Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdęk, Kinga Brzdęk, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michaluk

Steatotic liver disease and chronic viral hepatitis

Clinical and Experimental Hepatology 2025

DOI: 10.5114/ceh.2025.154220

IF 1.7, 20 MNiSW

Analiza bibliometryczna publikacji autorstwa Pana Jakuba Janczury*

ORCID ID 0009-0004-7977-9797

I. Oryginalne pełnotekstowe prace naukowe (bez streszczeń zjazdowych i konferencyjnych, prac w suplementach czasopism, listów do redakcji oraz udziału autora wymienionego w dodatku (appendix) jako uczestnika badań wielośrodkowych, recenzji):

A. W czasopismach z Impact Factor:

Rok	Tytuł czasopisma	Liczba prac	JIF Q	IF	Punkty MNISW
2025	Polish Archives of Internal Medicine	1	Q1	4.7	200
2025	World Journal of Hepatology	1	Q2	2.5	100
Łącznie:		2		7.2	300

B. W czasopismach bez Impact Factor: 0

Opisy przypadków:

A. W czasopismach z Impact Factor: 0

B. W czasopismach bez Impact Factor: 0

Prace poglądowe / przeglądowe:

A. W czasopismach z Impact Factor:

Rok	Tytuł czasopisma	Liczba prac	JIF Q	IF	Punkty MNISW
2025	Clinical and Experimental Hepatology	1	Q3	1.7	20
Łącznie:		1		1.7	20

B. W czasopismach bez Impact Factor: 0

II. Oryginalne pełnotekstowe prace naukowe, w których autor wymieniony jest jako uczestnik badań wielośrodkowych: 0

III. Monografie naukowe (autorstwo lub współautorstwo):

A. W języku obcym: 0

B. W języku polskim: 0

*Na podstawie zweryfikowanej listy publikacji dostarczonej przez Autora.

IV. Rozdziały w monografiach naukowych:	
A. W języku obcym:	0
B. W języku polskim:	0
V. Redakcja wieloautorskiej monografii naukowej:	
A. W języku obcym:	0
B. W języku polskim:	0
VI. Redaktor naczelny czasopisma o zasięgu:	
A. Międzynarodowym:	0
B. Krajowym:	0
<u>Informacje dodatkowe:</u>	
VII. Streszczenia pokonferencyjne:	0
VIII. Publikacje naukowe niepuktowane:	0
IX. Publikacje popularnonaukowe:	0
Łączna liczba publikacji:	3
Łączna punktacja Impact Factor:	8.9
Łączna punktacja MNiSW:	320
Liczba cytowań (Web of Science Core Collection):	
sumaryczna liczba cytowań:	4
liczba cytowań bez autocytowań:	3
indeks Hirscha:	1
Liczba cytowań (Scopus):	
sumaryczna liczba cytowań:	4
liczba cytowań bez autocytowań:	1
indeks Hirscha:	1

Wicedyrektor Biblioteki Uniwersyteckiej
ds. Informacji Naukowej, Innowacji i Współpracy

mgr Karolina Wicha

Podpis osoby zatwierdzającej

Strona 2 z 2

Wstęp

Stłuszczeniowa choroba wątroby (ang. Steatotic liver disease, SLD) jest obecnie uznawana za najczęstszą przyczynę przewlekłej choroby wątroby na świecie [1]. Termin ten, wprowadzony w 2023 roku w ramach konsensusu Delphi, zastąpił wcześniejsze określenie „niealkoholowa stłuszczeniowa choroba wątroby” (ang. Nonalcoholic fatty liver disease, NAFLD) [2]. SLD stanowi pojęcie zbiorcze, obejmujące szerokie spektrum chorób związanych z nadmiernym gromadzeniem tłuszczu w hepatocytach, wynikających z różnorodnych przyczyn, takich jak dysfunkcje metaboliczne, uszkodzenia polekowe, choroby monogenowe oraz nadużywanie alkoholu [2]. W ramach tej klasyfikacji szczególne miejsce zajmuje metabolicznie uwarunkowana stłuszczeniowa choroba wątroby (ang. Metabolic dysfunction-associated steatotic liver disease, MASLD), będąca najczęstszą postacią SLD. Charakteryzuje się ona obecnością stłuszczenia u osób z metabolicznymi czynnikami ryzyka, takimi jak otyłość, cukrzyca typu 2 (ang. Type 2 Diabetes Mellitus, T2DM), dyslipidemia czy nadciśnienie tętnicze [3].

Szacuje się, że SLD dotyka obecnie około 25-33% populacji dorosłych na świecie, a częstość jej występowania wykazuje wyraźną tendencję wzrostową w związku z globalną epidemią otyłości, cukrzycy oraz chorób sercowo-naczyniowych [1,4]. Choć u części chorych choroba przebiega stabilnie, u innych może postępować, prowadząc do zapalenia, włóknienia, marskości oraz raka wątrobowokomórkowego (ang. Hepatocellular Carcinoma, HCC) [5]. Szczególnie niekorzystny przebieg obserwuje się w sytuacji współwystępowania SLD z innymi czynnikami uszkadzającymi wątrobę, w tym przewlekłymi zakażeniami wirusami hepatotropowymi: HBV (ang. Hepatitis B virus) oraz HCV (ang. Hepatitis C virus) [5].

W przebiegu zakażenia wirusem HCV stłuszczenie wątroby obserwuje się znacznie częściej niż w populacji ogólnej, według danych epidemiologicznych dotyczy ono 45-79% pacjentów [6]. Na jego rozwój wpływają zarówno czynniki związane z gospodarzem, przede wszystkim elementy zespołu metabolicznego, jak i mechanizmy swoiste dla samego wirusa. Szczególne znaczenie ma genotyp 3 HCV, który poprzez zaburzenia w wydzielaniu lipoprotein o bardzo małej gęstości (ang. Very-low Density Lipoprotein, VLDL) bezpośrednio indukuje proces stłuszczenia hepatocytów [7]. Globalnie zakażeniem HCV dotkniętych jest około 50 milionów osób, a każdego roku odnotowuje się blisko milion nowych przypadków [8]. W 2022 roku infekcja HCV była przyczyną około 242 tysięcy zgonów na świecie [8]. Pomimo przełomu terapeutycznego, jaki przyniosło wprowadzenie leków o bezpośrednim działaniu przeciwwirusowym (ang. Direct-acting antivirals, DAAs), które pozwalają na uzyskanie

trwałej odpowiedzi wirusologicznej u ponad 95% chorych, nadal pozostają istotne pytania dotyczące wpływu współistniejącej SLD na skuteczność leczenia oraz długoterminowe rokowanie pacjentów [9].

W przewlekłym zakażeniu HBV współwystępowanie SLD może modyfikować przebieg kliniczny choroby, rokowanie oraz skuteczność leczenia analogami nukleozydów/nukleotydów (ang. nucleos(t)ide analogs, NA) [10]. Skala problemu jest istotna także z perspektywy globalnej. Z przewlekłym zakażeniem HBV żyje około 250 milionów osób, z czego ponad milion rocznie umiera, głównie z powodu marskości i HCC [11].

Dotychczasowe badania dotyczące współwystępowania SLD u chorych z przewlekłymi wirusowymi zapaleniami wątroby prowadzone były głównie w krajach azjatyckich i dotyczyły wirusowego zapalenia wątroby typu B (PZWB). Wyniki te nie zawsze są w pełni przekładalne na populacje z innych regionów świata, w tym Europy Środkowej o niskiej endemiczności HBV. Dlatego też istnieje potrzeba prowadzenia badań opartych na danych w warunkach codziennej praktyki klinicznej, uwzględniających lokalne uwarunkowania epidemiologiczne i kliniczne, aby lepiej ocenić znaczenie współistnienia SLD i przewlekłych zakażeń HBV lub HCV dla przebiegu i skuteczności leczenia tych schorzeń.

Celem niniejszej rozprawy była ocena częstości występowania, uwarunkowań klinicznych oraz potencjalnych konsekwencji współwystępowania SLD u pacjentów z PZWB i przewlekłym wirusowym zapaleniem wątroby typu C (PZWC) w warunkach codziennej praktyki klinicznej z uwzględnieniem znaczenia wyników dla postępowania klinicznego.

Rosnąca częstość występowania SLD stanowi coraz poważniejsze obciążenie dla systemu ochrony zdrowia, a jej znaczenie jest szczególnie istotne u chorych z innymi przewlekłymi chorobami wątroby. Współistnienie tych schorzeń może wpływać nie tylko na nasilenie przebiegu choroby, lecz także na skuteczność leczenia przeciwwirusowego, zmieniając rokowanie, strategie terapeutyczne oraz wymagania dotyczące monitorowania hepatologicznego. Dotychczas brakuje analiz tego typu przeprowadzonych w polskiej populacji w oparciu o dane pochodzące z praktyki klinicznej odnoszących się do stosowania terapii analogami nukleozydów/nukleotydów u chorych z PZWB i schematami DAA u chorych z PZWC. Niniejsza praca ma na celu wypełnienie tej luki, dostarczając wiedzy przydatnej zarówno klinicytom, jak i decydom systemu opieki zdrowotnej. Przeprowadzone analizy stanowią istotny wkład w aktualny stan wiedzy, dostarczając

pierwszych tak obszernych danych pochodzących z polskiej codziennej praktyki klinicznej, które porównują przebieg choroby oraz skuteczność leczenia przeciwwirusowego u pacjentów z PZWB i PZWC, w zależności od obecności lub braku współistniejącej SLD. Uzyskane wyniki mogą wspierać praktykę kliniczną poprzez ułatwienie podejmowania decyzji terapeutycznych oraz lepsze monitorowanie pacjentów obciążonych chorobami metabolicznymi. Praca ta stanowi również podstawę do ewentualnej aktualizacji zaleceń klinicznych i opracowania nowych strategii postępowania diagnostyczno-terapeutycznego, które uwzględniają znaczenie SLD jako czynnika modyfikującego przebieg i rokowanie przewlekłych wirusowych zapaleń wątroby. W dłuższej perspektywie uzyskane wyniki mogą przełożyć się na wymierne korzyści dla pacjentów w tym wcześniejsze rozpoznawanie choroby, bardziej spersonalizowane leczenie, ograniczenie powikłań i poprawę jakości życia.

Publikacje stanowiące rozprawę doktorską

Steatotic liver disease in patients treated for chronic hepatitis B

Jakub Janczura¹, Michał Brzdek¹, Krystyna Dobrowolska¹, Robert Flisiak², Diana Martonik², Kinga Brzdek¹, Robert Pleśniak³, Dominika Kukla-Woźnica³, Małgorzata Wajdowicz², Dorota Zarębska-Michaluk⁴

¹ Collegium Medicum, Jan Kochanowski University, Kielce, Poland

² Department of Infectious Diseases and Hepatology, Medical University of Białystok, Białystok, Poland

³ Clinical Department of Infectious Diseases with Hepatology Subdivision, Medical College of Rzeszów University, Rzeszów, Poland

⁴ Department of Infectious Diseases and Allergy, Jan Kochanowski University, Kielce, Poland

KEY WORDS

hepatitis B,
nucleos(t)ide analogs,
steatotic liver disease

ABSTRACT

INTRODUCTION Steatotic liver disease (SLD) can worsen the prognosis of other chronic liver diseases, including viral hepatitis.

OBJECTIVES The aim of the study was to assess patients with chronic hepatitis B virus (HBV) infection according to the presence or absence of SLD.

PATIENTS AND METHODS The study included consecutive white patients with chronic hepatitis B treated with nucleos(t)ide analogs (NAs), entecavir or tenofovir, for a median (interquartile range) of 6 (2–11) years, and evaluated between January 2023 and June 2024.

RESULTS Of the 273 patients included in the analysis, 86 were diagnosed with SLD. Men constituted the majority of the overall population, with a higher percentage in the SLD group (77.9% vs 63.6%; $P = 0.02$). The burden of comorbidities was higher in the SLD group than in the non-SLD group ($P < 0.001$), including obesity ($P < 0.001$), diabetes ($P = 0.004$), and gout ($P = 0.03$). Cirrhosis was diagnosed in 16.3% of the patients with SLD and 11.8% of those without SLD ($P = 0.31$). Aminotransferase activity was higher in the SLD group ($P < 0.001$), while HBe antigen positivity was significantly less frequent in this population, and HBV DNA viral load was comparable between the groups. More than 97% of all patients achieved HBV DNA clearance during therapy, with a negative rate of 69.5% and 66.7% in the SLD and non-SLD groups, respectively, after 1 year of treatment.

CONCLUSIONS Liver steatosis was diagnosed in nearly one-third of HBV-infected patients treated with NAs. These patients were more likely to have obesity, diabetes, and gout, as compared with the non-SLD population. Despite higher baseline aminotransferase activity in the SLD group, virological HBV activity and response to therapy were comparable between the patients with and without SLD.

Correspondence to:

Michał Brzdek, MD, PhD,
Jan Kochanowski University,
Alpa 9, Włocławek, 19A,
25-317 Kielce, Poland,
phone: +48 41 349 0326,
Received: December 16, 2024,
Revised accepted:
January 27, 2025,
Published online: January 31, 2025.
Pit Acta Intern Med. 2025;
135 (3): 16940
doi:10.20452/pamw.16940
Copyright by the Author(s), 2025.

INTRODUCTION The term *steatotic liver disease* (SLD) replaced *nonalcoholic fatty liver disease* (NAFLD) following publication of the 2023 multi-society Delphi consensus statement.¹ SLD serves as an umbrella term for hepatic steatosis of various etiologies, including metabolic disorders, alcohol abuse, specific etiologies in the course of drug-induced liver injury, monogenic diseases, and other conditions. This new nomenclature is changing our understanding of the disease, whose prevalence is increasing globally.

SLD unrelated to alcohol abuse is estimated to affect approximately one-third of the world's adult population. However, when alcoholic steatohepatitis (that fit the current SLD definition) is included, the true burden of the disease appears to be even greater.² This makes SLD a leading cause of chronic liver disease worldwide. The rising prevalence of diabetes, obesity, and cardiovascular diseases—cardiometabolic risk factors for hepatic steatosis—is expected to further drive the growing incidence

WHAT'S NEW?

Steatotic liver disease, whose incidence is increasing worldwide, can worsen the prognosis of other chronic liver diseases. Nearly one-third of patients with chronic hepatitis B virus infection receiving antiviral treatment had coexisting steatohepatitis. Although these patients had higher aminotransferase activity and were more often diagnosed with cirrhosis, their response to antiviral treatment was comparable to that observed in the patients without steatosis. The uniqueness of our analysis lies in the assessment of the coexistence of hepatitis B virus infection and hepatic steatosis in a white population, as most studies on this topic have focused on Asian populations.

of SLD, thus increasing its burden both globally and locally.^{2,3}

Regardless of its etiology, SLD can lead to cirrhosis, increasing the risk of liver failure and hepatocellular carcinoma (HCC).^{4,5} These risks are further heightened when SLD is complicated by liver damage of other etiologies, such as chronic infection with hepatotropic viruses (eg, hepatitis B virus [HBV] and hepatitis C virus [HCV]).⁶⁻⁸ The global burden of chronic HBV infection and SLD co-occurrence is particularly significant, with HBV infection affecting an estimated 250 million people worldwide, resulting in over 1 million new infections and about 1.1 million deaths annually, primarily due to cirrhosis and HCC.⁹

A comprehensive understanding of the interplay between hepatic steatosis and HBV infection—both at the molecular and clinical levels—is crucial for optimizing patient management. This interaction can influence the prognosis of individuals with chronic hepatitis B (CHB) infection as well as the course and outcomes of antiviral therapy.¹⁰⁻¹² Most of the studies that have evaluated the characteristics of patients with CHB infection and concomitant hepatic steatosis, its impact on the progression of the disease, and the outcome of antiviral therapy relative to patients without steatosis, have been conducted in highly endemic Asian populations.^{6,10,13,14} However, given the distinct characteristics of CHB infection in Asian populations—including high prevalence of hepatitis B envelope antigen (HBeAg), increased viral replication, differing HBV genotypes, and varying risk of HCC—studies from other geographic regions are necessary.

To address this gap, we conducted a retrospective, real-world study comparing patients with and without SLD treated for CHB infection with nucleos(t)ide analogs (NAs) in Poland, a Central European country with low HBV endemicity.

PATIENTS AND METHODS **Study population** A real-world retrospective study was conducted at 3 hepatology centers in Poland: the Department of Infectious Diseases in Kielce, the Department of Infectious Diseases with Hepatology Subdivision in Łańcut, and the Department of Infectious Diseases and Hepatology in Białystok. Patients were assessed between January 2023 and June 2024 during routine outpatient visits

in accordance with the drug program schedule, which requires therapy monitoring tests every 6 months.

The analysis included 273 consecutive patients with CHB who were treated with NAs under the drug program of the National Health Fund. Data were obtained from patients' medical records and included laboratory, virological, and clinical parameters.

Data collection Retrospective data were collected at 2 time points: at the start of antiviral therapy and during a follow-up visit that took place between September 2023 and June 2024. Records included demographic and clinical data, encompassing comorbidities, coinfections with HCV, hepatitis D virus (HDV), and HIV, as well as a history of HBV infection and prior antiviral therapy for this indication.

The status of HBeAg and anti-HBe antibody, along with HBV DNA viral load, were assessed at baseline and during antiviral treatment. HBV DNA was quantified using the GeneProof real-time polymerase chain reaction (PCR) method (COBAS, Roche Diagnostics, Basel, Switzerland). Some patients had their HBV genotype determined prior to the therapy using PCR sequencing. All patients were tested for anti-HDV antibodies using the LIAISON XL Murex anti-HDV assay (DiaSorin, Saluggia, Italy) via chemiluminescence immunoassay on serum samples. HDV RNA testing was also performed. One patient tested positive for anti-HDV antibodies. In this case, both qualitative and quantitative determination of HDV RNA were conducted using real-time PCR.

Additionally, laboratory parameters were gathered at baseline and during treatment. They included blood count, activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), creatinine, albumin, and bilirubin levels, and international normalized ratio (INR).

Liver disease The severity of liver disease was assessed by liver biopsy, noninvasive methods such as transient elastography (TE) with FibroScan or shear wave elastography with Aixplorer (SuperSonic Imagine, Aix-en-Provence, France), or clinical evaluation in combination with the serum Fibrosis-4 (FIB-4) index.¹⁵

SLD was diagnosed based on the presence of hepatic steatosis, identified via imaging modalities, such as abdominal ultrasound, liver biopsy, or TE.¹⁶ While liver biopsy remains the gold standard for diagnosing hepatic steatosis, its invasiveness and the associated risk of complications limits its widespread use. In contrast, abdominal ultrasound is a widely available, non-invasive, and cost-effective alternative, utilizing attenuation coefficient, backscatter coefficient, and speed of sound for detection.¹⁷ TE not only enables the identification of steatosis, but also allows for the quantification of fat content through the controlled attenuation parameter;

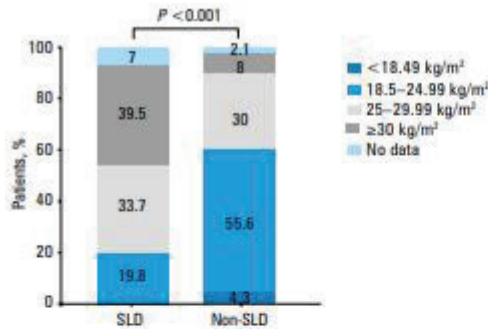


FIGURE 1 Comparison of baseline body mass index between the patients with and without steatotic liver disease (SLD)

however, its use is contingent on FibroScan availability.¹⁷

The SLD group was further categorized into metabolic dysfunction-associated SLD, metabolic dysfunction and alcohol-related liver disease, and alcohol-related liver disease, based on established diagnostic criteria.⁷

Ethical considerations This retrospective, cross-sectional study was approved by the Bioethics Committee of the Jan Kochanowski University in Kielce (57/2024). Access to medical records and data on patient treatment was granted with the prior consent of hospital management of respective facilities. Patients were included in the study after receiving full information regarding its purpose. They gave a written consent to enter the therapeutic program.

Statistical analysis Qualitative variables were analyzed by determining the frequency and percentage distributions. Group comparisons for qualitative variables were performed using either the χ^2 test or Fisher exact test. For quantitative variables, the median, quartiles, minimum, and maximum values were calculated. Due to the non-normal distribution of quantitative data, comparisons between 2 groups were made using the Mann-Whitney test for independent variables, and the Wilcoxon signed-rank test was used for dependent samples. The normality of distribution was assessed using the Shapiro-Wilk test. To control for multiple comparisons, the Bonferroni correction was applied. Statistical significance was set at a P value below 0.05. All statistical analyses were performed using Statistica, version 13 (StatSoft, Tulsa, Oklahoma, United States) and GraphPad Prism 5.1 packages (GraphPad Software, Inc., La Jolla, California, United States).

RESULTS Characteristics of the study population We included 273 consecutive white patients treated with NAs for CHB. All participants underwent abdominal ultrasound; additionally, 72 patients underwent liver biopsy and 56 underwent

FibroScan. SLD was diagnosed in 86 individuals (31.5%); of those, 20 underwent liver biopsy and 23 FibroScan.

Patient demographic and clinical characteristics are presented in TABLE 1. At the time of evaluation, the median age was comparable between the SLD and non-SLD groups. Both subpopulations were predominantly male, with a higher proportion in the SLD group ($P = 0.02$). The patients with SLD had a higher burden of comorbidities ($P < 0.001$), particularly diabetes, gout, and obesity. The distribution of body mass index in both groups is presented in FIGURE 1.

There were no cases of HIV infection, while HCV coinfection was diagnosed in 12 patients, mainly in the non-SLD group (TABLE 1). A small percentage of patients in both groups reported a history of alcohol abuse (defined as alcohol intake >20 g/d for women and >30 g/d for men), but all declared abstinence since qualifying for antiviral therapy and during the treatment. Among the patients with SLD, 79 (91.9%) met the criteria for metabolic dysfunction-associated SLD, 7 (8.1%) for metabolic dysfunction and alcohol-related liver disease, and none for alcohol-related liver disease.

HBV genotype determination data were available for 64 patients, with a majority being infected with genotype A, and its distribution was comparable between the SLD and non-SLD groups. Cirrhosis was diagnosed in 16.3% of the patients with SLD and 11.8% of those without SLD ($P = 0.31$). Liver disease severity was evaluated by liver biopsy in 72 patients, by TE in 56 patients, and by shear wave elastography in 78 patients. In the remaining 67 patients, clinical assessment was supplemented with the calculation of the serum FIB-4 index.

Treatment characteristics The treatment characteristics of the study population are presented in TABLE 2. There were less treatment-experienced patients in the SLD group, as compared with the non-SLD group. Lamivudine was the most common drug in the whole study population. The primary reason for switching antiviral drugs in most patients was treatment inefficacy. However, in 4 individuals from each group, the switch to the analog was prompted by changes in the provisions of the National Health Fund drug program, and in these cases, HBV DNA was already undetectable at the start of the current therapy.

The median HBV DNA load at baseline and the distribution of baseline viremia were comparable between the groups (TABLE 2, FIGURE 2). However, the proportion of patients with HBeAg positivity was lower in the SLD group ($P = 0.004$; TABLE 2). The patients with SLD also exhibited higher median aminotransferase activity, as compared with those without steatosis ($P < 0.001$ for ALT and $P = 0.004$ for AST; TABLE 2, FIGURE 3). Liver function parameters, including bilirubin level and INR, were similar in both subpopulations, while albumin concentrations were lower in the patients with SLD ($P = 0.02$).

TABLE 1 Demographic and clinical characteristics of the study population with regard to the presence of steatotic liver disease

Parameter	SLD (n = 86)	Non-SLD (n = 187)	P value	
Sex	Women	19 (22.1)	68 (36.4)	0.02
	Men	67 (77.9)	119 (63.6)	
Age, y, median (IQR; range)	52 (44–60; 31–71)	50 (39–60; 28–98)	0.5	
BMI, kg/m ² , median (IQR)	28.5 (25.8–32.5)	23.8 (21.8–26.2)	<0.001	
Overweight	29 (33.7)	55 (29.4)	0.47	
Obesity	34 (39.5)	15 (8)	<0.001	
Any comorbidity	57 (66.3)	74 (39.6)	<0.001	
Chronic kidney disease	3 (3.5)	17 (9.1)	>0.99	
Hypertension	34 (39.5)	46 (24.6)	0.14	
Ischemic heart disease	4 (4.7)	15 (8)	>0.99	
Stroke	0	1 (0.5)	>0.99	
Non-HCC malignancy	11 (12.8)	24 (12.8)	>0.99	
Autoimmune disease	5 (5.8)	11 (5.9)	>0.99	
Diabetes	13 (15.1)	6 (3.2)	0.004	
Dyslipidemia	19 (22.1)	19 (10.2)	0.09	
Gout	5 (5.8)	0	0.03	
Chronic respiratory disease	3 (3.5)	7 (3.7)	>0.99	
History of HCC	1 (1.2)	1 (0.5)	0.53	
HCV coinfection	1 (1.2)	11 (5.9)	0.11	
HDV coinfection	0	0	–	
History of alcohol intake	7 (8.1)	7 (3.7)	0.13	
Cirrhosis	14 (16.3)	22 (11.8)	0.31	
History of liver decompensation	Ascites	1 (1.2)	3 (1.6)	>0.99
	Hepatic encephalopathy	1 (1.2)	0	

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: BMI, body mass index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; SLD, steatotic liver disease

Treatment outcomes More than 97% of all patients achieved HBV DNA clearance during NA therapy (TABLE 2). One year after treatment initiation, the percentage of patients with negative HBV DNA results was comparable between the groups. HBe seroconversion rates were also similar, with 42.9% of those positive at baseline achieving seroconversion.

Both groups demonstrated a biochemical response to NA therapy, reflected by a decrease in median ALT activity ($P < 0.001$ in both SLD and non-SLD groups). Among the 12 patients coinfecting with HCV, 11 had detectable HCV RNA and received antiviral therapy, predominantly direct-acting antivirals (73%), during the course of NA treatment for HBV, and all achieved a sustained virological response. At the time of analysis, anti-HDV antibodies were detected in a single patient from the non-SLD group, but HDV RNA evaluation was negative. No patient in either group experienced liver decompensation during NA treatment. However, HCC was diagnosed in

4 individuals: a single case in the SLD group and 3 cases in the non-SLD group.

DISCUSSION The evolution of the terminology related to liver steatosis, with the most recent change in June 2023, has resulted in different terms for steatohepatitis being used in papers published at different time points. This should be acknowledged to clarify any inconsistencies in naming conventions.

A recent global analysis estimated the prevalence of NAFLD at 32.4%. Although the study included data from only 17 of 195 countries, the results are in line with reports from Europe and the National Health and Nutrition Examination Survey, which indicate SLD prevalence of 26.9% and 31.3% in the general population, respectively.^{4,18,19} Among the HBV-infected patients, the rate of comorbid SLD was approximately 32% and was higher in men ($P = 0.009$). No differences in prevalence were noted based on geographic regions or diagnostic techniques.²⁰ Our findings are consistent with these results, as we identified SLD in 31.5% of the patients treated for CHB, with a higher prevalence in men ($P = 0.02$).

The novelty and uniqueness of our study stem from its evaluation of the coexistence of HBV infection and liver steatosis in a white population, whereas most research on this topic has focused on Asian populations.

The molecular mechanisms underlying liver steatosis in patients with CHB infection remain unclear. The HBx protein has been suggested as a contributing factor, as it interferes with lipid secretion by apolipoprotein B. Additionally, HBx can modulate the expression of genes involved in lipid synthesis and degradation, leading to abnormal lipid accumulation within hepatocytes.^{10–12}

We documented male predominance in our study population, consistent with previous reports indicating a higher risk of HBV chronicity in men.^{21–24} The liver is considered a sexually dimorphic organ, with its cells expressing androgen and estrogen receptors that respond to the respective sex hormones. Androgen stimulation has been shown to increase HBV transcription, whereas estrogen has the opposite effect. In addition, HBx protein increases androgen receptor activity in the liver.²⁴

The predominance of men in the study population was even more pronounced among the patients diagnosed with SLD, which is consistent with the results of a worldwide analysis indicating a higher proportion of men (52.3%) among patients with NAFLD.¹⁸ This trend is also influenced by sex hormones, with testosterone increasing the risk of SLD, and estrogen acting as a protective factor through estrogen receptor- α signaling. Estrogen also mitigates the risk of insulin resistance, a known risk factor for SLD, and reduces lipogenesis.²⁵ Differences in chromosomal composition have also been implicated in hepatic

TABLE 2 Characteristics of the past and current antiviral therapy

Parameter	SLD (n = 86)	Non-SLD (n = 187)	P value	
Treatment-experienced	Total	31 (36)	95 (50.8)	0.02
	ETV	5 (16.1)	16 (16.8)	>0.99
	TDV	2 (6.5)	1 (1.1)	0.23
	ADV	2 (6.5)	4 (4.2)	>0.99
	LMV	13 (41.9)	49 (51.6)	0.04
(peg)IFN	9 (29)	25 (26.3)	0.49	
Current therapy	ETV	55 (64)	128 (68.4)	0.46
	TDV	31 (36)	59 (31.6)	
Time on the current therapy, y, median (IQR; range)	5 (2–10; 0–16)	6 (3–11; 0–17)	0.07	
HBeAg(+) at baseline	7 (8.1)	42 (22.5)	0.004	
HBe seroconversion during therapy in relation to HBeAg(+) patients, n/N (%)	3/7 (42.9)	18/42 (42.9)	>0.99	
HBV DNA at baseline, IU/ml, median (IQR)	6442 (1280–69250)	11820 (2180–103000)	0.29	
HBV DNA clearance in the 1st year of therapy in relation to HBV DNA-positive at baseline, n/N (%)	57/82 (69.5)	122/183 (66.7)	0.65	
HBV DNA clearance during therapy in relation to HBV DNA-positive at baseline, n/N (%)	80/82 (97.6)	179/183 (97.8)	0.89	
HCC diagnosed during therapy	1 (1.2)	3 (1.6)	>0.99	
Liver decompensation during therapy	0	0	–	
HDV coinfection diagnosed during therapy	0	1 (0.5)	>0.99	

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: ADV, adefovir; ETV, entecavir; HBV, hepatitis B virus; HDV, hepatitis D virus; HBeAg, hepatitis B envelope antigen; LMV, lamivudine; (peg)IFN, pegylated interferon; TDV, tenofovir disoproxil; others, see TABLE 1

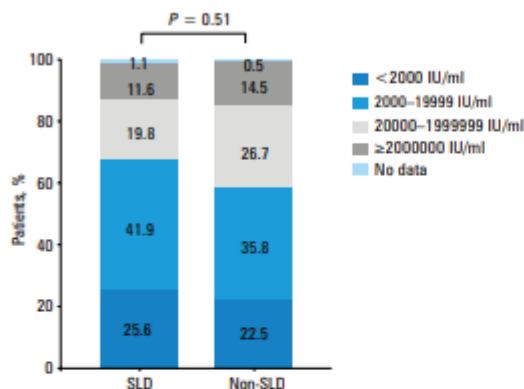


FIGURE 2 Comparison of baseline hepatitis B virus DNA load in the patients with and without steatotic liver disease (SLD)

steatosis, as demonstrated by studies on animals and individuals with genetic syndromes involving an extra chromosome X.²⁶

Our study revealed a significantly higher burden of comorbidities in the patients with SLD, as

compared with those without steatosis. Established metabolic risk factors for SLD, such as diabetes mellitus and obesity, were more prevalent among the patients with steatosis ($P = 0.004$ for diabetes mellitus and $P < 0.001$ for obesity). Similarly, other risk factors, including dyslipidemia and hypertension, were more common among the patients with SLD than in the HBV-infected individuals without steatosis, although statistical significance was not reached. These findings are consistent with previous studies.^{18,27} Additionally, we observed a higher prevalence of gout in the patients with SLD. A cross-sectional study involving more than 4000 individuals in the United States demonstrated that higher uric acid levels are independently associated with an increased risk of liver steatosis.²⁸

Alcohol consumption is another important risk factor for SLD.^{29,30} Our findings did not show any difference in the history of alcohol abuse; however, it was more frequently reported in the patients with SLD than in those without steatosis. Notably, since the initiation of antiviral therapy, all patients in our analysis declared abstinence, which allowed us to assess the impact of past alcohol consumption.

The effect of hepatic steatosis on liver disease progression in HBV-infected patients, including fibrosis and HCC, remains a subject of an ongoing debate. Some studies suggest that fatty liver disease accelerates liver disease progression, while others show no significant association.^{13,14,29,31} In our study, although the percentage of cirrhosis cases was higher in the SLD group, the difference did not reach significance. Similarly, a retrospective study of 555 patients with CHB infection who received treatment (187 with NAFLD and 368 without) found comparable rates of compensated cirrhosis ($P = 0.84$) and similar odds of advanced fibrosis/cirrhosis assessed noninvasively by FIB-4 ($P = 0.28$).¹³ Severe or advanced liver fibrosis has been linked more closely to the degree of necrotizing inflammation and host factors rather than hepatic steatosis in patients with CHB infection.³¹ However, several previous works, including a meta-analysis of 20 studies involving 6232 patients, indicated an association between hepatic steatosis and advanced fibrosis in CHB infection, suggesting that steatosis may contribute to fibrosis.^{14,20}

We found no difference in HCC history between the SLD and non-SLD groups. This is in contrast to some studies that reported a limited impact of hepatic steatosis on HCC in patients with CHB infection.^{32,33} However, our results are in line with those of a retrospective cohort study, which also found no association between hepatic steatosis and HCC risk.³⁴

Elevated liver enzyme activity is often a key indicator of liver damage and inflammation, making its association with hepatic steatosis in HBV-infected patients a subject of ongoing research. In our study, we observed higher activity of ALT and AST in the SLD group, as compared with

TABLE 3 Laboratory parameters of the study patients at baseline of therapy

Parameter	SLD (n = 86)	Non-SLD (n = 187)	P value
ALT, IU/l	47 (29–82)	30 (21–52)	<0.001
AST, IU/l	38 (27–63)	28 (21–44)	0.004
PLT, × 1000/μl	174 (147.5–227.5)	199 (168–244)	0.005
Creatinine, mg/dl	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.75
INR	1.1 (1–1.1)	1 (1–1.1)	0.84
Bilirubin, mg/dl	0.8 (0.6–1.1)	0.7 (0.6–1)	0.52
Albumin, g/dl	4.2 (3.8–4.5)	4.3 (4.1–4.7)	0.02

Data are presented as median (IQR).

SI conversion factors: to convert ALT or AST to μkat/l, multiply by 0.0167; PLT to × 10⁹/l, by 1; creatinine to μmol/l, by 88.4; bilirubin to μmol/l, by 17.1; albumin to g/l, by 10.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PLT, platelet count; others, see TABLE 1

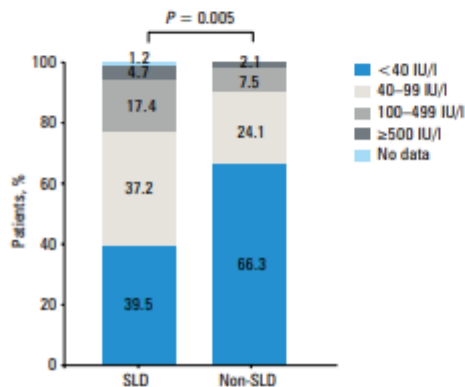


FIGURE 3 Comparison of baseline alanine aminotransferase activity in the patients with and without steatotic liver disease (SLD)

the non-SLD group. However, meta-analyses of 22 studies on ALT and 16 studies on AST reported no differences in liver enzyme activity between CHB patients with and without hepatic steatosis. These findings suggest that while hepatic steatosis can influence liver enzymes in certain contexts, its effects may not be universally observed across all CHB populations.³³

The present analysis showed that HBV DNA levels at the start of antiviral therapy were comparable in the SLD and non-SLD groups. However, previous studies suggested an inverse relationship between HBV replication and hepatic steatosis. A meta-analysis of 17 studies including 4100 patients with HBV infection found a strong negative association between HBV DNA levels and steatosis ($P < 0.001$), suggesting a potential protective effect of HBV infection against steatosis.³⁴ A review of studies conducted in Asian populations showed that concomitant NAFLD may inhibit HBV replication and promote the seroclearance of hepatitis B surface antigen.³⁴ In contrast, a meta-analysis by Jiang et al³⁵ did

not show a relationship between HBV DNA levels and SLD.

Despite inconsistent findings regarding HBV DNA, it has been shown that patients with HBeAg-positive CHB infection have a lower risk of hepatic steatosis. Jiang et al³⁵ reported an odds ratio (OR) of 0.81 (95% CI, 0.7–0.93) based on data from 34 studies. Similarly, another meta-analysis with data from 13151 patients found a reduced risk of hepatic steatosis in HBeAg-positive individuals (OR, 0.82; 95% CI, 0.75–0.91; $P < 0.001$).³⁶ Our study confirms this relationship, showing a lower incidence of HBeAg positivity in the SLD group, as compared with the non-SLD group (8.1% vs 22.5%; $P = 0.004$). This concordance highlights the potential interaction between HBV replication and metabolic factors in the pathogenesis of liver disease.

The impact of hepatic steatosis on the outcomes of antiviral treatment in patients with CHB infection remains unclear. An analysis of patients treated with pegylated interferon showed comparable treatment responses between groups with and without steatosis, regardless of HBeAg status.¹² Similarly, in patients with CHB infection receiving NA treatment, hepatic steatosis appears to have no impact on virological response.^{12,37} On the other hand, a prospective study conducted among Chinese patients treated with entecavir showed that hepatic steatosis was an independent factor for treatment failure, possibly due to reduced entecavir bioavailability in hepatocytes caused by lipid accumulation and diminished cytochrome activity.³⁸ Furthermore, a global meta-analysis identified hepatic steatosis as an independent negative predictor of virological response.³⁹ In our analysis, findings related to HBV DNA clearance and treatment duration were comparable between the groups.

Limitations and strengths Our study has several limitations impacting the significance of our findings. As an observational study using real-world evidence and retrospective data, it is subject to potential biases, such as entry errors and underreporting of side effects. Liver disease severity was assessed using different methods, which may introduce inconsistencies and affect the reliability of comparisons of the disease progression. Additionally, steatosis assessment did not include the controlled attenuation parameter in FibroScan, a more precise, noninvasive tool, potentially limiting the accuracy in steatosis measurement.

Metabolic data on lipid and carbohydrate profiles were not detailed, despite their relevance for evaluating metabolic influences on liver disease in patients with CHB infection and SLD. Information on hypoglycemic treatments did not differentiate between insulin and oral medications, which may have distinct interactions with liver disease and treatment response. Concomitant medications, including lipid-lowering

therapies, were also not accounted for, despite their potential influence on SLD and overall liver health. The follow-up duration varied among patients, complicating long-term treatment comparisons. Furthermore, alcohol consumption was self-reported without objective biomarkers, potentially introducing recall bias and underestimation of alcohol intake.

Nonetheless, the strengths of our study include the representative dataset collected from 3 different centers across Poland, ensuring that patients from different geographic regions were treated under uniform guidelines in accordance with drug program regulations and national recommendations. This allows for the generalization of our findings and their application in everyday clinical practice. Additionally, unlike many previous studies that have focused primarily on Asian populations with various serological and virological characteristics of HBV infection, our work uniquely evaluates a white patient cohort.

Conclusions Liver steatosis was diagnosed in nearly one-third of patients treated with NAs for chronic HBV infection. These patients were more likely to have obesity, diabetes, and gout, as compared with those without SLD. Despite higher baseline biochemical activity in the patients with SLD, virological HBV activity and response to therapy were comparable between the groups.

ARTICLE INFORMATION

ACKNOWLEDGMENTS

FUNDING The science project of the Jan Kochanowski University in Kielce, Poland (project number, SUPB.RN.24.041; to MB).

CONTRIBUTION STATEMENT JJ, MB, KD, RF, KB, MW, and DZ-M drafted the manuscript; JJ prepared the manuscript for submission; MB and KB analyzed and interpreted the data; DZ-M and RF conceived the study design; JJ, KD, DM, RP, DK-W, and DZ-M acquired the data; all authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing anyone to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, including commercial purposes, provided the original work is properly cited.

HOW TO CITE Janczewska J, Borkajk M, Dobrowolaka K, et al. Steatotic liver disease in patients treated for chronic hepatitis B. *Pol Arch Intern Med.* 2025; 135: 16942. doi:10.20452/pamw.16942

REFERENCES

- Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Ann Hepatol.* 2024; 29: 101133. [DOI](#)
- Tong ML, Ng CH, Huang QQ, et al. Global incidence and prevalence of nonalcoholic fatty liver disease. *Clin Mol Hepatol.* 2023; 29: S32-S42. [DOI](#)
- Fernandez CJ, Nagenda L, Pappachan JM. Metabolic dysfunction-associated fatty liver disease: an urgent call for global action. *touchREV Endocrinol.* 2024; 20: 5-9.
- Chen Y-T, Chen T-L, Yang T-H, et al. Long-term risks of cirrhosis and hepatocellular carcinoma across steatotic liver disease subtypes. *Am J Gastroenterol.* 2024; 119: 2241-2250. [DOI](#)
- Laombia R, Friedman SL, Shalman G. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell.* 2021; 184: 2537-2594. [DOI](#)
- Lee M-H, Chen Y-T, Huang Y-H, et al. Chronic viral hepatitis B and C out-weigh MASLD in the associated risk of cirrhosis and HCC. *Clin Gastroenterol Hepatol.* 2024; 22: 1275-1285.e2. [DOI](#)
- Lanardo A, Adinolfi LE, Loria P, et al. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology.* 2004; 126: 586-597. [DOI](#)

- Flisiak R, Zarybka-Michalak D, Dobrowolaka K, et al. Treatment of HCV infection in patients with steatotic liver disease. *Clin Exp Hepatol.* 2024; 10: 159-164. [DOI](#)
- World Health Organization. Hepatitis B. <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>. Accessed December 10, 2024.
- Bacik MO, Reyes KD, Liles VR, et al. Hepatic steatosis in chronic hepatitis B: a study of metabolic and genetic factors. *Int J Med Epidemiol Genet.* 2016; 9: 13-19.
- Fernandez CJ, Alkhalifah M, Afari H, Pappachan JM. Metabolic dysfunction-associated fatty liver disease and chronic viral hepatitis: the interlink. *Pathogens.* 2024; 13: 68. [DOI](#)
- Lin CT, Kumar R. Hepatitis B and concomitant hepatic steatosis. *Ann Transl Med.* 2017; 5: 38. [DOI](#)
- Tong X, Sang Y, Yin S, et al. Clinical impact and mechanisms of hepatitis B virus infection concurrent with non-alcoholic fatty liver disease. *Clin Med J (Engl).* 2022; 135: 1653-1663. [DOI](#)
- Yang M, Wei L. Impact of NAFLD on the outcome of patients with chronic hepatitis B in Asia. *Liver Int.* 2022; 42: 1981-1990. [DOI](#)
- Blanco-Grau A, Gabriel-Medina P, Rodriguez-Algarra E, et al. Assessing liver fibrosis using the FIB4 index in the community setting. *Diagnostica (Basel).* 2021; 11: 2236. [DOI](#)
- Chaloeai N, Yousoori Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology.* 2018; 67: 328-357. [DOI](#)
- Ferreiral O, Bar RG. Recent advances in noninvasive assessment of liver steatosis. *Pol Arch Intern Med.* 2024; 134: 16703. [DOI](#)
- Razi K, Auhari H, Charitta JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2022; 7: 651-661. [DOI](#)
- Cholongitas E, Papatheodorou I, Papatheodoridis M, et al. Epidemiology of nonalcoholic fatty liver disease in Europe: a systematic review and meta-analysis. *Ann Gastroenterol.* 2021; 34: 404-414. [DOI](#)
- Zhang Q, Zou R, Wu Y, et al. Systematic review with meta-analysis: prevalence of hepatic steatosis, fibrosis and associated factors in chronic hepatitis B. *Aliment Pharmacol Ther.* 2021; 54: 1100-1109. [DOI](#)
- Hyara KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis.* 1995; 20: 992-1000. [DOI](#)
- Kulierskii S, Huang DG, Yeh M-L, et al. Sex and ethnic disparities in hepatitis B evaluation and treatment across the world. *J Hepatol.* 2024; 81: 53-61. [DOI](#)
- European Centre for Disease Prevention and Control. Hepatitis B – annual epidemiological report for 2022. <https://www.ecdc.europa.eu/en/publications-data/hepatitis-b-annual-epidemiological-report-2022>. Accessed December 12, 2024.
- Wang S-H, Chen F-J, Yeh S-H. Gender disparity in chronic hepatitis B: mechanisms of sex hormones. *J Gastroenterol Hepatol.* 2015; 30: 1237-1245. [DOI](#)
- Nagrai A, Bangar M, Meneses S, et al. Gender differences in non-alcoholic fatty liver disease. *Euroasian J Hepatogastroenterol.* 2022; 12: 519-525. [DOI](#)
- Bardsley MJ, Falkner S, Kowal K, Ross JL. Insulin resistance and metabolic syndrome in prepubertal boys with Klinefelter syndrome. *Acta Paediatr.* 2011; 100: 866-870. [DOI](#)
- Yi S, Ren G, Zhu Y, Cong Q. Correlation analysis of hepatic steatosis and hepatitis B virus: a cross-sectional study. *Viral J.* 2024; 21: 22. [DOI](#)
- Duan H, Zhang R, Chen X, et al. Associations of uric acid with liver steatosis and fibrosis applying vibration controlled transient elastography in the United States: a nationwide cross-section study. *Front Endocrinol (Lausanne).* 2022; 13: 930224. [DOI](#)
- Donohue TM Jr. Alcohol-induced steatosis in liver cells. *World J Gastroenterol.* 2007; 13: 4974-4978. [DOI](#)
- Libur CS. Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis. *Alcohol.* 2004; 34: 9-19. [DOI](#)
- Karacacir Z, Oksar G, Cernik H, Altan D. Is there an influence of hepatic steatosis on fibrosis and necroinflammation in young patients with chronic viral hepatitis B? *Postgrad Med.* 2016; 128: 697-700. [DOI](#)
- Peking H, Issachar A, Sneh Arbib D, et al. Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load. *JHEP Rep.* 2019; 1: 9-16. [DOI](#)
- Chan AWH, Wong GLH, Chan H-Y, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. *J Gastroenterol Hepatol.* 2017; 32: 667-676. [DOI](#)
- Lee YB, Ha Y, Chen YE, et al. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. *Clin Mol Hepatol.* 2019; 25: 52-64. [DOI](#)
- Jiang D, Chen C, Liu X, et al. Concurrence and impact of hepatic steatosis on chronic hepatitis B patients: a systematic review and meta-analysis. *Ann Transl Med.* 2021; 9: 1718. [DOI](#)
- Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison

with hepatitis C infected patients. *J Gastroenterol Hepatol.* 2011; 26: 1361-1367. [↗](#)

37 Charatcharoenwitthaya P, Pongpiakul A, Kasornbunwattana U, et al. The prevalence of steatohepatitis in chronic hepatitis B patients and its impact on disease severity and treatment response. *Liver Int.* 2017; 37: 542-551. [↗](#)

38 Jin X, Chen Y-P, Yang Y, et al. Association between hepatic steatosis and entecavir treatment failure in Chinese patients with chronic hepatitis B. *PLoS One.* 2012; 7: e34198. [↗](#)

Observational Study

Steatotic liver disease in patients with chronic hepatitis C

Jakub Janczura, Michal Brzdek, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdek, Piotr Rzymiski, Dorota Zarebska-Michaluk

Specialty type: Gastroenterology and hepatology.

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Giangregorio F, Assistant Professor, Chief Physician, Director, Italy

Received: August 31, 2025

Revised: September 9, 2025

Accepted: November 20, 2025

Published online: December 27, 2025

Processing time: 118 Days and 1.6 Hours



Jakub Janczura, Michal Brzdek, Krystyna Dobrowolska, Collegium Medicum, Jan Kochanowski University, Kielce 25-516, Poland

Michal Brzdek, Department of Gastroenterology, Medical University of Lodz, Lodz 92-213, Poland

Robert Flisiak, Department of Infectious Diseases and Hepatology, Medical University of Bialystok, Bialystok 15-540, Poland

Kinga Brzdek, Department of Rheumatology and Connective Tissue Diseases, Nicolaus Copernicus Memorial Hospital in Lodz, Lodz 93-513, Poland

Piotr Rzymiski, Department of Environmental Medicine, Poznan University of Medical Sciences, Poznan 60-806, Poland

Dorota Zarebska-Michaluk, Department of Infectious Diseases and Allergology, Jan Kochanowski University, Kielce 25-516, Poland

Corresponding author: Michal Brzdek, Collegium Medicum, Jan Kochanowski University, aleja IX Wiekow Kielc 19A, Kielce 25-516, Poland.

Abstract

BACKGROUND

Steatotic liver disease (SLD) including metabolic dysfunction-associated SLD is the most prevalent chronic liver disease worldwide and is strongly associated with metabolic dysfunction as well as chronic hepatitis C (CHC).

AIM

To compare the characteristics of patients with CHC virus infection and the treatment with direct-acting antivirals (DAAs), considering the presence of SLD comorbidity.

METHODS

The study included all consecutive hepatitis C virus-infected patients treated with pan-genotypic DAA regimens at a single tertiary hepatology center in 2018-2024. SLD was diagnosed via abdominal ultrasound.

RESULTS

Among 688 patients included in the study, 290 (42.2%) had comorbid SLD. The highest prevalence (62.3%) was observed in patients infected with genotype 3. The

SLD group was predominantly male (62.8%), in contrast to the non-SLD group, where women predominated. Patients with SLD were significantly older ($P = 0.0007$), had a higher body mass index ($P < 0.0001$), and more frequently pre-sented with diabetes ($P = 0.01$), obesity ($P < 0.0001$), hyperlipidemia ($P = 0.004$), and a history of alcohol abuse ($P < 0.0001$). They also had more advanced liver disease as indicated by a higher rate of cirrhosis (35.5% vs 12% in the non-SLD group, $P < 0.0001$), elevated aminotransferase activity ($P < 0.0001$), bilirubin concentration ($P < 0.0001$), and international normalized ratio values ($P = 0.0001$), and lower albumin concentration ($P = 0.0028$). While most patients in both groups completed treatment as planned, adverse events, including severe events and deaths, were more frequent in the SLD group. A sustained virologic response was achieved in 97.6% of the overall population but was significantly lower among patients with SLD compared to the non-SLD group (95.6% vs 99.0%, $P = 0.0081$). However, logistic regression analysis did not identify SLD as an independent predictor of treatment failure.

CONCLUSION

Comorbid SLD was common among CHC patients treated with DAAs and was associated with adverse baseline characteristics, including older age, higher body mass index, greater comorbidity burden, and more advanced liver disease. Although SLD patients achieved slightly lower rates of sustained virologic response, SLD itself was not an independent predictor of treatment failure. These findings suggest that poorer treatment outcomes in this subgroup are largely attributable to coexisting risk factors rather than SLD per se, highlighting the need for comprehensive management of metabolic and liver-related comorbidities to optimize antiviral therapy outcomes.

Key Words: Hepatitis C; Steatotic liver disease; Direct-acting antivirals; Real-world study; Hepatitis C virus

©The Author(s) 2025. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Steatotic liver disease (SLD) is common in patients with chronic hepatitis C and shapes their overall health and treatment journey. In our real-world study, SLD patients were older, had higher body mass index, and carried more metabolic and liver-related risks, leading to lower response rates to antiviral therapy. Yet, SLD itself was not the culprit - other comorbidities were. This highlights that successful treatment depends not only on antivirals but also on managing the broader metabolic and lifestyle factors that impact liver health.

Citation: Janczura J, Brzdęk M, Flisiak R, Dobrowolska K, Brzdęk K, Rzymiski P, Zarębska-Michaluk D. Steatotic liver disease in patients with chronic hepatitis C. *World J Hepatol* 2025; 17(12): 113639

URL: <https://www.wjgnet.com/1948-5182/full/v17/i12/113639.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v17.i12.113639>

INTRODUCTION

Steatotic liver disease (SLD) is a recently redefined umbrella term encompassing a spectrum of liver conditions characterized by hepatocellular fat accumulation[1]. The term includes liver damage attributable to metabolic dysfunction, monogenic disorders, certain medications, and alcohol abuse. In 2023, the Delphi consensus led to a shift in terminology, replacing the previously used "nonalcoholic fatty liver disease" with SLD, and reflecting a broader recognition of the metabolic determinants of SLD and its strong associations with systemic comorbidities such as obesity, type 2 diabetes mellitus, dyslipidemia, and arterial hypertension[2,3]. This terminological change also underscores the clinical need to consider SLD as a heterogeneous but highly prevalent condition that interacts with a wide range of chronic diseases.

Notably, chronic hepatitis C (CHC) is increasingly associated with the presence of SLD. Epidemiological studies indicate that hepatic steatosis occurs in approximately 50% of individuals with CHC, a prevalence significantly higher than that observed in the general population[3]. In hepatitis C virus (HCV)-related SLD, multiple risk factors contribute to the development of hepatic steatosis, including both host-related and virus-related mechanisms[4]. Host-related factors largely mirror those seen in the general population, particularly components of metabolic syndrome, such as obesity and type 2 diabetes mellitus. These factors are especially prevalent in Western countries, where the burden of metabolic disorders is high[4]. However, in contrast to hepatitis B virus-related SLD, HCV infection also involves virus-specific mechanisms, most notably associated with HCV genotype 3 (GT3)[5,6]. This GT is strongly linked to the development of hepatic steatosis due to its direct interference with lipid metabolism, particularly through impaired very-low-density lipoprotein secretion[5]. As a result, steatosis occurs with significantly higher prevalence in individuals infected with GT3 compared to those infected with non-GT3 viral variants.

HCV infection continues to represent a significant global concern. According to the World Health Organization, an estimated 50 million individuals are currently living with CHC, with approximately 1 million new infections occurring annually[7]. In 2022 alone, HCV infection was associated with an estimated 242000 deaths worldwide[7]. HCV infection is a well-recognized contributor to severe liver disease, with cirrhosis and hepatocellular carcinoma (HCC) representing its

most severe and life-threatening complications[8]. Currently, SLD is considered the most prevalent chronic liver disease globally[9]. The coexistence of SLD and HCV therefore represents a major clinical challenge, not only because both conditions independently contribute to liver disease progression, but also because their interaction may amplify the risk of fibrosis, cirrhosis, and HCC. Although direct-acting antivirals (DAAs) have revolutionized the treatment of HCV, leading to cure rates exceeding 95% in most populations, real-world evidence on treatment outcomes in patients with comorbid SLD remains valuable yet sometimes inconsistent[10,11]. To address this issue, we designed an observational, single-center real-world study, comparing patients with and without SLD who were treated for chronic HCV infection using pangenotypic DAAs regimens.

MATERIALS AND METHODS

Study population

A real-world, observational study was conducted at a single tertiary hepatology center - the Department of Infectious Diseases in Kielce, Poland. The analysis included all consecutive patients with CHC treated with pangenotypic DAAs under the reimbursed National Health Fund program. The patients started antiviral therapy from the beginning of the availability of pangenotypic regimens in Poland, i.e., from July 2018 to December 2024. Data were collected from patients' medical records and included laboratory results, virological profiles, and relevant clinical parameters.

Data collection

Observational data were collected at the start of antiviral therapy and during drug program-required follow-up visits. Records at the start of therapy included demographic and clinical information, including comorbidities and medications used, history of prior antiviral treatment and hepatitis B virus or human immunodeficiency virus co-infection, data on current and past drug or alcohol abuse, diagnosis of HCC, and information regarding liver transplantation. Virological status, including GT and viral load, was assessed by polymerase chain reaction with a lower detection limit of 15 IU/mL. Laboratory parameters included complete blood count, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, creatinine, albumin, and bilirubin concentration, and international normalized ratio. The effectiveness of DAA therapy was assessed 12 weeks after its completion by evaluating HCV RNA. During treatment and the 12-week post-therapy period, the safety of treatment was assessed based on its course, the occurrence of adverse events, including severe ones, and deaths.

Liver disease

The stage of liver disease was assessed using non-invasive methods, by shear wave elastography with Aixplorer (SuperSonic Imagine, Aix-en-Provence, France). Liver stiffness evaluation was complemented by calculation of serum-based indices such as fibrosis-4 index (FIB-4) or aspartate aminotransferase to platelet ratio index (APRI)[12]. In addition, in all patients who were diagnosed with cirrhosis, data were collected regarding the decompensation of liver function in the past and at the start of therapy, the presence of oesophageal varices, and the baseline Child-Pugh score was calculated. The diagnosis of SLD was based on the detection of hepatic steatosis, identified through imaging by abdominal ultrasound, which was performed in all patients during the baseline visit.

Ethical considerations

This observational, single-center study was conducted following the approval of the Bioethics Committee of Jan Kochanowski University in Kielce (approval No. 57/2024, dated July 25, 2024). Access to medical records and the use of patient treatment data were granted with the prior consent of the hospital's management. All patients were informed about the purpose of the study, and their inclusion was contingent upon providing informed consent.

Statistical analysis

Categorical variables were expressed as absolute numbers and percentages. Continuous variables were presented as medians along with interquartile ranges. The normality of distribution for continuous data was assessed using the Shapiro-Wilk test. Comparisons of continuous variables between groups were performed using the Mann-Whitney *U* test. Differences in categorical data, such as event frequencies between patients with and without SLD, were assessed using Pearson's χ^2 test, or Fisher's exact test when appropriate. Based on univariate analyses identifying factors associated with achieving or not achieving sustained virologic response (SVR) at 12 weeks post-treatment, multivariate logistic regression models were constructed to estimate the odds of treatment failure. $P < 0.05$ was considered statistically significant. All analyses were carried out using Statistica version 13 (Dell Inc., Round Rock, TX, United States).

RESULTS

Characteristics of the study population

Of the 688 consecutive Caucasian patients treated with pangenotypic DAAs for CHC, 290 individuals (42.2%) were diagnosed with SLD. The median age of patients in the SLD group was significantly higher compared to those without SLD ($P = 0.0007$) with higher proportion of individuals aged over 50 years (54.5% vs 41.7%) (Table 1). The SLD population

Table 1 Baseline characteristics in the steatotic liver disease and non-steatotic liver disease groups, n (%)

Parameter	SLD (n = 290)	Non-SLD (n = 398)	P value
Age (years), median (Q1-Q3)	54 (38-64)	43.0 (35.0-62)	0.0007
Age ≥ 50	158 (54.5)	166 (41.7)	0.0009
Gender, women/men	109 (37.2)/182 (62.8)	235 (59.0)/163 (41.0)	< 0.0001
BMI (kg/m ²), median (Q1-Q3)	26.5 (23.8-30)	24.6 (22.3-27)	< 0.0001
BMI ≥ 25 kg/m ²	181 (62.4)	109 (27.4)	< 0.0001
Comorbidities			
Any comorbidity	242 (83.4)	291 (73.1)	0.0014
Diabetes	41 (14.1)	32 (8.0)	0.0103
Obesity	75 (25.9)	42 (10.6)	< 0.0001
Autoimmune disorders	18 (6.2)	24 (6.0)	0.9238
Arterial hypertension	108 (37.2)	131 (32.9)	0.2392
Non-HCC tumors	17 (5.9)	30 (7.5)	0.3896
Renal disease	23 (7.9)	38 (9.5)	0.4613
Cholelithiasis	61 (21.0)	93 (23.4)	0.4686
Hyperlipidemia	50 (17.2)	39 (9.8)	0.0041
Concomitant medications	192 (66.2)	236 (59.3)	0.0649
HBV coinfection (HBsAg+)	1 (0.3)	2 (0.5)	0.7566
HIV coinfection	2 (0.7)	0	0.0971
IVDU current/past	5 (1.7)	9 (2.3)	0.7866
Alcohol abuse in the past	67 (23.1)	15 (3.8)	< 0.0001

SLD: Steatotic liver disease; Q: Quartile; BMI: Body mass index; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HIV: Human immunodeficiency virus; IVDU: Intravenous drug use.

was predominantly male, whereas the non-SLD group consisted mainly of women (59%). Patients with SLD had a significantly higher median of body mass index (BMI) compared to those without SLD (26.5 vs 24.6, respectively, $P < 0.0001$). Importantly, 62.4% of individuals in the SLD group had a BMI exceeding 25, indicating a high prevalence of overweight or obesity within this population (Table 1). The distribution of BMI values across both groups is illustrated in Figure 1A. The SLD group was more burdened with comorbidities ($P = 0.0014$), with statistically significant differences observed for diabetes, hyperlipidemia, and obesity (Table 1). While the overall prevalence of hypertension did not differ significantly between groups, patients with this diagnosis were significantly less likely to have SLD, 45.2% ($P = 0.0354$) (Table 2). A significantly higher percentage of patients in the SLD group reported a history of alcohol abuse (defined as alcohol intake exceeding 20 g/day for females and 30 g/day for males) compared to the non-SLD group (23.1% vs 3.8%, respectively). Of the 82 people who reported a history of alcohol abuse, the majority, 67 (81.7%, $P < 0.0001$), belonged to the SLD group (Table 2). Since qualifying for and during antiviral therapy, all patients declared abstinence (Table 1).

Treatment and liver disease characteristics

The median baseline HCV RNA viral load was comparable between the SLD and non-SLD groups (Table 3). Patients with SLD demonstrated significantly higher median aminotransferase activity, with elevated levels of both alanine aminotransferase and aspartate aminotransferase ($P < 0.0001$ for both) (Table 3). Other liver function parameters also differed significantly between the groups: Patients with SLD exhibited higher gamma-glutamyltransferase and bilirubin levels, lower albumin concentrations and platelet counts, and increased international normalized ratio values (Table 3). A significantly lower proportion of patients in the SLD group were treatment-naïve compared to those without SLD (Table 4). Notably, previous non-response to both interferon-based regimens and DAA therapy was more frequently documented among patients with SLD (Table 4). Throughout the study, the most frequently used therapy in the SLD group was sofosbuvir/velpatasvir with or without ribavirin, accounting for 54.5% of treatments, whereas the glecaprevir/pibrentasvir regimen predominated in the non-SLD group (61.6%) (Table 4).

Clinical indicators of advanced liver disease were more prevalent in the SLD population. A significantly higher proportion of patients with SLD had a documented history of hepatic decompensation, including ascites and/or hepatic encephalopathy (8.6% vs 2.0%, respectively, $P = 0.0001$). Similarly, the presence of documented oesophageal varices was significantly more frequent in the SLD group ($P < 0.0001$). This pattern persisted at baseline evaluation, where patients

Table 2 Share of steatotic liver disease among patients with risk factors, n (%)

Parameter	Arterial hypertension	Diabetes	Hyperlipidemia	Overweight + obesity	Alcohol	GT3
All/688	239 (34.7)	73 (10.6)	89 (12.9)	290 (42.2)	82 (11.9)	114 (16.6)
SLD	108 (45.2)	41 (56.2)	50 (56.2)	181 (56.2)	67 (81.7)	71 (62.3)
Non-SLD	131 (54.8)	32 (43.8)	39 (43.8)	109 (43.8)	15 (18.3)	43 (37.7)
P value	0.0354	0.1363	0.0991	< 0.0001	< 0.0001	0.0002

GT3: Genotype 3; SLD: Steatotic liver disease.

Table 3 Baseline laboratory parameters in the steatotic liver disease and non-steatotic liver disease groups, median (Q1-Q3)

Parameter	SLD (n = 290)	Non-SLD (n = 398)	P value
ALT (IU/L)	71.0 (47-106)	46 (32-76)	< 0.0001
AST (IU/L)	58.5 (40-95)	38 (28-58)	< 0.0001
GGTP (IU/L)	67 (37-136)	36.5 (20-71)	< 0.0001
Albumin (g/dL)	4.0 (3.6-4.4)	4.1 (3.9-4.4)	0.0028
Bilirubin (mg/dL)	0.7 (0.6-1.1)	0.6 (0.5-0.9)	< 0.0001
Haemoglobin (g/dL)	14.6 (13.2-15.6)	14.2 (13.4-15.3)	0.1461
Platelets (× 1000/μL)	176 (108-223)	198 (159-237)	< 0.0001
Creatinine (mg/dL)	0.8 (0.7-0.9)	0.8 (0.7-0.9)	0.9771
INR	1.04 (1.00-1.18)	1.00 (1.00-1.10)	0.0001
HCV RNA (× 10 ⁶ IU/mL)	1.0 (0.3-2.5)	0.9 (0.3-2.8)	0.9636

Q: Quartile; SLD: Steatotic liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGTP: Gamma-glutamyl transpeptidase; INR: International normalized ratio; HCV: Hepatitis C virus; RNA: Ribonucleic acid.

with SLD continued to show a higher prevalence of ascites and/or encephalopathy compared to the non-SLD subpopulation (7.9% vs 2.3%, $P = 0.0005$). Patients with SLD had a significantly higher prevalence of GT3 infection compared to the non-SLD group (24.5% vs 10.8%) (Table 4, Figure 1B). Among the 114 patients infected with HCV GT3, nearly one-third had SLD ($P = 0.0002$) (Table 2). Nevertheless, GT 1b predominates, so this GT remained the most prevalent in both groups (Figure 1B). Fibrosis staging revealed a significantly greater proportion of patients with fibrosis stage 4 (F4) in the SLD group compared to the non-SLD group (35.8% vs 12.0%, $P < 0.0001$) (Figure 1C). Additionally, the proportion of patients classified as Child-Pugh B or C among those with F4 fibrosis was higher in the SLD group (29.1%) than in the non-SLD group (25.0%) (Table 4). Consistently, the SLD subpopulation demonstrated a higher proportion of patients with an APRI score ≥ 1 compared to the non-SLD group (46.6% vs 19.1%, respectively) (Figure 1D). Similarly, FIB-4 scores were significantly higher in the SLD group, with the largest subgroup consisting of patients with FIB-4 > 2.67 , accounting for 43.5% of the SLD group, in contrast to 19.1% in the non-SLD population (Figure 1E). Furthermore, HCC was more frequently diagnosed in patients with SLD than in those without (3.4% vs 1.0%, $P = 0.0299$) (Table 4).

Treatment safety and outcomes

The effectiveness of DAA therapy differed significantly between the SLD and non-SLD groups in both the intention-to-treat (ITT) and per-protocol (PP) analyses. In the ITT analysis, 91.0% of patients in the SLD group achieved SVR, compared to 98.2% in the non-SLD group ($P < 0.0001$) (Figure 1F). Similarly, in the PP analysis, the SVR rate was 95.6% in the SLD group to 99.0% in the non-SLD group ($P = 0.0025$) (Figure 1F). Patients in the SLD subgroup were more likely to experience serious adverse events during treatment ($P = 0.0054$), mainly non-liver related. Adverse events of special interest, ascites and encephalopathy, were also significantly more frequent in patients with SLD (Tables 4 and 5). The mortality rate was significantly higher among patients with SLD compared to the non-SLD group (3.8% vs 1.0%, $P = 0.0168$). Across both study groups, 13 patients failed to achieve SVR. The majority of non-responders were male (92.3%) and were characterized by significantly higher BMI and poorer laboratory parameters compared to responders (Table 6). Among non-responders, 53.8% were infected with HCV GT3. Clinical indicators of advanced liver disease were more prevalent among non-responders as compared to responders, 5 out of 13 patients (38.5%) presented with hepatic encephalopathy and/or ascites ($P < 0.0001$), and 69.2% had cirrhosis ($P = 0.0002$) (Table 6). Multivariate analysis documented that GT3 infection and cirrhosis appeared to be independent predictors of SLD in patients with CHC, $P = 0.0234$ and $P = 0.0046$, respectively (Table 7).

Table 4 Characteristics of antiviral therapy and liver disease in the steatotic liver disease and non-steatotic liver disease groups, n (%)

Parameter	SLD (n = 290)	Non-SLD (n = 398)	P value
GT3	71 (24.5)	43 (10.8)	< 0.0001
History of antiviral therapy			0.0315
Treatment-naïve	257 (88.6)	380 (95.5)	
Treatment-experienced, non-responder to IFN-based regimens	19 (6.6)	15 (3.8)	
Treatment-experienced, non-responder to DAA regimens	14 (4.8)	3 (0.7)	
Current treatment regimen			< 0.0001
GLE/PIB	127 (43.8)	245 (61.6)	
SOF/VEL ± RBV	158 (54.5)	153 (38.4)	
SOF/VEL/VOX	5 (1.7)	0	
History of hepatic decompensation			
Ascites and/or encephalopathy	25 (8.6)	8 (2.0)	0.0001
Ascites	24 (8.3)	8 (2)	0.0002
Encephalopathy	8 (2.7)	2 (0.5)	0.0209
Documented esophageal varices	38 (13.1)	17 (4.3)	< 0.0001
Liver decompensation at baseline			
Ascites and/or encephalopathy	23 (7.9)	9 (2.3)	0.0005
Ascites	23 (7.9)	8 (2)	0.0003
Encephalopathy	11 (3.8)	3 (0.8)	0.0108
F4	104 (35.8)	48 (12)	< 0.0001
Child-Pugh, in relation to F4			
B + C	30 (29.1)	12 (25)	0.0001
HCC	10 (3.4)	4 (1.0)	0.0299
OLTx	0	0	NA

SLD: Steatotic liver disease; GT3: Genotype 3; IFN: Interferon; DAA: Direct-acting antiviral; GLE/PIB: Glecaprevir/pibrentasvir; SOF/VEL: Sofosbuvir/velpatasvir; SOF/VEL ± RBV: Sofosbuvir/velpatasvir with or without ribavirin; F4: Fibrosis stage 4; HCC: Hepatocellular carcinoma; OLTx: Orthotopic liver transplantation.

DISCUSSION

The prevalence of SLD among individuals with chronic HCV infection varies widely according to available data, with estimates ranging from 27% to 79% [3,13-15]. The values obtained in our analysis fall within this range, as SLD was confirmed in 42.2% of the study population. Discrepancies in the prevalence of steatosis in patients with HCV infection reported in different studies may be due to differences in the characteristics of the populations analyzed, including the percentage of patients infected with GT3, the severity of liver fibrosis, the burden of cardiometabolic risk factors, and geographical regions [13]. The influence of geographical region was demonstrated in the latest meta-analysis conducted by Li *et al* [3], covering 321 eligible studies on SLD in HCV-infected individuals. This paper reported a pooled prevalence of 49%, which aligns closely with our findings, with the highest frequency of 52% observed in the World Health Organization Region of the Americas. However, the majority of studies included in the meta-analysis by Li *et al* [3], used liver biopsy as the diagnostic gold standard, which may contribute to a higher reported prevalence due to the ability to detect even mild degrees of steatosis [16,17]. Therefore, the method used to diagnose hepatic steatosis also appears to influence the results obtained [18].

Despite its undoubted advantages, liver biopsy as a diagnostic method has largely become obsolete in recent decades and has been replaced by noninvasive examinations [19]. Currently, shear-wave or transient elastography or even serum markers such as APRI or FIB-4 are used to assess liver fibrosis. Using transient elastography with controlled attenuation parameter assessment, it is also possible to assess liver steatosis. This method was used in the analysis of a population of 328 Spanish patients with HCV mono-infection, among whom 45% had coexisting SLD, which is also very similar to our results [20]. However, due to the cost and limited availability of this examination, ultrasound, which does not have these

Table 5 Safety of direct-acting antiviral therapy in the steatotic liver disease and non-steatotic liver disease groups, n (%)

Parameter	SLD (n = 290)	Non-SLD (n = 398)	P value
Treatment course			0.0784
According to schedule	279 (96.2)	394 (99)	
Therapy modification	2 (0.7)	1 (0.2)	
Therapy discontinuation	8 (2.8)	3 (0.8)	
No data	1 (0.3)	0	
Serious adverse events	20 (6.9)	10 (2.5)	0.0054
Liver-related	9 (45) ¹	2 (20) ²	0.2465
Non-liver-related	11 (55)	8 (80)	0.2465
AEs leading to treatment discontinuation	7 (2.4)	3 (0.8)	0.1049
Patients with at least one AE	46 (15.9)	33 (8.3)	0.0021
Weakness/fatigue	16 (5.5)	12 (3)	0.1010
Anemia	1 (0.3)	3 (0.7)	0.6423
Headache	4 (1.4)	1 (0.2)	0.1670
AEs of particular interest			
Ascites	10 (3.4)	1 (0.3)	0.0011
Hepatic encephalopathy	10 (3.4)	3 (0.8)	0.0194
Gastrointestinal bleeding	0	0	NA
Death	11 (3.8)	4 (1.0)	0.0168
Liver-related	5 (81.8) ³	2 (50) ⁴	> 0.9999
Non-liver-related	6 (18.2)	2 (50)	> 0.9999

¹Five cases of liver decompensation, one case of drug-induced liver injury after bosentan, one case of liver transplantation during direct-acting antiviral therapy, two cases of hepatocellular carcinoma diagnosed simultaneously with hepatitis C virus infection.

²One case of liver decompensation, one case of hepatocellular carcinoma diagnosed simultaneously with hepatitis C virus infection.

³Three cases of liver decompensation, two cases of hepatocellular carcinoma.

⁴One case of liver decompensation, one case of hepatocellular carcinoma.

SLD: Steatotic liver disease; AE: Adverse event.

limitations, is the most commonly used method for diagnosing SLD[21].

The population-based study conducted from 2007 to 2020, which covered a population of nearly 300000 Egyptian patients infected with HCV, was based on the diagnosis of liver steatosis using ultrasound, the same approach as in our study[22]. The researchers documented a 41.9% prevalence of SLD, which is almost identical to the value found in our analysis. A very similar result was obtained in a study from Taiwan, which included nearly 6000 patients, with an SLD rate of 36.8% and ultrasound as the predominant diagnostic method[23].

With an overall prevalence of 42% in our study, we documented a significantly higher prevalence in patients infected with GT3, reaching as high as 62.3%. GT3 is a well-established virus-related risk factor for hepatic steatosis and has been consistently associated with a significantly greater prevalence of SLD compared to non-GT3 GTs[6,24]. Our findings align closely with those reported by Rubbia-Brandt *et al*[25], who reported a steatosis prevalence of 61.2% among GT3-infected patients. A retrospective RWE study involving 98 Swedish patients infected with HCV showed that steatosis assessed by the liver biopsy was significantly more common in individuals infected with the GT3, and this association appeared to be independent of the host-related risk factors, suggesting a GT-specific, virus-induced mechanism of fat accumulation in the liver[26].

When comparing HCV-infected patients according to the presence of hepatic steatosis, we documented a significantly higher age ($P = 0.0007$) and a clear predominance of men (< 0.0001) in the SLD population. Our results regarding the higher incidence of SLD in men are consistent with the results of a study conducted in an Italian cohort of 400 patients infected with HCV[27]. This analysis also showed a significantly higher prevalence of cardiometabolic risk factors associated with SLD in men. Both sex and age are well-known non-modifiable risk factors for SLD, regardless of the presence of HCV infection. In the general population, the incidence of SLD is higher in men than in women, partly due to the influence of sex hormones, with estrogen acting as a protective factor and testosterone increasing the risk of SLD[28, 29]. In a large follow-up Japanese study investigating the relationship between age, menopause, and SLD incidence, premenopausal women were found to have the lowest SLD prevalence out of the analyzed group, followed by postmenopausal women (15%), and men (24%)[30]. Interestingly, age was found to be an independent risk factor for hepatic

Table 6 Comparison of responders and virologic non-responders, univariate analysis, median (Q1-Q3)/n (%)

Parameter	Responders (n = 656)	Non-responders (n = 13)	P value
Gender, women/men	339 (51.7)/317 (48.3)	1 (7.7) / 12 (92.3)	0.0014
Age (years)	47 (36-63)	45 (42-52)	0.5863
Age ≥ 50	304 (46.3)	5 (38.5)	0.7802
BMI (kg/m ²)	25.3 (22.7-28.4)	27.8 (25.1-32.4)	0.0250
ALT (IU/L)	55 (36-91)	77 (69-111)	0.0544
Albumin (g/dL)	4.1 (3.8-4.4)	3.3 (2.5-4)	0.0078
Bilirubin (mg/dL)	0.7 (0.5-0.9)	1.5 (1-2.3)	0.0000
Haemoglobin	14.4 (13.4-15.5)	14.4 (12.6-15.1)	0.3643
Platelets (× 1000/μL)	192 (145-234)	79 (74-158)	0.0001
Creatinine (mg/dL)	0.8 (0.7-0.9)	0.9 (0.8-1)	0.4954
INR	1.0 (1-1.1)	1.2 (1.1-1.4)	0.0001
HCV RNA (× 10 ⁶ IU/mL)	1 (0.3-2.6)	0.6 (0.4-2.9)	0.7697
Current treatment regimen			
SOF/VEL ± RBV	287 (43.7)	9 (69.2)	0.0900
GLE/PIB	364 (55.5)	4 (30.8)	0.0937
SOF/VEL/VOX	5 (0.8)	0	> 0.9999
Comorbidities			
Any	504 (76.8)	10 (76.9)	> 0.9999
Hypertension	231 (35.2)	2 (15.4)	0.2376
Diabetes mellitus	66 (10.1)	2 (15.4)	0.6324
Obesity	112 (17.1)	4 (30.8)	0.2559
Autoimmune disorders	41 (6.3)	0	> 0.9999
Renal disease	56 (8.5)	1 (7.7)	> 0.9999
Non-HCC tumors	42 (6.4)	1 (7.7)	0.5818
Concomitant medications	401 (61.1)	11 (84.6)	0.0847
GT3	105 (16.0)	7 (53.8)	0.0022
History of previous therapy			
Treatment-naïve	611 (93.1)	9 (69.2)	
Treatment-experienced	45 (6.9)	4 (30.8)	
History of hepatic decompensation			
Encephalopathy and/or ascites	19 (2.9)	5 (38.5)	< 0.0001
Ascites	17 (2.6)	5 (38.5)	< 0.0001
Encephalopathy	3 (0.5)	1 (7.7)	0.0756
Documented esophageal varices	41 (6.3)	7 (53.8)	< 0.0001
Hepatic decompensation at baseline			
Encephalopathy and/or ascites	18 (2.7)	5 (38.5)	< 0.0001
Encephalopathy	7 (1.1)	1 (7.7)	0.1460
Ascites	17 (2.6)	4 (30.8)	0.0004
METAVIR F4	128 (19.5)	9 (69.2)	0.0002
CP B/C, in relation to F4	26 (20.3)	6 (46.2)	0.0026
HIV	1 (0.2)	0	> 0.9999

HBV (HBsAg+)	3 (0.5)	0	> 0.9999
HCC	8 (1.2)	1 (7.7)	0.1628
OLTx	0	0	NA

Q: Quartile; BMI: Body mass index; ALT: Alanine aminotransferase; INR: International normalized ratio; HCV: Hepatitis C virus; SOF/VEL ± RBV: Sofosbuvir/velpatasvir with or without ribavirin; GLE/PIB: Glecaprevir/pibrentasvir; SOF/VEL/VOX: Sofosbuvir/velpatasvir/voxilaprevir; HCC: Hepatocellular carcinoma; GT3: Genotype 3; F4: Fibrosis stage 4; CP B/C: Child-Pugh Class B or C; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; OLTx: Orthotopic liver transplantation.

Table 7 Factors associated with treatment failure in multivariate analysis

Effect	Effect measure	OR	95%CI	P value
Intercept		0.001	< 0.001-0.007	< 0.0001
Gender	Male	6.962	0.851-56.938	0.0704
GT3 infection	Yes	3.986	1.206-13.182	0.0254
History of previous therapy	Experienced	3.054	0.764-12.206	0.1142
Fibrosis	4	6.716	1.80-25.062	0.0046
BMI	≥ 30 kg/m ²	0.684	0.168-2.787	0.5958
SLD	Yes	2.505	0.488-12.859	0.2712

OR: Odds ratio; CI: Confidence interval; GT: Genotype; BMI: Body mass index; SLD: Steatotic liver disease.

steatosis only in premenopausal women[30]. The results of the Eurostat report released in July 2024 note an increasing percentage of overweight people with age in several European countries. In Poland, the percentage increases steadily from 40.9% for the 25-34 years group to 72.8% for those aged 65-74 years[31]. The increasing incidence of hepatic steatosis in an ageing European population may be due to the increasing burden of comorbidities, including metabolic disorders [32]. In a large prospective Chinese study performed from 2021 to 2022, age ≥ 60 years was associated with a higher prevalence of SLD[33].

Past alcohol abuse was another parameter that we documented as significantly more common in patients with SLD ($P < 0.0001$). Since alcohol-related liver disease is a separate category of SLD, our findings are not surprising[2]. The development of SLD is also undeniably linked to the presence of other modifiable conditions, such as diabetes, obesity and dyslipidaemia, which are elements of metabolic syndrome[5,34]. This is reflected in our study, as individual cardiometabolic risk factors such as obesity (25.9% vs 10.6%, $P < 0.0001$), hyperlipidaemia (17.2% vs 9.8%, $P = 0.0041$), diabetes (14.1% vs 8%, $P = 0.0103$) and hypertension (37.2% vs 32.9%, $P = 0.2392$) were significantly more common in the SLD population as compared to non-SLD patients. These observations are consistent with the results obtained by many other researchers[5,15,22,23].

The number of metabolic syndrome components is important to factor in, as the presence of multiple metabolic disorders can be associated with the progression of liver disease, development of liver fibrosis or even cirrhosis, and a higher risk of HCC[5,35]. Each component of metabolic syndrome increases the risk of liver-related mortality[36]. We demonstrated a significantly higher occurrence of cirrhosis and advanced liver fibrosis in patients with SLD compared to the non-SLD group, accompanied by significantly increased noninvasive markers such as APRI and FIB-4 (35.8% vs 12% and 12.1% vs 6.3%, $P < 0.0001$ for cirrhosis and F3 fibrosis in SLD and non-SLD groups, respectively). According to data available in the literature, the documented progression of liver disease in HCV infection in the case of coexisting steatosis may result not only from its presence per se, but also from risk factors leading to the development of SLD[37,38].

Another important element of our analysis was the assessment of whether the co-occurrence of SLD in HCV-infected patients affects the effect of antiviral therapy. We assessed the use of pangenotypic regimens to include patients infected with various GTs, including GT3, in the analyzed population because in the interferon era, hepatic steatosis was a well-documented negative predictor of SVR, especially in patients infected with GT3[39]. In our study, despite all patients receiving modern pangenotypic DAA regimens, SVR rates remained significantly lower in the SLD group compared to the non-SLD group in both ITT and PP analyses. However, it is noteworthy that findings from other real-world studies have been inconsistent regarding the role of SLD in treatment outcomes. For instance, data from the German Hepatitis C-Registry - a national multicenter real-world cohort - showed that no significant differences were observed in SVR between those with and without steatosis[40]. Similarly, another large-scale study involving 14,346 patients treated with interferon-free regimens found no significant difference in SVR rates between patients with or without hepatic steatosis [5]. In our cohort, although SVR was lower in the SLD group, multivariate analysis did not confirm SLD as an independent risk factor for non-response. We hypothesize that the observed poorer treatment outcomes in this population may be attributed to a higher prevalence of advanced liver disease, more frequent GT3 infection, and a predominance of male sex - all of which are recognized independent predictors of treatment failure, as demonstrated in previous research

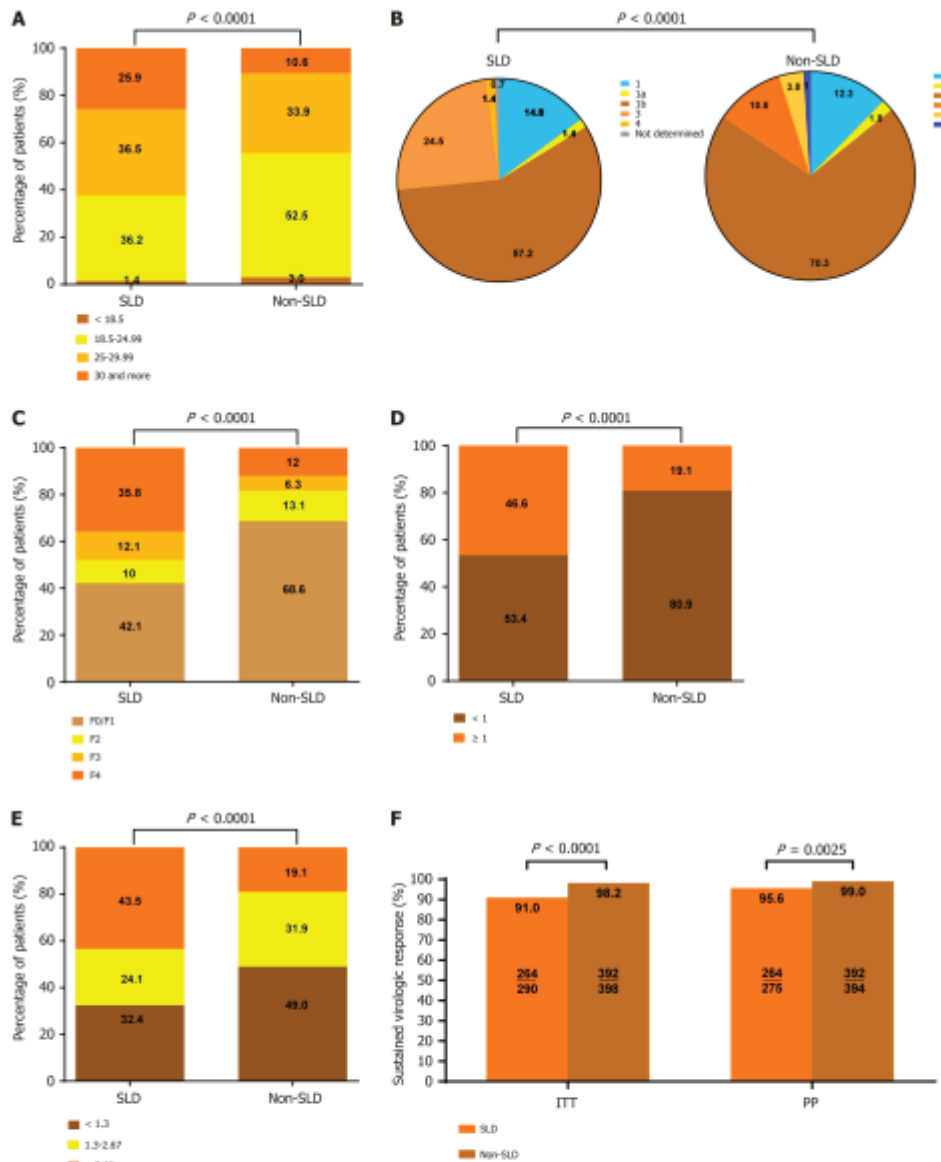


Figure 1 Comparison chart of the steatotic liver disease group and the non-steatotic liver disease group. A: Distribution of body mass index categories; B: Distribution of genotypes; C: Liver disease severity based on elastography; D: Distribution of aspartate aminotransferase to platelet ratio index categories; E: Distribution of fibrosis-4 index categories; F: Effectiveness of direct-acting antiviral therapy. SLD: Steatotic liver disease; F: Fibrosis; ITT: Intention-to-treat; PP: Per-protocol.

[41,42].

In our study, not only effectiveness but also safety differed between patients with and without SLD. Patients with liver steatosis experienced a higher overall rate of adverse events during DAA treatment, which appears to be primarily related to their more advanced liver disease and greater burden of comorbidities, rather than to steatosis itself. Both hepatic (e.g., ascites, hepatic encephalopathy) and extrahepatic complications occurred more frequently in the SLD group. Although serious liver-related adverse events and liver-related deaths were also more common among patients with SLD,

these differences did not reach statistical significance. These findings underscore the need for careful monitoring of patients with advanced liver disease and multiple comorbidities.

Our study has limitations, which we are aware of. These arise from the real-world nature and observational design of the analysis, with possible bias and data gaps. There is potential for unmeasured confounding factors, such as dietary habits, levels of physical activity, and other lifestyle variables, that could not be fully accounted for in our analysis. We assessed the presence of liver steatosis based on ultrasound examination, which is a widely available and inexpensive method, but has low diagnostic efficiency in mild SLD and people with a BMI > 40 kg/m². It may have underestimated the actual prevalence of SLD in the analyzed population. The single-center nature of the study prevents drawing general conclusions about the prevalence of SLD among the HCV-infected population throughout the country, which is also a limitation. Furthermore, our study lacks follow-up data on SLD status after achieving SVR. Consequently, we are unable to determine whether hepatic steatosis resolved or whether associated metabolic factors improve, which are key considerations for the long-term management of this patient population. Finally, it should be remembered that the diagnosis of liver steatosis based on ultrasound examination is reliable when the process involves 20%-30% of hepatocytes; moreover, in individuals with a BMI > 40, this test is less accurate, and these factors should be taken into account when interpreting the result[21]. At the same time, however, the single-center nature of the study is its strength, as all patients analyzed were treated according to the same principles by the same team of doctors, and all tests were performed in the same laboratory. Ultrasound examination and elastography were also performed by the same researchers using the same equipment.

CONCLUSION

We documented a 42% rate of SLD comorbidity in a real-world population of HCV-infected patients treated with DAAs. Patients with liver steatosis were older, had a higher BMI, a higher burden of comorbidities, more frequent GT3 infection, and more advanced liver disease compared to those without SLD. Due to these negative predictors, the effectiveness of DAA treatment was significantly lower than in patients without SLD. These findings underscore the importance of systematically assessing SLD in HCV-infected individuals, not only as a comorbidity but also as a clinically relevant modifier of treatment response and prognosis. Integrating non-invasive tools for steatosis evaluation into routine HCV management could help identify high-risk patients, guide closer monitoring, and inform adjunctive interventions aimed at reducing metabolic risk factors. Given the ageing population and the rising prevalence of obesity and metabolic disorders, SLD is likely to play an increasingly important role in determining long-term liver health in those with past or ongoing HCV infection. Addressing this challenge will require both improved clinical pathways for risk stratification and broader public health strategies to mitigate the growing burden of metabolic disease.

FOOTNOTES

Author contributions: Janczura J, Flisiak R, and Zarębska-Michaluk D conceived the study design; Janczura J, Dobrowolska K, and Zarębska-Michaluk D acquired the final version of the manuscript; Brzdęk M and Brzdęk K prepared tables and figures; Brzdęk M performed the statistical analysis, prepared manuscript for the submission; all authors contributed to analyzed and interpreted the data, drafted the manuscript, and approved the final version of the manuscript.

Institutional review board statement: This observational, single-center study was conducted following the approval of the Bioethics Committee of Jan Kochanowski University in Kielce (approval No. 57/2024, dated July 25, 2024).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Dataset available upon reasonable request to the corresponding author.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Open Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country of origin: Poland

ORCID number: Michał Brzdęk 0000-0002-1180-9230; Robert Flisiak 0000-0003-3394-1635; Krystyna Dobrowolska 0000-0003-0352-9893; Piotr Rzymiski 0000-0002-4713-0801; Dorota Zarębska-Michaluk 0000-0003-0938-1084.

S-Editor: Hu XY



L-Editor: A

P-Editor: Zhang YL

REFERENCES

- Vaz J, Jepsen P, Strömberg U, Midlöv P, Eriksson B, Buchebner D, Hagström H. Metabolic dysfunction-associated steatotic liver disease has become the most common cause of hepatocellular carcinoma in Sweden: A nationwide cohort study. *Int J Cancer* 2025; **156**: 40-51 [RC4] [PMID: 39016032 DOI: 10.1002/ijc.35097] [FullText]
- Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, Romero D, Abdelmalek MF, Anstee QM, Arab JP, Arrese M, Bataller R, Beuers U, Boursier J, Bugianesi E, Byrne CD, Narro GEC, Chowdhury A, Cortez-Pinto H, Cryer DR, Cusi K, El-Kassas M, Klein S, Eskridge W, Fan J, Gawrieh S, Guy CD, Harrison SA, Kim SU, Koot BG, Korenjak M, Kowdley KV, Laccaille F, Loomba R, Mitchell-Thain R, Morgan TR, Powell EE, Roden M, Romero-Gómez M, Silva M, Singh SP, Sookoian SC, Spearman CW, Tiniakos D, Valenti L, Vos MB, Wong VW, Xanthakos S, Yilmaz Y, Younossi Z, Hobbs A, Villota-Rivas M, Newsome PN; NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Ann Hepatol* 2024; **29**: 101133 [RC4] [PMID: 37364816 DOI: 10.1016/j.aohp.2023.101133] [FullText]
- Li J, Zhou J, Li P, Wang Y, Ridderhof N, Al-Tawfiq JA, Brouwer WP, Chen K, de Knegt RJ, Peppelenbosch MP, Hansen BE, Engel MFM, Zheng MH, Memish ZA, Eslam M, Janssen HLA, Pan Q, Ayada L. The global prevalence and impact of steatotic liver disease and viral infections: A systematic review and meta-analysis. *Hepatal Commun* 2025; **9**: e0689 [RC4] [PMID: 40227096 DOI: 10.1097/H9.0000000000000689] [FullText] [Full Text(PDF)]
- Gonzalez-Aldaco K, Torres-Reyes LA, Ojeda-Granados C, Leal-Mercado L, Roman S, Panduro A. Metabolic Dysfunction-Associated Steatotic Liver Disease in Chronic Hepatitis C Virus Infection: From Basics to Clinical and Nutritional Management. *Clin Pract* 2024; **14**: 2542-2558 [RC4] [PMID: 39585028 DOI: 10.3390/clinpract14060200] [FullText]
- Flisiak R, Zarębska-Michaluk D, Dobrowolska K, Janocha-Litwin J, Dybowska D, Sitko M, Socha Ł, Lorenc B, Klapaczynski J, Brodowski J. Treatment of HCV infection in patients with steatotic liver disease. *Clin Exp Hepatol* 2024; **10**: 159-164 [RC4] [PMID: 39697371 DOI: 10.5114/ceh.2024.141699] [FullText] [Full Text(PDF)]
- Zarębska-Michaluk D. Genotype 3-hepatitis C virus' last line of defense. *World J Gastroenterol* 2021; **27**: 1006-1021 [RC4] [PMID: 33776369 DOI: 10.3748/wjg.v27.i11.1006] [FullText] [Full Text(PDF)]
- World Health Organization. Hepatitis C. July 25, 2025. [cited 3 August 2025]. Available from: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>
- Zheng J, Wang S, Xia L, Sun Z, Chan KM, Bernards R, Qin W, Chen J, Xia Q, Jin H. Hepatocellular carcinoma: signaling pathways and therapeutic advances. *Signal Transduct Target Ther* 2025; **10**: 35 [RC4] [PMID: 39915447 DOI: 10.1038/s41392-024-02075-w] [FullText] [Full Text(PDF)]
- Manikar R, Ahmed A, Kim D. Current epidemiology of chronic liver disease. *Gastroenterol Rep (Oxf)* 2024; **12**: goae069 [RC4] [PMID: 38915345 DOI: 10.1093/gastro/goae069] [FullText] [Full Text(PDF)]
- Dobrowolska K, Brzdęk M, Rzymiski P, Flisiak R, Pawłowska M, Janczura J, Brzdęk K, Zarębska-Michaluk D. Revolutionizing hepatitis C treatment: next-gen direct-acting antivirals. *Expert Opin Pharmacother* 2024; **25**: 833-852 [RC4] [PMID: 38768013 DOI: 10.1080/14656566.2024.2358139] [FullText]
- Brzdęk M, Zarębska-Michaluk D, Invernizzi F, Cilla M, Dobrowolska K, Flisiak R. Decade of optimizing therapy with direct-acting antiviral drugs and the changing profile of patients with chronic hepatitis C. *World J Gastroenterol* 2023; **29**: 949-966 [RC4] [PMID: 36844142 DOI: 10.3748/wjg.v29.i6.949] [FullText] [Full Text(PDF)]
- Lee J, Vali Y, Boursier J, Spijker R, Anstee QM, Bossuyt PM, Zafarmand MH. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: A systematic review. *Liver Int* 2021; **41**: 261-270 [RC4] [PMID: 32946642 DOI: 10.1111/liv.14669] [Full Text] [Full Text(PDF)]
- Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, Colombo M, Craxi A, Crespo J, Day CP, Eguchi Y, Geier A, Kondili LA, Kroy DC, Lazarus JV, Loomba R, Manns MP, Marchesini G, Nakajima A, Negro F, Petta S, Ratziu V, Romero-Gomez M, Sanyal A, Schattenberg JM, Tacke F, Tanaka J, Trautwein C, Wei L, Zeuzem S, Razavi H. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol* 2018; **69**: 896-904 [RC4] [PMID: 29886156 DOI: 10.1016/j.jhep.2018.05.036] [FullText]
- Lonardo A, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology* 2004; **126**: 586-597 [RC4] [PMID: 14762795 DOI: 10.1053/j.gastro.2003.11.020] [FullText]
- Rafi H, Kabbaj N, Salihoun M, Amrani L, Acharki M, Guedira M, Nya M, Amrani N. Influence of steatosis on progression of fibrosis and virological response in chronic hepatitis C cases. *Arab J Gastroenterol* 2011; **12**: 136-138 [RC4] [PMID: 22055591 DOI: 10.1016/j.ajg.2011.07.003] [FullText]
- Scheuer PJ, Ashrafzadeh P, Sherlock S, Brown D, Dusheiko GM. The pathology of hepatitis C. *Hepatology* 1992; **15**: 567-571 [RC4] [PMID: 1551631 DOI: 10.1002/hep.1840150402] [FullText]
- Bach N, Thung SN, Schaffner F. The histological features of chronic hepatitis C and autoimmune chronic hepatitis: a comparative analysis. *Hepatology* 1992; **15**: 572-577 [RC4] [PMID: 1551632 DOI: 10.1002/hep.1840150403] [FullText]
- Fang JM, Cheng J, Chang MF, Ahn J, Westerhoff M. Transient elastography versus liver biopsy: discordance in evaluations for fibrosis and steatosis from a pathology standpoint. *Mod Pathol* 2021; **34**: 1955-1962 [RC4] [PMID: 34108635 DOI: 10.1038/s41379-021-00851-5] [Full Text]
- Bojanic K, Bogojevic MS, Vukadin S, Sikora R, Ivanac G, Lucic NR, Smolic M, Tabl AA, Wu GY, Smolic R. Noninvasive Fibrosis Assessment in Chronic Hepatitis C Infection: An Update. *J Clin Transl Hepatol* 2023; **11**: 1228-1238 [RC4] [PMID: 37577224 DOI: 10.14218/JCTH.2022.00365] [FullText] [Full Text(PDF)]
- Fernandez-Fuertes M, Macías J, Corma-Gómez A, Rincón P, Merchante N, Gómez-Mateos J, Pineda JA, Real LM. Similar prevalence of hepatic steatosis among patients with chronic hepatitis C with and without HIV coinfection. *Sci Rep* 2020; **10**: 6736 [RC4] [PMID: 32317646 DOI: 10.1038/s41598-020-62671-y] [FullText] [Full Text(PDF)]

- 21 Ferraioli G, Soares Monteiro LB. Ultrasound-based techniques for the diagnosis of liver steatosis. *World J Gastroenterol* 2019; **25**: 6053-6062 [RC4] [PMID: 31686762 DOI: 10.3748/wjg.v25.i40.6053] [FullText] [Full Text(PDF)]
- 22 Attia D, Abdel Alem S, El-Akel W, Abdel-Razek W, Eslam M, Foad Y, Waked I. Prevalence and clinical characteristics of patients with metabolic dysfunction-associated fatty liver disease with hepatitis C virus infection-a population-based study. *Aliment Pharmacol Ther* 2022; **56**: 1581-1590 [RC4] [PMID: 36168675 DOI: 10.1111/apt.17233] [FullText]
- 23 Huang CF, Dai CY, Lin YH, Wang CW, Jang TY, Liang PC, Lin TC, Tsai PC, Wei YJ, Yeh ML, Hsieh MY, Huang CK, Huang JF, Chuang WL, Yu ML. Dynamic change of metabolic dysfunction-associated steatotic liver disease in chronic hepatitis C patients after viral eradication: A nationwide registry study in Taiwan. *Clin Mol Hepatol* 2024; **30**: 883-894 [RC4] [PMID: 39069721 DOI: 10.3350/cmh.2024.0414] [FullText] [Full Text(PDF)]
- 24 Hui JM, Kench J, Farrell GC, Lin R, Samarasinghe D, Liddle C, Byth K, George J. Genotype-specific mechanisms for hepatic steatosis in chronic hepatitis C infection. *J Gastroenterol Hepatol* 2002; **17**: 873-881 [RC4] [PMID: 12164963 DOI: 10.1046/j.1440-1746.2002.02813.x] [FullText]
- 25 Rubbia-Brandt L, Fabris P, Paganin S, Leandro G, Male PJ, Giostra E, Carlotto A, Bozzola L, Smedile A, Negro F. Steatosis affects chronic hepatitis C progression in a genotype specific way. *Gut* 2004; **53**: 406-412 [RC4] [PMID: 14960525 DOI: 10.1136/gut.2003.018770] [FullText]
- 26 Westin J, Nordlander H, Lagging M, Norkrans G, Wejstål R. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. *J Hepatol* 2002; **37**: 837-842 [RC4] [PMID: 12445426 DOI: 10.1016/s0168-8278(02)00299-4] [FullText]
- 27 Abdallah H, Khalil M, Awada E, Lanza E, Di Ciaula A, Portincasa P. Metabolic dysfunction-associated steatotic liver disease (MASLD). Assessing metabolic dysfunction, cardiovascular risk factors, and lifestyle habits. *Eur J Intern Med* 2025; **138**: 101-111 [RC4] [PMID: 40436716 DOI: 10.1016/j.ejim.2025.05.018] [FullText]
- 28 Cholongitas E, Pavlopoulou I, Papatheodoridis M, Markakis GE, Bouras E, Haidich AB, Papatheodoridis G. Epidemiology of nonalcoholic fatty liver disease in Europe: a systematic review and meta-analysis. *Ann Gastroenterol* 2021; **34**: 404-414 [RC4] [PMID: 33948067 DOI: 10.20524/aog.2021.0604] [FullText] [Full Text(PDF)]
- 29 Nagral A, Bangar M, Menezes S, Bhatia S, Butt N, Ghosh J, Manchayake JH, Mahtab MA, Singh SP. Gender Differences in Nonalcoholic Fatty Liver Disease. *Euroasian J Hepatogastroenterol* 2022; **12**: S19-S25 [RC4] [PMID: 36466099 DOI: 10.5005/jp-journals-10018-1370] [FullText] [Full Text(PDF)]
- 30 Hamaguchi M, Kojima T, Ohbora A, Takeda N, Fukui M, Kato T. Aging is a risk factor of nonalcoholic fatty liver disease in premenopausal women. *World J Gastroenterol* 2012; **18**: 237-243 [RC4] [PMID: 22294826 DOI: 10.3748/wjg.v18.i3.237] [FullText] [Full Text(PDF)]
- 31 Eurostat. Overweight and obesity - BMI statistics. July 2024. [cited 3 August 2025]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Overweight_and_obesity_-_BMI_statistics#Obesity_by_age_group
- 32 Divo MJ, Martinez CH, Mannino DM. Ageing and the epidemiology of multimorbidity. *Eur Respir J* 2014; **44**: 1055-1068 [RC4] [PMID: 25142482 DOI: 10.1183/09031936.00059814] [FullText]
- 33 Liu CJ, Seto WK, Yu ML. Dual-etiology MAFLD: the interactions between viral hepatitis B, viral hepatitis C, alcohol, and MAFLD. *Hepatol Int* 2024; **18**: 897-908 [RC4] [PMID: 39115632 DOI: 10.1007/s12072-024-10699-x] [FullText]
- 34 Man S, Deng Y, Ma Y, Fu J, Bao H, Yu C, Lv J, Liu H, Wang B, Li L. Prevalence of Liver Steatosis and Fibrosis in the General Population and Various High-Risk Populations: A Nationwide Study With 5.7 Million Adults in China. *Gastroenterology* 2023; **165**: 1025-1040 [RC4] [PMID: 37380136 DOI: 10.1053/j.gastro.2023.05.053] [FullText]
- 35 Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003; **37**: 917-923 [RC4] [PMID: 12668987 DOI: 10.1053/jhep.2003.50161] [FullText]
- 36 Golabi P, Ogonosuren M, de Avila L, Sayiner M, Rafiq N, Younossi ZM. Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). *Medicine (Baltimore)* 2018; **97**: e0214 [RC4] [PMID: 29595666 DOI: 10.1097/MD.00000000000010214] [FullText] [Full Text(PDF)]
- 37 Cross TJ, Quaglia A, Hughes S, Joshi D, Harrison PM. The impact of hepatic steatosis on the natural history of chronic hepatitis C infection. *J Viral Hepat* 2009; **16**: 492-499 [RC4] [PMID: 19200134 DOI: 10.1111/j.1365-2893.2009.01098.x] [FullText]
- 38 Siphpho PY, Liu YT, Shabangu CS, Huang JF, Huang CF, Yeh ML, Yu ML, Wang SC. The Impact of Steatosis on Chronic Hepatitis C Progression and Response to Antiviral Treatments. *Biomedicines* 2021; **9**: 1491 [RC4] [PMID: 34680608 DOI: 10.3390/biomedicines9101491] [FullText] [Full Text(PDF)]
- 39 Shah SR, Patel K, Marcellin P, Foster GR, Manns M, Kottitil S, Healey L, Pulkstenis E, Subramanian GM, McHutchison JG, Sulkowski MS, Zeuzem S, Nelson DR. Steatosis is an independent predictor of relapse following rapid virologic response in patients with HCV genotype 3. *Clin Gastroenterol Hepatol* 2011; **9**: 688-693 [RC4] [PMID: 21640198 DOI: 10.1016/j.cgh.2011.04.029] [FullText] [Full Text(PDF)]
- 40 Rau M, Buggisch P, Mauss S, Boeker KHW, Klinker H, Müller T, Stoehr A, Schattenberg JM, Geier A. Prognostic impact of steatosis in the clinical course of chronic HCV infection-Results from the German Hepatitis C-Registry. *PLoS One* 2022; **17**: e0264741 [RC4] [PMID: 35709466 DOI: 10.1371/journal.pone.0264741] [FullText] [Full Text(PDF)]
- 41 Pabjan P, Brzdęk M, Chrapęk M, Dziedzic K, Dobrowolska K, Paluch K, Garbat A, Błoniarczyk P, Reczek K, Stępień P, Zarębska-Michalak D. Are There Still Difficult-to-Treat Patients with Chronic Hepatitis C in the Era of Direct-Acting Antivirals? *Viruses* 2022; **14**: 96 [RC4] [PMID: 35062302 DOI: 10.3390/v14010096] [FullText] [Full Text(PDF)]
- 42 Ioannou GN, Beste LA, Chang MF, Green PK, Lowy E, Tsai JI, Su F, Berry K. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Health Care System. *Gastroenterology* 2016; **151**: 457-471.e5 [RC4] [PMID: 27267053 DOI: 10.1053/j.gastro.2016.05.049] [FullText]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjnet.com>



Review paper

Steatotic liver disease and chronic viral hepatitis

Jakub Janczura¹, Alessandra Mangia², Krystyna Dobrowolska¹, Michał Brzdek¹, Kinga Brzdek¹, Małgorzata Wajdowicz³, Iwona Gorczyca-Głowacka⁴, Piotr M. Stepien⁵, Dorota Zarebska-Michaluk⁵

¹Collegium Medicum, Jan Kochanowski University, Kielce, Poland

²Liver Unit, Fondazione "Casa Sollievo della Sofferenza", IRCCS San Giovanni Rotondo, Rotondo, Italy

³Clinical Department of Infectious Diseases with Hepatology Subdivision, Collegium Medicum University of Rzeszow, Rzeszów, Poland

⁴Department of Psychiatry, Jan Kochanowski University, Kielce, Poland

⁵Department of Infectious Diseases and Allergology, Jan Kochanowski University, Kielce, Poland

Abstract

Steatotic liver disease (SLD) is a condition characterized by excessive fat accumulation within hepatocytes. In recent years, the nomenclature and diagnostic framework of the disease have evolved and the term SLD has replaced the previous fatty liver disease classification. This change reflects a more inclusive understanding of the metabolic drivers of the disease and its strong association with systemic conditions. With the rising global prevalence of metabolic disorders, the burden of SLD has increased significantly, making it the leading cause of chronic liver disease worldwide. While many cases of SLD remain non-progressive, metabolic dysfunction associated steatohepatitis (MASH) may advance to fibrosis, cirrhosis, or hepatocellular carcinoma. The risk of disease progression may be greater when liver steatosis coexists with other hepatic insults, particularly chronic infections with hepatitis B virus or hepatitis C virus. This review explores the prevalence, interactions, and therapeutic implications of SLD in patients with chronic viral hepatitis.

Key words: HBV, HCV, liver steatosis, chronic hepatitis.

Address for correspondence:

Jakub Janczura, Collegium Medicum, Jan Kochanowski University, Kielce, Poland, e-mail: kuba.janczura@gmail.com

Introduction

Steatotic liver disease (SLD) is an umbrella term for a wide range of conditions associated with metabolic dysfunction. SLD encompasses liver disorders characterized by excessive fat accumulation in hepatocytes, resulting from various causes such as metabolic disorders, monogenic diseases, drug-induced liver damage and alcohol abuse [1]. In recent years, there has been a change in the nomenclature and diagnostic framework for the disease, with the acronym SLD replacing the previously used term "nonalcoholic fatty liver disease" (NAFLD) in accordance with the 2023 Delphi Consensus [2]. The change, endorsed by hepatology experts, reflects a more comprehensive understanding of the metabolic basis of SLD and its strong association with systemic disorders, including obesity, type 2 diabetes mellitus (T2DM), dyslipidemia and hypertension [3]. The global

burden of SLD has increased dramatically, fueled mainly by the obesity pandemic, making it the most common cause of chronic liver disease in recent years [4]. Currently SLD affects about 30% of the world's population, more often men. Its distribution varies significantly across different regions of the world (Fig. 1) [4, 5]. While many cases of SLD remain clinically stable without significant progression, some may progress to severe forms of the disease, such as advanced liver fibrosis, cirrhosis with risk of liver failure, and hepatocellular carcinoma (HCC). The progressive form of SLD is defined as metabolic dysfunction associated steatohepatitis (MASH), which is characterized by liver inflammation and fibrosis resulting from the accumulation of fat in the liver [6]. The risk of progression becomes even higher when steatosis coexists with liver damage of other etiologies, including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections [6]. Chronic viral hepatitis caused by



Legend: Created by authors. Based on reference [5].

Fig. 1. Prevalence of steatotic liver disease diagnosed by ultrasound, 2019

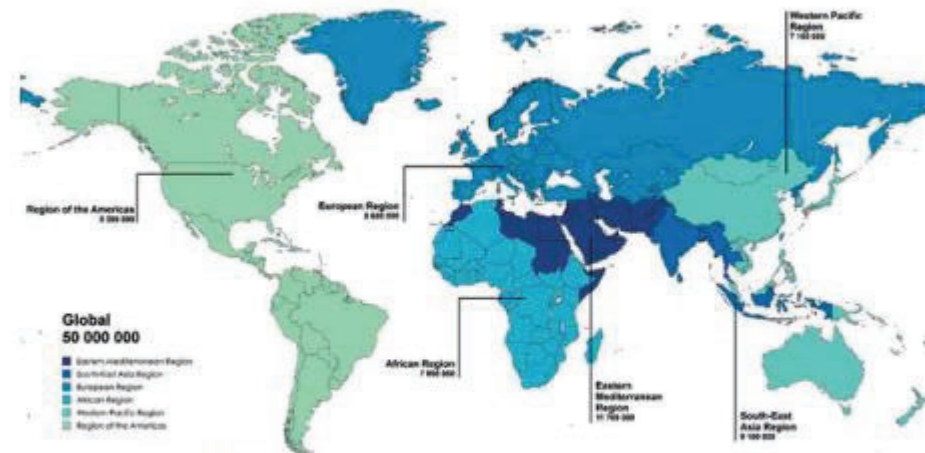
HBV and HCV continues to be a significant contributor to liver disease and liver-related mortality.

Steatotic liver disease and chronic hepatitis C

Epidemiology

HCV infection remains a significant public health problem worldwide. According to the World Health Organization (WHO), about 50 million people are currently living with chronic HCV infection, making

it one of the leading causes of chronic liver disease, cirrhosis and HCC (Fig. 2) [7]. Hepatic steatosis, defined as excessive lipid accumulation in hepatocytes, is a common histopathological feature in patients with chronic hepatitis C (CHC). Studies indicate that the prevalence of hepatic steatosis in patients with CHC ranges from 45% to 79%, which is significantly higher than in the general population [8]. Significant geographic differences have also been observed in the epidemiology of hepatic steatosis in patients with



Legend: Created by authors. Based on reference [7].

Fig. 2. Prevalence of chronic hepatitis C by WHO region, 2022

CHC. In countries such as France, Germany, Italy, and the United States, due to the increased prevalence of T2DM and obesity, steatosis associated with the metabolic syndrome predominate [8]. In South Asia and Australia, where there is a higher percentage of patients infected with HCV genotype 3, the predominant viral-related steatosis present in more than 50% of infected patients [9]. Ethnic and genetic factors may also influence the variation in the prevalence and severity of steatosis [8]. Although the most common form observed in patients with CHC is mild steatosis [10], its clinical consequences should not be underestimated. In HCV-infected individuals, steatosis is often associated with more advanced histological changes and faster progression of fibrosis [10]. Another emerging issue is steatohepatitis, in which, in addition to fat ac-

cumulation in liver cells, inflammation develops with damage to hepatocytes and their ballooning degeneration. It is estimated that steatohepatitis occurs in about 10% of patients with CHC [10].

Risk factors associated with the development of hepatic steatosis and progression of liver disease in patients with CHC

The development of hepatic steatosis in patients with CHC is determined by numerous risk factors, which can be broadly divided into viral and metabolic factors (Table 1). Steatosis associated with viral factors is mainly the result of direct effects of HCV, especially genotype 3, on lipid metabolism [11]. Figure 3 presents the main molecular mechanisms by which HCV

Table 1. Differences between host- and virus-related steatosis in chronic hepatitis C

Category	Main drivers	Mechanisms	Prevalence	Clinical impact
Host-related SLD	Metabolic factors (insulin resistance, obesity, T2DM, alcohol use)	Insulin resistance, increased visceral fat, chronic inflammation, cytokine dysregulation (TNF- α , IL-6), reduced adiponectin	Predominates in Western countries with high obesity and T2DM rates	Independent risk factor for fibrosis progression; associated with metabolic syndrome and worse prognosis
Virus-related SLD	Direct viral effects, particularly HCV genotype 3	Disrupted lipid metabolism via impaired VLDL secretion, upregulation of SREBP-1, reduced MTP, PPAR- α , PTEN activity	Highly prevalent in regions with high HCV GT3 infection rates	Closely related to viral load; associated with faster fibrosis progression

CHC - chronic hepatitis C, GT3 - genotype 3, HCV - hepatitis C virus, MTP - microsomal triglyceride transfer protein, PPAR- α - peroxisome proliferator-activated receptor α , PTEN - phosphatase and tensin homolog, SLD - steatotic liver disease, SREBP-1 - sterol regulatory element-binding protein-1, T2DM - type 2 diabetes mellitus, VLDL - very low-density lipoprotein



HCV - hepatitis C virus, MTP - microsomal triglyceride transfer protein, VLDL - very-low-density lipoprotein, SREBPs - sterol regulatory element binding proteins, FAS - fatty-acid synthase, PPAR- α - peroxisome proliferator-activated receptor α , FFAs - free fatty acids, TNF- α - tumor necrosis factor α , SOCS3 - suppressor of cytokine signaling 3, IRS-1 - insulin receptor substrate signaling, ROS - reactive oxygen species
Legend: Created by authors.

Fig. 3. Influence of HCV on liver steatosis development. Green and red show upregulation and downregulation, respectively

induces steatosis, depending on the genotype. Steatosis associated with host metabolic disorders results from the influence of factors such as insulin resistance, obesity, and diabetes. However, these two forms of steatosis are not completely separate and often coexist, leading to complex interactions that make it difficult to determine their individual impact on liver disease progression [11].

Steatosis in patients with CHC associated with metabolic factors

Metabolic factors play a key role in the pathogenesis of hepatic steatosis in HCV, one of which is insulin resistance. Insulin resistance is considered a direct consequence of HCV infection and is the mechanism leading to lipid accumulation in the liver [11]. It results in increased hepatic glucose production, reduced lipid oxidation, and increased fat accumulation in hepatocytes [11]. A study of 500 patients with CHC found that insulin resistance (OR: 1.80, 1.15-2.81, $p = 0.009$) was a factor that independently increased the risk of developing advanced liver fibrosis [12]. One of the most significant metabolic risk factors for steatosis in CHC is T2DM. A meta-analysis of 34 epidemiological studies showed that HCV infection increases the risk of T2DM by about 68% compared to uninfected individuals [13]. This is likely related to changes in insulin signaling pathways, the development of insulin resistance, and chronic inflammation caused by the virus. Insulin resistance, hyperglycemia, and chronic inflammation promote fat accumulation in the liver and the progression of disease in this organ [11]. Overweight and obesity, especially of the abdominal type, are much more common in people with hepatic steatosis [13]. The increase in visceral fat is associated with elevated levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor α [13]. These cytokines interfere with insulin signaling and inhibit adiponectin secretion, leading to insulin resistance. Such metabolic changes contribute to the development and progression of hepatic steatosis, further accelerating the progression of liver disease in patients with CHC. A study of 324 patients with CHC in the United States found that both obesity and overweight were independently associated with hepatic steatosis [14]. Moreover, multivariate analysis confirmed that hepatic steatosis, especially in advanced stages, is an independent risk factor for fibrosis progression in patients with CHC. Alcohol consumption, even in amounts that do not meet the definition of abuse according to gender, is a known factor that worsens the course of CHC. It increases the risk of serious compli-

cations such as cirrhosis, and alcohol-dependent patients, especially women, have a higher risk of death compared to the group without CHC [15]. According to data from a meta-analysis examining the effect of alcohol on liver disease progression in CHC, each drink containing 12 grams of pure alcohol increases the risk of developing cirrhosis by 11% [15]. Alcohol abuse also leads to the development of hepatic steatosis. In a study that analyzed data from the National Health and Nutrition Examination Survey (NHANES), the effect of alcohol consumption was found to be less significant than that of metabolic factors. The increase in the controlled attenuation parameter (CAP) index, used to measure liver steatosis using FibroScan, was statistically significant only in patients who consumed alcohol 5-7 times a week. Frequency of consumption was also more important for the development and progression of steatosis than the amount of alcohol consumed per day [16]. An analysis including a cohort from Spain and the US with liver steatosis associated with metabolic factors showed that alcohol consumption was a factor that independently increased the risk of fibrosis and steatohepatitis. Moreover, already moderate alcohol consumption acted additively with metabolic factors to increase the risk of fibrosis progression. According to the authors, there is no safe daily dose of alcohol [17].

HCV-related liver steatosis

Although metabolic factors play an important role in the development of hepatic steatosis in CHC, viral factors, particularly HCV genotype, are also crucial. Patients infected with GT3 HCV have approximately five times the risk of developing moderate to severe hepatic steatosis compared to those infected with other genotypes [18]. The presence and severity of steatosis in GT3 patients are closely related to viral load [18]. The pathogenesis of HCV-associated hepatic steatosis involves multiple mechanisms affecting lipid metabolism. These include impaired secretion of very low-density lipoprotein (VLDL), increased levels of fatty acid synthase, overregulation of sterol regulatory element-binding protein-1 (SREBP-1), decreased activity of microsomal triglyceride transfer protein (MTTP), and decreased expression of the sterol regulatory element-binding protein-1 (SREBP-1). MTTP reduced expression of peroxisome proliferator-activated receptor alpha (PPAR- α), and impaired function of phosphatase and tensin homolog (PTEN) [19]. Although GT3 is most commonly associated with these disorders, other HCV genotypes may also contribute to lipid accumulation in the liver. The exact mechanisms underlying HCV-mediated steatosis in infec-

tions with other genotypes are not well understood. However, genotype 1 has been shown to be associated with increased expression of suppressor of cytokine signaling-3 (SOCS-3) and tumor necrosis factor alpha, increased levels of reactive oxygen species, decreased adiponectin levels, increased free fatty acids, and impaired fatty acid oxidation due to decreased oxidase activity [10]. Figure 2 presents the main molecular mechanisms by which HCV induces steatosis, depending on the genotype. Liver steatosis is also associated with progression of liver fibrosis. A retrospective study of 603 African-American patients with CHC at Howard University Hospital found that steatosis was an independent risk factor for fibrosis progression (OR: 1.6, $p = 0.002$), and patients with advanced fibrosis were more likely to have severe hepatic steatosis compared to those with mild fibrosis [20]. Similar observations were reported in a study of 180 patients with CHC [21]. Some studies also suggest that GT3 may be associated with accelerated fibrosis progression [22]. Moreover, a growing amount of evidence points to a link between hepatic steatosis and an increased risk of developing HCC in people with chronic HCV infection [23]. This underscores the importance of monitoring and treating hepatic steatosis as an essential component of strategies to prevent liver disease progression in HCV-infected patients.

Impact of hepatic steatosis on the outcome of CHC treatment

In the era of interferon-based therapy, the presence of hepatic steatosis was considered a significant risk factor for treatment failure in patients with chronic HCV infection [24]. Compared to other well-known predictors of treatment failure, such as viral genotype, the exact impact of steatosis on response to therapy has remained unclear. Studies have shown that insulin resistance may play a role not only in the development of steatosis, but also in treatment failure [12]. An analysis evaluating the effect of insulin resistance and viral factors on achieving a sustained virologic response (SVR) in patients with CHC who were treated with pegylated interferon (pegIFN) and ribavirin showed that the insulin resistance index was an independent predictor of SVR [25]. The percentage of GT1-infected patients with insulin resistance who achieved SVR was lower than in the corresponding group without insulin resistance. In addition, steatosis was associated with a higher rate of relapse in GT3 HCV-infected patients [26]. The analysis, which included more than 400 patients treated with pegIFN and ribavirin for six months, examined the effect of metabolic syndrome on treatment

outcomes. It was observed that in the group that met the criteria for a diagnosis of metabolic syndrome, the percentage of patients achieving SVR was lower compared to the group without metabolic syndrome (72.2% vs. 43.7%, $p < 0.05$) [27]. The introduction of therapies based on direct-acting antivirals (DAAs) has dramatically changed the landscape of HCV treatment [28]. DAAs provide significantly higher SVR rates in a variety of patient populations, rendering many factors that previously influenced treatment failure, including steatosis and insulin resistance, largely irrelevant [28, 29]. Analysis of Polish patients from the EpiTer-2 database showed that although patients with HCV infection and steatosis differed from those without steatosis in terms of body mass index (BMI), genotype distribution, and comorbidities, the effectiveness of DAA therapy was equally high in both groups [30]. In addition, a large cohort study that included more than 8000 German patients did not detect significant differences in treatment efficacy depending on the presence or absence of hepatic steatosis. SVR remained above 96% in both groups, demonstrating that in the era of DAA therapy, steatosis is no longer a significant predictor of treatment failure [31].

Effect of SVR on hepatic steatosis

Direct-acting antiviral therapy and achievement of SVR in patients with CHC is associated with regression of liver fibrosis [32]. However, the effect of HCV elimination on metabolic disorders and hepatic steatosis remains controversial [32]. In a study involving 41 patients following DAA treatment with significant hepatic steatosis, a significant decrease in CAP was observed, accompanied by an increase in low-density lipoprotein (LDL) levels [33]. Increased dyslipidemia may be related to the elimination of HCV particles that bind to lipoproteins during ongoing infection [32]. In contrast, a prospective observational study of Egyptian patients observed increased steatosis one year after DAA treatment, and the presence of steatosis and high BMI were found to be negative predictors of fibrosis regression after therapy [34]. A meta-analysis of 97 original papers that examined changes in metabolic factors, including changes in the severity and presence of hepatic steatosis after DAA treatment, showed a great heterogeneity of results. The inconsistent and relatively short follow-up in the studies that were analyzed also remains a problem [32]. Pre-treatment of existing metabolic disorders, once SVR is achieved, may lead to increased hepatic steatosis and progressive fibrosis, thereby increasing the risk of cirrhosis and HCC despite virus eradication [32]. On the oth-

er hand, in patients with genotype 3 infection without metabolic comorbidities, but with hepatic steatosis before therapy, its reduction was observed after achieving SVR [22]. A multidisciplinary approach to patients with metabolic risk factors for hepatic steatosis and an attempt to eliminate them before implementing DAA treatment is needed. The discrepancies in the analyses published to date underscore the need for further research in this area.

Steatotic liver disease and chronic hepatitis B

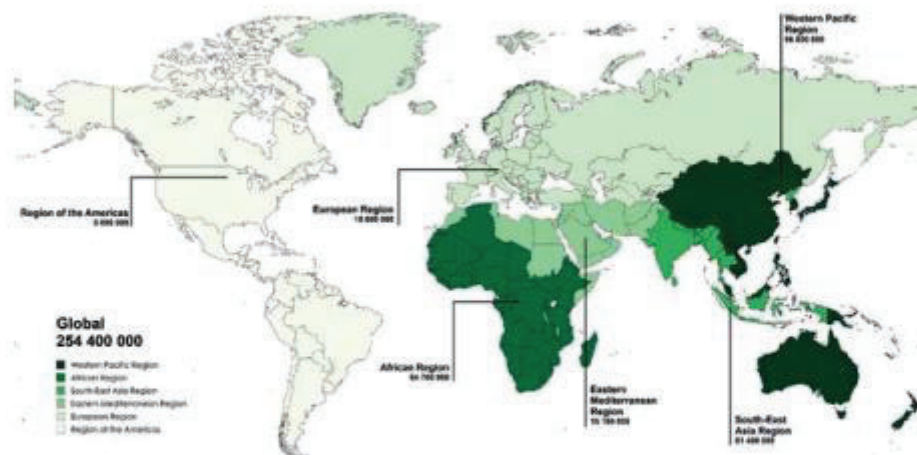
Epidemiology

According to a WHO report in 2022, about 254 million people worldwide are chronically infected with HBV, with 1.2 million new infections recorded each year (Fig. 4) [35]. Chronic hepatitis B (CHB) is responsible for about 1.1 million deaths each year, mainly from cirrhosis and HCC [35]. Hepatic steatosis is a common histopathological feature observed in patients with CHB, with a prevalence of 14% to 70%, depending mostly on differences in study populations, diagnostic methods, grading criteria, and genetic or ethnic factors [36]. However, there is no direct evidence to suggest that chronic HBV infection itself increases the risk of hepatic steatosis. The results of available studies indicate that the incidence of hepatic steatosis in patients with CHB is comparable to that in the general population. A recent meta-analysis in-

volving nearly 29 000 patients with CHB found that the incidence of hepatic steatosis was 32.8% (95% CI: 28.9-37.0), which closely mirrors that in the general population [37]. Another meta-analysis, which included 4,100 HBV-infected patients, found an overall SLD prevalence of 29.6% [38], which is consistent with patterns observed in the general population. These findings suggest that hepatic steatosis in patients with CHB is mainly due to metabolic factors rather than HBV infection itself. Notably, several studies have reported an inverse relationship between HBV DNA levels and hepatic steatosis, indicating a protective effect of HBV infection on hepatic steatosis [39]. In patients with CHB and concomitant SLD, a progressive decrease in median HBV DNA levels was observed as the severity of steatosis increased. Interestingly, higher degrees of steatosis were independently associated with lower serum HBV DNA levels, suggesting that steatosis may have a suppressive effect on HBV replication [40].

Risk factors associated with the development of hepatic steatosis and progression of liver disease in patients with CHB

The development of hepatic steatosis in patients with CHB, as in the general population, appears to be directly related to the presence of metabolic risk factors, such as central obesity, unfavorable lipid profile and diabetes. Steatosis can develop in any age group, but because the prevalence of metabolic risk factors



Legend: Created by authors. Based on reference [35]

Fig. 4. Prevalence of chronic hepatitis B by WHO region, 2022

increases with age, patients with CHB and SLD tend to be older than patients in control groups [41, 42]. Due to the protective role of estrogen in women, which delays the development of SLD, gender also plays an important role [41, 42]. In a meta-analysis aimed at analyzing factors affecting the development of steatosis in patients with SLD, both male sex and older age were found to be positive predictors of the presence of SLD. Similar results were found for metabolic risk factors [37]. In a case-control study in which groups were matched for age, gender, treatment status, and duration, among patients with CHB and SLD who had not received prior treatment, 80% had at least one metabolic risk factor for developing steatosis. Moreover, regardless of treatment status, both BMI and obesity independently increased the risk of developing SLD. In the untreated group, the presence of steatosis was also considered a predictor of a metabolic syndrome [40]. The influence of metabolic risk factors on the development of SLD in patients with CHB, independent of the virological component, was confirmed in a study in which more than 30 000 patients were included, and more than 9% were infected with HBV. Regardless of virological status, patients with SLD were predominantly male, older, and characterized by central obesity, higher blood pressure, and impaired lipid metabolism. In multivariate analysis, metabolic risk factors independently increasing the risk of developing SLD were similar in both patients with HBV and in the uninfected group [42].

Interaction between hepatic steatosis and CHB

The interaction between chronic HBV infection and SLD is complex and is the subject of ongoing research, with many reporting that hepatic steatosis can inhibit HBV replication. SLD is associated with increased immune activity, including higher expression of Th17 cell-related genes and increased levels of interleukin 21, leading to production of inflammatory cytokines, decreased HBV replication, and clearance of HBV DNA and HBV viral e antigen (HBeAg) [43]. In addition, SLD-induced metabolic stress can lead to inhibition of HBV replication and apoptosis of HBV-infected cells, helping to clear the virus and limit the progression of HBV-related disease [43]. However, despite lower HBV replication, patients with CHB and SLD often experience faster progression of liver disease compared to patients with only CHB or SLD [44]. The synergistic effect of chronic HBV infection and SLD in driving liver disease progression is often explained by the "two-strike theory". In this model, viral infection serves as the first hit, causing initial

liver damage, while steatohepatitis serves as the second hit, exacerbating inflammation and fibrosis and accelerating disease progression. HBV HBx protein stimulates genes associated with lipid accumulation, such as PPAR, SREBP and FABP1, promoting steatosis and hepatocyte proliferation while suppressing apoptosis, contributing to the development of HCC [45]. In addition, oxidative stress associated with SLD can create a pro-fibrotic and pro-carcinogenic environment, further promoting carcinogenesis [45]. Studies from daily clinical practice involving large patient populations have confirmed higher rates of liver cancer and mortality in patients with CHB coexisting with SLD. A study in Hong Kong found a 7.3-fold increase in liver cancer risk in patients with CHB and SLD [46]. Similarly, Lee *et al.* found that concurrent hepatic steatosis in patients with CHB was associated with a higher risk of HCC [47].

Management of CHB-SLD patients

The treatment of SLD in patients with CHB requires a comprehensive and multifaceted approach. Non-invasive measurements, such as elastography with CAP assessment using FibroScan, can effectively assess both liver fibrosis and steatosis and nowadays represents a valuable alternative to histopathological examination, which in the past was the gold standard for determining the etiology and severity of liver disease [48]. Antiviral treatment remains key in the treatment of CHB, and nucleos(t)ide analogues (NAs) such as tenofovir and entecavir are effective in inhibiting HBV replication [49]. The decision to implement antiviral therapy in patients with chronic HBV infection is based on the current criteria contained in the recommendations of international and national scientific societies taking into account three parameters: alanine aminotransferase activity, HBV viral load, and the stage of fibrosis in the liver [49-51]. To date, no drugs have been registered to treat MASH with fibrosis in Europe, but ongoing clinical trials, many of which are already in Phase 3, offer hope that such forms of treatment will be available in the near future [52]. The first candidate appears to be resmetirom, an oral thyromimetic drug approved in March 2024 by the US Food and Drug Administration for the treatment of MASH in patients without cirrhosis [53]. Thus, for the time being, lifestyle modification remains the standard of care for a patient with SLD, including a patient with concomitant CHB. Patients who are overweight or obese are advised to lose weight, in particular to reduce 3-5% of total body weight to improve steatosis and 7-10% to obtain MASH resolution [54]. Patients with diabetes and arterial hypertension

are recommended to effectively treat these conditions under the supervision of medical specialists. The results of analyses on the effects of antiviral treatment for patients with CHB and SLD are inconsistent; some studies show lower virological response rates, while others show no difference compared to patients without SLD. A recent meta-analysis involving 48,472 patients found that coexisting hepatic steatosis was negatively associated with response to antiviral treatment in patients with SLD [55]. Similarly, Jin *et al.* identified hepatic steatosis as an independent factor contributing to treatment failure with entecavir [56]. However, other studies have reported no significant differences in outcomes between CHB patients with and without SLD treated with NAs [57]. Taken together, these results underscore the importance of regular monitoring of disease progression in patients with CHB and SLD.

Summary

The co-occurrence of SLD with chronic hepatotropic virus infection is comparable to the prevalence of SLD in the general population for HBV and higher for HCV. In addition to the contribution of classic patient-related metabolic risk factors such as obesity, diabetes and hypertension, virus-related factors such as HCV genotype influence disease progression. The coexistence of SLD with chronic viral hepatitis can exacerbate liver damage, accelerate fibrosis progression, and increase the risk of developing cirrhosis, while data on the impact on the effects of antiviral therapy are inconclusive.

Disclosures

This research received no external funding.
Institutional review board statement: Not applicable.
The authors declare no conflict of interest.

References

1. Teng ML, Ng CH, Huang DQ, et al. Global incidence and prevalence of nonalcoholic fatty liver disease. *Clin Mol Hepatol* 2023; 29: S32-S42.
2. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023; 78: 1966-1986.
3. Gorczyca-Glowacka I, Welnicki M, Mamcarz A, et al. Metabolic associated fatty liver disease and cardiovascular risk: The expert opinion of the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society. *Kardiol Pol* 2023; 81: 207-214.
4. Amini-Salehi E, Letafatkar N, Norouzi N, et al. Global prevalence of nonalcoholic fatty liver disease: An updated review meta-analysis comprising a population of 78 million from 38 countries. *Arch Med Res* 2024; 55: 103043.

5. Le MH, Yeo YH, Li X, et al. 2019 global NAFLD prevalence: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2022; 20: 2809-2817.e28.
6. Lee MH, Chen YT, Huang YH, et al. Chronic viral hepatitis B and C outweigh MASLD in the associated risk of cirrhosis and HCC. *Clin Gastroenterol Hepatol* 2024; 22: 1275-1285.e2.
7. The World Health Organization. Hepatitis C. Available from: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>.
8. Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol* 2018; 69: 896-904.
9. Hui JM, Kench J, Farrell GC, et al. Genotype-specific mechanisms for hepatic steatosis in chronic hepatitis C infection. *J Gastroenterol Hepatol* 2002; 17: 873-881.
10. Modaresi Eseh J, Ansari-Gilani K. Steatosis and hepatitis C. *Gastroenterol Rep (Oxf)* 2016; 4: 24-29.
11. Negro F. Facts and fictions of HCV and comorbidities: steatosis, diabetes mellitus, and cardiovascular diseases. *J Hepatol* 2014; 61: S69-78.
12. Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology* 2008; 134: 416-423.
13. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *J Hepatol* 2008; 49: 831-844.
14. Hu KQ, Kyulo NL, Esraillan E, et al. Overweight and obesity, hepatic steatosis, and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the United States. *J Hepatol* 2004; 40: 147-154.
15. Llamas-Falcón L, Shield KD, Gelovany M, et al. Impact of alcohol on the progression of HCV-related liver disease: A systematic review and meta-analysis. *J Hepatol* 2021; 75: 536-546.
16. Niezen S, Trivedi HD, Mukamal KJ, Jiang ZG. Associations between alcohol consumption and hepatic steatosis in the USA. *Liver Int* 2021; 41: 2020-2023.
17. Marti-Aguado D, Calleja JL, Vilar-Gomez E, et al. Low-to-moderate alcohol consumption is associated with increased fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease. *J Hepatol* 2024; 81: 930-940.
18. Leandro G, Mangia A, Hui J, et al. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology* 2006; 130: 1636-1642.
19. Adinolfi LE, Rinaldi I, Guerrero B, et al. NAFLD and NASH in HCV infection: Prevalence and significance in hepatic and extrahepatic manifestations. *Int J Mol Sci* 2016; 17: 803.
20. Afsari A, Lee E, Shokrani B, et al. Clinical and pathological risk factors associated with liver fibrosis and steatosis in African-Americans with chronic hepatitis C. *Dig Dis Sci* 2017; 62: 2159-2165.
21. Adinolfi LE, Gambardella M, Andreana A, et al. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; 33: 1358-1364.
22. Zarębska-Michaluk D. Genotype 3-hepatitis C virus' last line of defense. *World J Gastroenterol* 2021; 27: 1006-1021.
23. Ji D, Chen GF, Niu XX, et al. Non-alcoholic fatty liver disease is a risk factor for occurrence of hepatocellular carcinoma after sustained virologic response in chronic hepatitis C patients: A prospective four-years follow-up study. *Metabol Open* 2021; 10: 100090.

24. Poynard T, Ratziu V, McHutchison J, et al. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. *Hepatology* 2003; 38: 75-85.
25. Romero-Gómez M, Del Mar Vilorio M, Andrade RJ, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005; 128: 636-641.
26. Restivo L, Zampino R, Guerrero B, et al. Steatosis is the predictor of relapse in HCV genotype 3- but not 2-infected patients treated with 12 weeks of pegylated interferon-alpha-2a plus ribavirin and RVR. *J Viral Hepat* 2012; 19: 346-352.
27. Aziz H, Gill U, Raza A, Gill ML. Metabolic syndrome is associated with poor treatment response to antiviral therapy in chronic hepatitis C genotype 3 patients. *Eur J Gastroenterol Hepatol* 2014; 26: 538-543.
28. Brzdęk M, Zarębska-Michaluk D, Invernizzi F, et al. Decade of optimizing therapy with direct-acting antiviral drugs and the changing profile of patients with chronic hepatitis C. *World J Gastroenterol* 2023; 29: 949-966.
29. Dobrowolska K, Brzdęk M, Rzymiski P, et al. Revolutionizing hepatitis C treatment: next-gen direct-acting antivirals. *Expert Opin Pharmacother* 2024; 25: 833-852.
30. Flisiak R, Zarębska-Michaluk D, Dobrowolska K, et al. Treatment of HCV infection in patients with steatotic liver disease. *Clin Exp Hepatol* 2024; 10: 159-164.
31. Rau M, Buggisch P, Mauss S, et al. Prognostic impact of steatosis in the clinical course of chronic HCV infection-Results from the German Hepatitis C-Registry. *PLoS One* 2022; 17: e0264741.
32. Cespiati A, Coelho Rodrigues I, Santos I, et al. Effect of HCV eradication by DAAs on liver steatosis, carotid atherosclerosis, and associated metabolic comorbidities: A systematic review. *Liver Int.* 2024; 44: 1075-1092.
33. Shimizu K, Soroida Y, Sato M, et al. Eradication of hepatitis C virus is associated with the attenuation of steatosis as evaluated using a controlled attenuation parameter. *Sci Rep* 2018; 8: 7845.
34. Soliman H, Ziada D, Hamisa M, et al. The effect of HCV eradication after direct-acting antiviral agents on hepatic steatosis: A prospective observational study. *Endocr Metab Immune Disord Drug Targets* 2022; 22: 100-107.
35. The World Health Organization. Hepatitis C. Available from: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>.
36. Baclig MO, Reyes KG, Liles VR, et al. Hepatic steatosis in chronic hepatitis B: a study of metabolic and genetic factors. *Int J Mol Epidemiol Genet* 2018; 9: 13-19.
37. Zheng Q, Zou B, Wu Y, et al. Systematic review with meta-analysis: prevalence of hepatic steatosis, fibrosis and associated factors in chronic hepatitis B. *Aliment Pharmacol Ther* 2021; 54: 1100-1109.
38. Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. *J Gastroenterol Hepatol* 2011; 26: 1361-1367.
39. Yi S, Ren G, Zhu Y, Cong Q. Correlation analysis of hepatic steatosis and hepatitis B virus: a cross-sectional study. *Virology* 2024; 21: 22.
40. Hui RWH, Seto WK, Cheung KS, et al. Inverse relationship between hepatic steatosis and hepatitis B viremia: Results of a large case-control study. *J Viral Hepat* 2018; 25: 97-104.
41. Wong SW, Chan WK, Mohamed R. Fatty liver is associated with advanced fibrosis but does not predict adverse outcomes in patients with chronic hepatitis B. *J Viral Hepat* 2020; 27: 1297-1305.
42. Cheng YM, Hsieh TH, Wang CC, Kao JH. Impact of HBV infection on clinical outcomes in patients with metabolic dysfunction-associated fatty liver disease. *JHEP Rep* 2023; 5: 100836.
43. Tang L, Chen C, Gao X, et al. Interleukin 21 reinvigorates the antiviral activity of hepatitis B virus (HBV)-specific CD8+ T cells in chronic HBV infection. *J Infect Dis* 2019; 219: 750-759.
44. Lv H, Jiang Y, Zhu G, et al. Liver fibrosis is closely related to metabolic factors in metabolic associated fatty liver disease with hepatitis B virus infection. *Sci Rep* 2023; 13: 13888.
45. Wu YL, Peng XE, Zhu YB, et al. Hepatitis B virus X₁ protein induces hepatic steatosis by enhancing the expression of liver fatty acid binding protein. *J Virol* 2016; 90: 1729-1740.
46. Chan AWH, Wong GLH, Chan HY, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2017; 32: 667-676.
47. Lee YB, Ha Y, Chon YE, et al. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. *Clin Mol Hepatol* 2019; 25: 52-64.
48. Tapper EB, Lok ASF. Use of liver imaging and biopsy in clinical practice. *N Engl J Med* 2017; 377: 756-768.
49. Lampertico P, Agarwal K, Berg T, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370-398.
50. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; 67: 1560-1599.
51. Polish Group of Experts for HBV, Flisiak R, Halota W, Jaroszewicz J, et al. Recommendations for the treatment of hepatitis B in 2017. *Clin Exp Hepatol* 2017; 3: 35-46.
52. Kokkorakis M, Muzurović E, Volčanšek Š, et al. Steatotic liver disease: Pathophysiology and emerging pharmacotherapies. *Pharmacol Rev* 2024; 76: 454-499.
53. Guirguis E, Dougherty J, Thornby K, et al. Resmetivir: The first Food and Drug Administration-approved medication for non-alcoholic steatohepatitis (NASH). *Ann Pharmacother* 2025; 59: 162-173.
54. Younossi ZM, Loomba R, Rinella ME, et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology* 2018; 68: 361-371.
55. Jiang D, Zhang L, Liu W, et al. Trends in cancer mortality in China from 2004 to 2018: A nationwide longitudinal study. *Cancer Commun (Lond)* 2021; 41: 1024-1036.
56. Jin X, Chen Y-P, Yang Y, et al. Association between hepatic steatosis and entecavir treatment failure in Chinese patients with chronic hepatitis B. *PLoS One* 2012; 7: e34198.
57. Janczura J, Brzdęk M, Dobrowolska K, et al. Steatotic liver disease in patients treated for chronic hepatitis B. *Pol Arch Intern Med* 2025; 135: 16942.

Podsumowanie i wnioski

Cykl publikacji stanowiący podstawę niniejszej rozprawy doktorskiej obejmuje analizy, których celem była ocena przebiegu klinicznego pacjentów chorujących na PZWB i PZWC w zależności od obecności lub braku współistniejącej SLD. Analizie poddano profil hospitalizowanych chorych, ich stan kliniczny, wyniki badań laboratoryjnych (parametry morfologiczne i biochemiczne), wyniki badań obrazowych oraz skuteczność leczenia przeciwwirusowego. Wyniki tych badań przedstawiono w formie dwóch prac oryginalnych oraz jednej pracy przeglądowej - wszystkie z moim pierwszym autorstwem.

Pierwsza praca oryginalna pt. „**Steatotic liver disease in patients treated for chronic hepatitis B**”, opublikowana w 2025 roku w czasopiśmie Polish Archives of Internal Medicine (IF 4.7, 200 punktów MNiSW), dotyczyła wpływu i częstości współwystępowania SLD na przebieg kliniczny PZWB. Do analizy wykorzystano dane pochodzące z dokumentacji medycznej 273 kolejnych pacjentów leczonych NA w ramach programu lekowego Narodowego Funduszu Zdrowia. Dane zostały zgromadzone retrospektywnie w trzech polskich ośrodkach hepatologicznych: w Klinice Chorób Zakaźnych w Kielcach, Oddziale Chorób Zakaźnych z Pododdziałem Hepatologicznym w Łańcucie oraz Klinice Chorób Zakaźnych i Hepatologii w Białymstoku, w okresie od września 2023 do czerwca 2024 roku. Zgodnie z obowiązującymi przepisami wszyscy hospitalizowani pacjenci wyrazili świadomą zgodę na leczenie szpitalne oraz przetwarzanie danych osobowych. Niniejsze badanie zostało przeprowadzone po uzyskaniu zgody Komisji Bioetycznej Uniwersytetu Jana Kochanowskiego w Kielcach (uchwała nr 57/2024 z dnia 25 lipca 2024 r.). Dostęp do dokumentacji medycznej oraz wykorzystanie danych dotyczących leczenia pacjentów uzyskano za uprzednią zgodą dyrekcji szpitala. Populację objętą analizą podzielono na dwie grupy w zależności od obecności lub braku stłuszczeniowej choroby wątroby, diagnozowanej na podstawie biopsji wątroby lub metod nieinwazyjnych - elastografii przejściowej oraz elastografii fali poprzecznej. Charakterystyka wyjściowa pacjentów obejmowała dane demograficzne, takie jak płeć, wiek i wskaźnik masy ciała (ang. Body Mass Index, BMI), a także choroby współistniejące, koinfekcje innymi wirusami (HCV, HIV - ang. Human Immunodeficiency Virus), wywiad dotyczący nadużywania alkoholu oraz historię incydentów dekompensacji wątroby, w tym encefalopatii wątrobowej i obecności żylaków przełyku. Dane zbierano zarówno na początku terapii przeciwwirusowej, jak i podczas wizyt kontrolnych w trakcie leczenia. Spośród 273 kolejnych pacjentów rasy kaukaskiej leczonych NA z powodu PZWB, u 86 pacjentów (31,5%) rozpoznano współistniejącą SLD. Co istotne, grupy były porównywalne pod względem

mediany wieku (52 vs 50 lat w grupie z SLD i bez SLD, odpowiednio). W obu subpopulacjach dominowali mężczyźni, jednak w grupie z SLD przewaga ta była wyraźniejsza (77,9% vs 63,6%; $p = 0,02$). Choć odsetek pacjentów z marskością wątroby nie różnił się istotnie statystycznie między grupami, był wyższy w subpopulacji z SLD (16,3% vs 11,8%). Pacjenci z SLD charakteryzowali się istotnie większym obciążeniem chorobami współistniejącymi (66,3% vs 39,6%; $p < 0,001$). Różnice statystycznie istotne dotyczyły częstości występowania cukrzycy ($p = 0,004$), dny moczanowej ($p = 0,03$) oraz otyłości ($p < 0,001$), które występowały częściej w grupie pacjentów z SLD. Ponadto, znacznie wyższy odsetek chorych z SLD cechował się BMI >30 kg/m² w porównaniu do pacjentów bez SLD (39,5% vs 8%). Pojedyncze przypadki dekompensacji czynności wątroby występowały w obu grupach, jednak bez istotnych różnic statystycznych. Odsetek pacjentów uprzednio leczonych przeciwwirusowo był istotnie niższy w grupie z SLD (36% vs 50,8% w grupie bez SLD), przy czym w obu grupach najczęściej stosowanym wcześniej lekiem była lamiwudyna. Czas trwania aktualnej terapii NA do momentu analizy był krótszy w populacji z SLD (mediana 5,0 vs 6,0 lat), choć różnica nie osiągnęła istotności statystycznej. Wyjściowe miano HBV DNA było porównywalne między grupami, natomiast odsetek pacjentów HBeAg-dodatnich był istotnie niższy w grupie z SLD ($p = 0,004$). Aktywność biochemiczna choroby, wyrażona medianą aktywności aminotransferaz, była wyraźnie wyższa wśród pacjentów z SLD w porównaniu do osób bez stłuszczenia (ALT: 47 vs 30 IU/l, $p < 0,001$; AST: 38 vs 28 IU/l, $p = 0,004$). Parametry czynności wątroby, takie jak stężenie bilirubiny i wskaźnik INR (ang. International Normalized Ratio), były zbliżone w obu grupach, natomiast stężenie albumin było istotnie niższe u pacjentów z SLD (4,2 vs 4,3 g/dl; $p = 0,02$). Niezależnie od obserwowanych różnic między grupami, ponad 97% pacjentów z obu populacji osiągnęło eliminację HBV DNA w trakcie aktualnej terapii NA. W obu subpopulacjach odnotowano również istotną poprawę biochemiczną w postaci spadku aktywności ALT - z 47 do 29,5 IU/l ($p < 0,001$) w grupie z SLD oraz z 30 do 26 IU/l ($p < 0,001$) w grupie bez SLD. Pomimo wyższej wyjściowej aktywności enzymów wątrobowych wśród pacjentów z SLD, odpowiedź wirusologiczna i skuteczność leczenia były porównywalne w obu grupach.

Druga praca oryginalna z moim pierwszym autorstwem, wchodząca w skład cyklu tworzącego rozprawę doktorską, nosi tytuł „**Steatotic liver disease in patients with chronic hepatitis C**” i została opublikowana w 2025 roku w czasopiśmie World Journal of Hepatology (IF 2,5; 100 punktów MNiSW). Celem analizy była ocena częstości i wpływu współistniejącej SLD na przebieg kliniczny i efekty leczenia PZWC. Dane zgromadzono retrospektywnie w Klinice Chorób Zakaźnych w Kielcach, a analizą objęto kolejnych 688 pacjentów z PZWC,

stanowiących jednocześnie wszystkich pacjentów leczonych z powodu PZWC od momentu wprowadzenia do praktyki klinicznej w Polsce pangenotypowych schematów leczenia tj, od lipca 2018 roku do grudnia 2024 roku. Wszyscy chorzy otrzymali pangenotypowe leki o bezpośrednim działaniu przeciwwirusowym w ramach programu lekowego Narodowego Funduszu Zdrowia. Dane pochodziły z dokumentacji medycznej i obejmowały dane kliniczne oraz wyniki badań dodatkowych, w tym laboratoryjnych, obrazowych i wirusologicznych. Dane zbierano retrospektywnie i obejmowały one informacje z początku leczenia i wizyt kontrolnych wymaganych w ramach programu terapeutycznego. Dokumentacja z momentu rozpoczęcia terapii zawierała dane demograficzne i kliniczne, w tym informacje dotyczące chorób współistniejących i stosowanego leczenia, historii wcześniejszej terapii przeciwwirusowej, koinfekcji HBV lub HIV, danych o aktualnym lub przebyłym nadużywaniu alkoholu lub substancji psychoaktywnych, rozpoznaniu HCC oraz transplantacji wątroby. Stopień zaawansowania choroby wątroby oceniano za pomocą metody nieinwazyjnej elastografii fali poprzecznej. Ocenę sztywności wątroby uzupełniano wyliczeniem wskaźników surowiczych FIB-4 (ang. Fibrosis-4 index) i APRI (ang. AST to Platelet Ratio Index). Rozpoznanie SLD ustalano na podstawie obecności stłuszczenia wątroby w badaniu ultrasonograficznym jamy brzusznej wykonywanym u wszystkich pacjentów podczas wizyty wstępnej. Spośród 688 pacjentów rasy kaukaskiej leczonych pangenotypowymi DAA z powodu PZWC, u 290 osób (42,2%) rozpoznano SLD; wśród chorych zakażonych genotypem 3 HCV odsetek ten wyniósł ponad 62%. Mediana wieku w grupie z SLD była istotnie wyższa niż u pacjentów bez SLD ($p = 0,0007$), a odsetek osób powyżej 50. roku życia wynosił odpowiednio 54,5% vs 41,7%. W populacji z SLD dominowali mężczyźni, natomiast w grupie bez SLD przeważały kobiety (59%). Pacjenci z SLD charakteryzowali się istotnie wyższą medianą BMI (26,5 vs 24,6; $p < 0,0001$), przy czym aż 62,4% osób w tej grupie miało BMI powyżej 25 kg/m², co wskazuje na wysoką częstość nadwagi i otyłości w tej grupie pacjentów. Chorzy z SLD byli również istotnie bardziej obciążeni chorobami współistniejącymi ($p = 0,0014$), zwłaszcza cukrzycą, hipercholesterolemią i otyłością. Istotnie częściej zgłaszali oni także nadużywanie alkoholu (23,1% vs 3,8%; $p < 0,0001$), przy czym spośród 82 osób z dodatnim wywiadem w tym zakresie aż 81,7% należało do grupy z SLD. Pacjenci z SLD wykazywali istotnie wyższą aktywność aminotransferaz (ALT i AST; $p < 0,0001$ dla obu) oraz GGTP, niższą liczbę płytek krwi, a także gorsze inne parametry funkcji wątroby: wyższe stężenie bilirubiny, niższe stężenie albumin oraz wyższy wskaźnik INR. Odsetek pacjentów wcześniej nieleczonych przeciwwirusowo był istotnie niższy w grupie z SLD, natomiast brak odpowiedzi na wcześniejsze leczenie interferonem lub DAA był częstszy właśnie w tej

populacji. Najczęściej stosowanym schematem terapeutycznym w grupie SLD był sofosbuwir/welpataswir (SOF/VEL) z lub bez rybawiryny (RBV) (54,5%), natomiast w grupie bez SLD dominował glekaprewir/pibrentaswir (GLE/PIB) - 61,6%. Istotnie większy odsetek pacjentów ze SLD miał w wywiadzie epizody dekompensacji wątroby (wodobrzusze i/lub encefalopatia wątrobowa; 8,6% vs 2,0%; $p = 0,0001$) oraz żylaki przełyku ($p < 0,0001$). Częstość zakażenia genotypem 3 HCV była znamiennej wyższa w grupie z SLD (24,5% vs 10,8%), choć w obu grupach dominował genotyp 1b, który jest genotypem występującym najczęściej w populacji światowej. W ocenie stopnia włóknienia według skali METAVIR odsetek pacjentów z marskością wątroby (F4) był istotnie większy w grupie z SLD (35,8% vs 12,0%; $p < 0,0001$). Podobny trend odnotowano w analizie wskaźników biochemicznych - APRI ≥ 1 występował u 46,6% pacjentów z SLD vs 19,1% bez SLD, natomiast FIB-4 $> 2,67$ odpowiednio u 43,5% vs 19,1%. Dodatkowo, HCC rozpoznano częściej u pacjentów z SLD (3,4% vs 1,0%; $p = 0,0299$). Skuteczność terapii DAA była istotnie niższa w grupie ze SLD zarówno w analizie ITT (ang. intention-to-treat), jak i PP (ang. per-protocol). W analizie ITT trwałą odpowiedź wirusologiczną (ang. Sustained Virologic Response, SVR) uzyskało 91,0% pacjentów z SLD w porównaniu do 98,2% w grupie bez SLD ($p < 0,0001$). W analizie PP wskaźniki SVR wynosiły odpowiednio 95,6% i 99,0% ($p = 0,0025$). Pacjenci z SLD częściej doświadczali ciężkich działań niepożądanych ($p = 0,0054$), głównie niezwiązanych bezpośrednio z wątrobą. Działania niepożądane o szczególnym znaczeniu klinicznym - takie jak wodobrzusze i encefalopatia wątrobowa - również występowały istotnie częściej w tej grupie. Śmiertelność była wyższa wśród pacjentów z SLD (3,8% vs 1,0%; $p = 0,0168$). Spośród całej badanej populacji 13 pacjentów nie uzyskało trwałej odpowiedzi wirusologicznej. Większość z nich stanowili mężczyźni (92,3%), charakteryzujący się wyższym BMI i gorszymi parametrami biochemicznymi w porównaniu z osobami, które osiągnęły SVR. Wśród pacjentów nieodpowiadających na leczenie ponad połowa (53,8%) było zakażonych genotypem 3 HCV. Analiza wieloczynnikowa wykazała, że zakażenie genotypem 3 oraz obecność marskości wątroby stanowią niezależne czynniki predykcyjne niepowodzenia leczenia u chorych z PZWC ($p = 0,0234$ i $p = 0,0046$, odpowiednio). Pacjenci z rozpoznaną stłuszczeniową chorobą wątroby byli starsi, mieli wyższy BMI, częściej występowały u nich choroby współistniejące, zakażenie HCV genotypem 3 oraz bardziej zaawansowane włóknienie wątroby w porównaniu z osobami bez SLD. Czynniki te wiązały się z istotnie niższą skutecznością leczenia DAA. Wyniki badania podkreślają znaczenie rutynowej oceny występowania SLD u osób zakażonych HCV - nie tylko jako choroby współistniejącej, lecz także jako istotnego modyfikatora odpowiedzi na leczenie i rokowania klinicznego.

Trzecia publikacja, będąca pracą przeglądową, również mojego pierwszego autorstwa, nosi tytuł „**Steatotic liver disease and chronic viral hepatitis**” i stanowi zamknięcie cyklu badań składających się na niniejszą rozprawę doktorską. Artykuł został opublikowany w 2025 roku w czasopiśmie *Clinical and Experimental Hepatology* (IF 1,7; 20 punktów MNiSW). Praca ta stanowi podsumowanie oraz przegląd aktualnej literatury światowej, a jednocześnie syntetyzuje najważniejsze informacje dotyczące wpływu SLD na przebieg i wyniki leczenia pacjentów z PZWB i PZWC. Jej celem był przegląd danych z literatury światowej na temat SLD u chorych z wirusowymi zapaleniami wątroby.

Stłuszczenie wątroby jest częstym zjawiskiem histopatologicznym obserwowanym u pacjentów z PZWB, a jego częstość waha się od 14% do 70% [10]. Dotychczas jednak nie wykazano jednoznacznych dowodów na to, że samo zakażenie HBV zwiększa ryzyko wystąpienia stłuszczenia. Metaanaliza obejmująca 4100 pacjentów zakażonych HBV wykazała, że częstość SLD wynosi 29,6%, co jest zgodne z obserwowanymi trendami w populacji ogólnej [12]. Oznacza to, że stłuszczenie u pacjentów z PZWB wynika głównie z czynników metabolicznych, a nie z samej infekcji wirusowej. Co interesujące, liczne badania wykazały odwrotną zależność między poziomem HBV DNA a nasileniem stłuszczenia, sugerując możliwy efekt ochronny infekcji HBV wobec rozwoju SLD [13]. Wyższy stopień stłuszczenia był niezależnie związany z niższym poziomem HBV DNA w surowicy, co może wskazywać na supresyjny wpływ stłuszczenia na replikację wirusa [14]. SLD może rozwijać się w każdym wieku, jednak ze względu na rosnącą częstość czynników metabolicznych wraz z wiekiem, pacjenci z PZWB i współistniejącą SLD są zazwyczaj starsi niż osoby z grup kontrolnych [15,16]. Istotną rolę odgrywa także płeć - estrogeny wywierają działanie ochronne u kobiet, opóźniając rozwój SLD [15,16]. Niezależnie od leczenia, zarówno wysoki wskaźnik BMI, jak i otyłość, stanowią czynniki ryzyka rozwoju stłuszczenia wątroby [14]. W grupie pacjentów nieleczonych obecność SLD wiązała się dodatkowo z wyższym ryzykiem występowania zespołu metabolicznego [14]. Zależność pomiędzy przewlekłym zakażeniem HBV a SLD jest złożona i wciąż stanowi przedmiot intensywnych badań. Wykazano, że SLD wiąże się ze zwiększoną aktywnością immunologiczną, w tym z nasileniem ekspresji genów związanych z limfocytami Th17 oraz wzrostem poziomu interleukiny 21, co prowadzi do zwiększonej produkcji cytokin zapalnych, ograniczenia replikacji HBV i eliminacji DNA HBV oraz antygeny HBeAg [17]. Mimo niższej aktywności wirusologicznej, pacjenci z jednoczesnym PZWB i SLD często wykazują szybszą progresję choroby wątroby niż osoby z izolowanym zakażeniem HBV lub samą SLD [18]. Zjawisko to tłumaczy tzw. „hipoteza dwóch uderzeń”,

według której infekcja wirusowa stanowi pierwsze „uderzenie”, prowadzące do pierwotnego uszkodzenia wątroby, natomiast współistniejące stłuszczenie i zapalenie - drugie „uderzenie” - nasilające stan zapalny, włóknienie i przyspieszające progresję choroby.

Zakażenie wirusem HCV pozostaje istotnym problemem zdrowia publicznego na świecie. Według danych Światowej Organizacji Zdrowia (ang. World Health Organization, WHO) około 50 milionów osób żyje obecnie z przewlekłą infekcją HCV, co czyni ją jedną z głównych przyczyn przewlekłej choroby wątroby, marskości i HCC [8]. Stłuszczenie wątroby występuje u 45-79% pacjentów z PZWC, co stanowi odsetek istotnie wyższy niż w populacji ogólnej [6]. Rozwój stłuszczenia wątroby u pacjentów z PZWC jest warunkowany przez liczne czynniki ryzyka, które można podzielić na dwie grupy - wirusowe i metaboliczne. Stłuszczenie uwarunkowane czynnikami wirusowymi wynika przede wszystkim z bezpośredniego wpływu HCV, zwłaszcza genotypu 3, na metabolizm lipidów [7]. Istotną rolę odgrywają również czynniki metaboliczne, z których kluczową jest insulinooporność [7]. Stanowi ona konsekwencję zakażenia HCV i prowadzi do zwiększonej produkcji glukozy w wątrobie, zmniejszenia oksydacji lipidów i nasilonego gromadzenia tłuszczu w hepatocytach [7]. Jednym z najważniejszych metabolicznych czynników ryzyka w PZWC jest T2DM. Metaanaliza 34 badań epidemiologicznych wykazała, że zakażenie HCV zwiększa ryzyko rozwoju T2DM o około 68% w porównaniu z osobami niezakażonymi [19]. Nadwaga i otyłość, zwłaszcza typu brzusznej, są znacznie częstsze u pacjentów ze stłuszczeniem wątroby [19]. Spożycie alkoholu, nawet w ilościach niespełniających definicji nadużywania, może dodatkowo pogarszać przebieg choroby, zwiększając ryzyko powikłań, w tym marskości wątroby, a u osób uzależnionych - szczególnie u kobiet - również śmiertelność [20]. Chociaż czynniki metaboliczne odgrywają kluczową rolę w patogenezie SLD u chorych z WZWC, czynniki wirusowe, zwłaszcza genotyp HCV, również pozostają istotne. Pacjenci zakażeni genotypem 3 HCV są około pięciokrotnie bardziej narażeni na rozwój umiarkowanego lub ciężkiego stłuszczenia wątroby w porównaniu z zakażonymi innymi genotypami [21]. Patogeneza stłuszczenia związanego z HCV obejmuje szereg zaburzeń w metabolizmie lipidów, takich jak: upośledzone wydzielanie VLDL, zwiększoną aktywność syntazy kwasów tłuszczowych, nadekspresję czynnika SREBP-1 (ang. Sterol Regulatory Element-Binding Protein 1), zmniejszoną aktywność mikrosomalnego białka przenoszącego trójglicerydy (ang. Microsomal Triglyceride Transfer Protein, MTP) oraz obniżoną ekspresję receptora aktywowanego przez proliferatory peroksysomów alfa (ang. Peroxisome Proliferator-Activated Receptor alpha, PPAR- α) [22]. W erze terapii interferonowych obecność stłuszczenia wątroby była uznawana

za istotny czynnik niepowodzenia leczenia u pacjentów z PZWC [23]. Wprowadzenie leków DAA diametralnie zmieniło jednak obraz leczenia HCV. Terapie te pozwalają na uzyskanie bardzo wysokich odsetków SVR w różnych grupach pacjentów, sprawiając, że czynniki wcześniej uznawane za niekorzystne prognostycznie, takie jak SLD czy insulinooporność, utraciły swoje znaczenie kliniczne [24]. Analiza danych polskich pacjentów z bazy EpiTer-2 wykazała, że mimo różnic w BMI, rozkładzie genotypów i chorobach współistniejących, skuteczność leczenia DAA była równie wysoka u pacjentów z i bez stłuszczenia wątroby [25]. Wyniki te potwierdziły także duże badanie kohortowe obejmujące ponad osiem tysięcy pacjentów z Niemiec, w którym odsetek uzyskanej odpowiedzi wirusologicznej przekraczał 96% niezależnie od obecności SLD [26]. Co interesujące, uzyskane wyniki różniły się od obserwacji pochodzących z naszych wcześniejszych badań. W analizie ITT SVR osiągnęło 91,0% pacjentów z rozpoznaną SLD w porównaniu z 98,2% w grupie bez SLD ($p < 0,0001$). W analizie PP odsetki te wynosiły odpowiednio 95,6% i 99,0% ($p = 0,0025$). Należy jednak podkreślić, że przeprowadzona analiza wieloczynnikowa wykazała, iż czynnikami bezpośrednio związanymi z gorszymi wynikami leczenia były zakażenie genotypem 3 wirusa HCV oraz obecność marskości wątroby, a nie samo współistnienie SLD. Ostatecznie, uzyskane dane potwierdzają, że w dobie terapii opartej na lekach o bezpośrednim działaniu przeciwwirusowym stłuszczeniowa choroba wątroby nie stanowi już istotnego czynnika ryzyka niepowodzenia leczenia. Niemniej jednak pozostaje ona ważnym elementem kompleksowej oceny klinicznej pacjentów z przewlekłym zakażeniem wirusem HCV, mogącym wpływać na przebieg choroby i długoterminowe rokowanie.

Wnioski końcowe:

1. Częstość występowania stłuszczeniowej choroby wątroby u pacjentów z PZWB jest porównywalna z częstością obserwowaną w populacji ogólnej i wynosi około 31%. Obecność SLD u chorych z PZWB wynika głównie z metabolicznych czynników ryzyka, takich jak otyłość i cukrzyca typu 2 i wiąże się z większym obciążeniem chorobami współistniejącymi oraz wyższą aktywnością aminotransferaz. Jednocześnie współistnienie SLD nie wpływa negatywnie na skuteczność długotrwałej terapii analogami nukleozydów/nukleotydu, mierzoną eliminacją HBV DNA.
2. U pacjentów z PZWC stłuszczeniowa choroba wątroby występuje częściej niż w populacji ogólnej, z częstością około 42%, a jej obecność związana jest zarówno z czynnikami metabolicznymi, jak i wirusowymi, w szczególności zakażeniem genotypem 3 HCV. SLD u chorych z PZWC częściej współistnieje z zaawansowanym włóknieniem lub marskością wątroby, gorszym profilem biochemicznym oraz epizodami dekomensacji czynności wątroby. Niższa skuteczność terapii przeciwwirusowej DAA wynika przede wszystkim z niezależnego wpływu marskości oraz zakażenia genotypem 3 HCV, a nie z samej obecności SLD.
3. Pacjenci z przewlekłym wirusowym zapaleniem wątroby typu B i C powinni być rutynowo oceniani w kierunku obecności SLD oraz modyfikowalnych czynników ryzyka metabolicznego. W PZWC ze współistniejącym stłuszczeniem wątroby wskazany jest nadzór kliniczny również po zakończeniu skutecznej terapii przeciwwirusowej. Uzyskane dane oparte na rzeczywistej praktyce klinicznej wypełniają istotną lukę w literaturze europejskiej i stanowią podstawę do dalszych badań prospektywnych, wielośrodkowych, z ujednoczoną oceną SLD, pozwalających precyzyjniej określić jej wpływ na długoterminowe rokowanie oraz optymalizację strategii terapeutycznych.

Bibliografia

- 1 Amini-Salehi E, Letafatkar N, Norouzi N, et al. Global prevalence of nonalcoholic fatty liver disease: An updated review meta-analysis comprising a population of 78 million from 38 countries. *Arch Med Res.* 2024; 55: 103043.
- 2 Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology.* 2023; 78: 1966-1986.
- 3 Gorczyca-Głowacka I, Wełnicki M, Mamcarz A, et al. Metabolic associated fatty liver disease and cardiovascular risk: The expert opinion of the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society. *Kardiol Pol.* 2023; 81: 207-214.
- 4 Le MH, Yeo YH, Li X, et al. 2019 global NAFLD prevalence: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2022; 20: 2809-2817.e28.
- 5 Lee M-H, Chen Y-T, Huang Y-H, et al. Chronic viral hepatitis B and C outweigh MASLD in the associated risk of cirrhosis and HCC. *Clin Gastroenterol Hepatol.* 2024; 22: 1275-1285.e2.
- 6 Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol.* 2018; 69: 896-904.
- 7 Negro F. Facts and fictions of HCV and comorbidities: steatosis, diabetes mellitus, and cardiovascular diseases. *J Hepatol.* 2014; 61: S69-78.
- 8 Hepatitis C. <https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>.
- 9 Dobrowolska K, Brzdęk M, Rzymiski P, et al. Revolutionizing hepatitis C treatment: next-gen direct-acting antivirals. *Expert Opin Pharmacother.* 2024; 25: 833-852.
- 10 Baclig MO, Reyes KG, Liles VR, et al. Hepatic steatosis in chronic hepatitis B: a study of metabolic and genetic factors. *Int J Mol Epidemiol Genet.* 2018; 9: 13-19.
- 11 Hepatitis B. <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>.
- 12 Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. *J Gastroenterol Hepatol.* 2011; 26: 1361-1367.
- 13 Yi S, Ren G, Zhu Y, Cong Q. Correlation analysis of hepatic steatosis and hepatitis B virus: a cross-sectional study. *Virol J.* 2024; 21: 22.

- 14 Hui RWH, Seto W-K, Cheung K-S, et al. Inverse relationship between hepatic steatosis and hepatitis B viremia: Results of a large case-control study. *J Viral Hepat.* 2018; 25: 97-104.
- 15 Wong S-W, Chan W-K, Mohamed R. Fatty liver is associated with advanced fibrosis but does not predict adverse outcomes in patients with chronic hepatitis B. *J Viral Hepat.* 2020; 27: 1297-1305.
- 16 Cheng Y-M, Hsieh T-H, Wang C-C, Kao J-H. Impact of HBV infection on clinical outcomes in patients with metabolic dysfunction-associated fatty liver disease. *JHEP Rep.* 2023; 5: 100836.
- 17 Tang L, Chen C, Gao X, et al. Interleukin 21 reinvigorates the antiviral activity of hepatitis B virus (HBV)-specific CD8⁺ T cells in chronic HBV infection. *J Infect Dis.* 2019; 219: 750-759.
- 18 Lv H, Jiang Y, Zhu G, et al. Liver fibrosis is closely related to metabolic factors in metabolic associated fatty liver disease with hepatitis B virus infection. *Sci Rep.* 2023; 13: 1388.
- 19 White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *J Hepatol.* 2008; 49: 831-844.
- 20 Llamosas-Falcón L, Shield KD, Gelovany M, et al. Impact of alcohol on the progression of HCV-related liver disease: A systematic review and meta-analysis. *J Hepatol.* 2021; 75: 536-546.
- 21 Leandro G, Mangia A, Hui J, et al. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology.* 2006; 130: 1636-1642.
- 22 Adinolfi LE, Rinaldi L, Guerrera B, et al. NAFLD and NASH in HCV infection: Prevalence and significance in hepatic and extrahepatic manifestations. *Int J Mol Sci.* 2016; 17: 803.
- 23 Poynard T, Ratziu V, McHutchison J, et al. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. *Hepatology.* 2003; 38: 75-85.
- 24 Brzdęk M, Zarębska-Michaluk D, Invernizzi F, et al. Decade of optimizing therapy with direct-acting antiviral drugs and the changing profile of patients with chronic hepatitis C. *World J Gastroenterol.* 2023; 29: 949-966.
- 25 Flisiak R, Zarębska-Michaluk D, Dobrowolska K, et al. Treatment of HCV infection in patients with steatotic liver disease. *Clin Exp Hepatol.* 2024; 10: 159-164.

- 26 Rau M, Buggisch P, Mauss S, et al. Prognostic impact of steatosis in the clinical course of chronic HCV infection-Results from the German Hepatitis C-Registry. PLoS One. 2022; 17: e0264741.

Streszczenie w języku polskim

Wstęp

SLD jest obecnie najczęstszą przyczyną przewlekłej choroby wątroby na świecie, a jej częstość stale rośnie w związku z epidemią otyłości i cukrzycy. Współistnienie SLD z przewlekłymi zakażeniami wirusami hepatotropowymi HBV i HCV może modyfikować przebieg kliniczny choroby, skuteczność leczenia przeciwwirusowego i rokowanie. Pomimo dużego znaczenia klinicznego, dane dotyczące tej zależności w populacji europejskiej, w tym polskiej, pozostają ograniczone.

Cel rozprawy

Celem niniejszej rozprawy była ocena częstości występowania, uwarunkowań klinicznych i wpływu współistniejącej stłuszczeniowej choroby wątroby na przebieg oraz skuteczność leczenia PZWB i PZWC w warunkach codziennej praktyki klinicznej.

Material i metodyka

Analiza obejmowała dwa badania oryginalne, których uzupełnieniem była jedna praca przeglądowa. W pierwszym badaniu retrospektywnym oceniono 273 pacjentów z PZWB leczonych NA w trzech polskich ośrodkach hepatologicznych. W drugim badaniu analizowano dane 688 pacjentów z PZWC leczonych DAA w latach 2018-2024. W obu badaniach porównywano pacjentów z i bez współistniejącej SLD w zakresie danych demograficznych, klinicznych, biochemicznych, obrazowych i skuteczności leczenia.

Wyniki

W grupie PZWB stłuszczenie występowało u 31,5% pacjentów i było związane z otyłością, cukrzycą oraz wyższą aktywnością aminotransferaz. Nie wpływało jednak na skuteczność długotrwałej terapii NA, mierzoną eliminacją HBV DNA. W PZWC SLD stwierdzono u 42,2% pacjentów, najczęściej wśród zakażonych genotypem 3 HCV. Chorzy ci częściej mieli zaawansowane włóknienie, gorsze parametry funkcji wątroby i epizody dekompensacji. Wskaźniki SVR były niższe w grupie z SLD (91% vs 98,2% w analizie ITT), jednak analiza wieloczynnikowa wykazała, że czynnikami niezależnie związanymi z niepowodzeniem leczenia były genotyp 3 i marskość wątroby, a nie sama obecność SLD.

Wnioski

Stłuszczeniowa choroba wątroby jest częstym zjawiskiem u pacjentów z przewlekłymi wirusowymi zapaleniami wątroby typu B i C, szczególnie u osób z zaburzeniami metabolicznymi. W PZWB SLD nie wpływa istotnie na skuteczność terapii przeciwwirusowej, natomiast w PZWC może współwystępować z bardziej zaawansowanym uszkodzeniem wątroby i niekorzystnym profilem klinicznym. Pacjenci z przewlekłym WZW B i C powinni być rutynowo oceniani pod kątem SLD oraz modyfikowalnych czynników ryzyka metabolicznego. Uzyskane dane oparte na realnej praktyce klinicznej wypełniają lukę w literaturze europejskiej i mogą stanowić podstawę do aktualizacji zaleceń klinicznych oraz strategii leczenia chorych z wirusowymi zapaleniami wątroby i współistniejącą SLD.

Streszczenie w języku angielskim

Introduction

SLD is currently the most common cause of chronic liver disease worldwide, and its prevalence continues to rise in connection with the global epidemics of obesity and diabetes. The coexistence of SLD with chronic hepatotropic viral infections caused by HBV and HCV may alter the clinical course of the disease, the effectiveness of antiviral therapy, and long-term prognosis. Despite its major clinical importance, data on this relationship within European populations, including the Polish cohort, remain limited.

Aim of the Study

The aim of this dissertation was to assess the prevalence, clinical determinants, and impact of coexisting SLD on the course and treatment outcomes of CHB and CHC in real-world clinical practice.

Material and Methods

The analysis included two original studies, supplemented by one review article. The first retrospective study evaluated 273 patients with CHB treated with NAs across three Polish hepatology centers. The second study analyzed data from 688 CHC patients treated with pangenotypic DAAs between 2018 and 2024. In both studies, patients with and without coexisting SLD were compared in terms of demographic, clinical, biochemical, imaging, and therapeutic outcome parameters.

Results

In the CHB group, hepatic steatosis was present in 31.5% of patients and was associated with obesity, diabetes, and elevated aminotransferase activity. However, it did not affect the long-term efficacy of NA therapy, as measured by HBV DNA suppression. In the CHC cohort, SLD was identified in 42.2% of patients, most frequently among those infected with HCV genotype 3. These patients more often exhibited advanced fibrosis, poorer liver function parameters, and decompensation episodes. The rate of SVR was lower in patients with SLD (91% vs. 98.2% in ITT analysis); however, multivariate analysis revealed that genotype 3 infection and liver cirrhosis, rather than the presence of SLD itself, were independent predictors of treatment failure.

Conclusions

SLD is a common condition among patients with chronic hepatitis B and C, particularly those with metabolic comorbidities. In CHB, SLD does not significantly affect antiviral treatment efficacy, whereas in CHC, it is often associated with more advanced liver damage and an unfavorable clinical profile. Patients with chronic HBV and HCV infections should be routinely evaluated for SLD and modifiable metabolic risk factors. The data obtained from real-world clinical practice fill an important gap in European literature and may serve as a foundation for updating clinical recommendations and optimizing therapeutic strategies for patients with viral hepatitis and coexisting SLD.

Informacje o charakterze udziału współautorów w publikacjach wraz z szacunkowym określeniem procentowego wkładu

W pracy „*Steatotic liver disease in patients treated for chronic hepatitis B*” Autorów: Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukła-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michaluk, opublikowanej w Polish Archives of Internal Medicine; DOI: 10.20452/pamw.16942.

Imię i nazwisko współautora	Charakter udziału	Wkład procentowy
Jakub Janczura	<ul style="list-style-type: none"> - opracowanie manuskryptu - przygotowanie manuskryptu do submisji - zbieranie danych - redakcja i zatwierdzenie ostatecznej wersji manuskryptu 	60%
Michał Brzdęk	<ul style="list-style-type: none"> - opracowanie manuskryptu - analiza i interpretacja danych - autor korespondencyjny - redakcja i zatwierdzenie ostatecznej wersji manuskryptu 	8%
Krystyna Dobrowolska	<ul style="list-style-type: none"> - opracowanie manuskryptu - zbieranie danych - redakcja i zatwierdzenie ostatecznej wersji manuskryptu 	4%
Robert Flisiak	<ul style="list-style-type: none"> - opracowanie manuskryptu - opracowanie koncepcji pracy 	5%

	- redakcja i zatwierdzenie ostatecznej wersji manuskryptu	
Diana Martonik	- zbieranie danych - redakcja i zatwierdzenie ostatecznej wersji manuskryptu	2%
Kinga Brzdęk	- opracowanie manuskryptu - analiza i interpretacja danych - redakcja i zatwierdzenie ostatecznej wersji manuskryptu	4%
Robert Pleśniak	- zbieranie danych - redakcja i zatwierdzenie ostatecznej wersji manuskryptu	2%
Dominika Kukla-Woźnica	- zbieranie danych - redakcja i zatwierdzenie ostatecznej wersji manuskryptu	2%
Małgorzata Wajdowicz	- opracowanie manuskryptu - redakcja i zatwierdzenie ostatecznej wersji manuskryptu	3%
Dorota Zarębska-Michaluk	- opracowanie manuskryptu - opracowanie koncepcji pracy - zbieranie danych - redakcja i zatwierdzenie ostatecznej wersji manuskryptu	10%

Wszyscy współautorzy wyrazili zgodę na wykorzystanie powyższej publikacji w pracy doktorskiej.

Informacje o charakterze udziału współautorów w publikacjach wraz z szacunkowym określeniem procentowego wkładu

W pracy „*Steatotic liver disease in patients with chronic hepatitis C*” Autorów: Jakub Janczura, Michał Brzdęk, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdęk, Piotr Rzymiski, Dorota Zarębska-Michaluk, opublikowanej w *World Journal of Hepatology*; DOI: 10.4254/wjh.v17.i12.113639.

Imię i nazwisko współautora	Charakter udziału	Wkład procentowy
Jakub Janczura	<ul style="list-style-type: none"> - opracowanie koncepcji pracy - analiza i interpretacja danych - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu 	65%
Michał Brzdęk	<ul style="list-style-type: none"> - przygotowanie tabel i figur - przeprowadzenie analizy statystycznej - przygotowanie manuskryptu do publikacji - analiza i interpretacja danych - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu 	5%
Robert Flisiak	<ul style="list-style-type: none"> - opracowanie koncepcji pracy - analiza i interpretacja danych - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu 	5%

Krystyna Dobrowolska	<ul style="list-style-type: none"> - analiza i interpretacja danych - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu 	5%
Kinga Brzdęk	<ul style="list-style-type: none"> - przygotowanie tabel i figur - analiza i interpretacja danych - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu 	5%
Piotr Rzymki	<ul style="list-style-type: none"> - opracowanie manuskryptu - analiza i interpretacja danych - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu 	5%
Dorota Zarębska-Michaluk	<ul style="list-style-type: none"> - opracowanie koncepcji pracy - analiza i interpretacja danych - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu - autor korespondencyjny 	10%

Wszyscy współautorzy wyrazili zgodę na wykorzystanie powyższej publikacji w pracy doktorskiej.

Informacje o charakterze udziału współautorów w publikacjach wraz z szacunkowym określeniem procentowego wkładu

W pracy „*Steatotic liver disease and chronic viral hepatitis*” Autorów: Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdęk, Kinga Brzdęk, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michaluk, opublikowanej w *Clinical and Experimental Hepatology*; DOI: 10.5114/ceh.2025.154220.

Imię i nazwisko współautora	Charakter udziału	Wkład procentowy
Jakub Janczura	<ul style="list-style-type: none"> - opracowanie koncepcji pracy - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu - przygotowanie figur - autor korespondencyjny - przygotowanie manuskryptu do publikacji 	65%
Alessandra Mangia	<ul style="list-style-type: none"> - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu 	5%
Krystyna Dobrowolska	<ul style="list-style-type: none"> - opracowanie koncepcji pracy - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu 	4%
Michał Brzdęk	<ul style="list-style-type: none"> - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu - przygotowanie figur 	4%
Kinga Brzdęk	<ul style="list-style-type: none"> - przygotowanie figur - opracowanie manuskryptu 	4%

	- zatwierdzenie ostatecznej wersji manuskryptu	
Małgorzata Wajdowicz	- opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu	2%
Iwona Gorczyca-Głowacka	- opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu	2%
Piotr M. Stępień	- opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu	2%
Dorota Zarębska-Michaluk	- opracowanie koncepcji pracy - opracowanie manuskryptu - zatwierdzenie ostatecznej wersji manuskryptu	12%

Wszyscy współautorzy wyrazili zgodę na wykorzystanie powyższej publikacji w pracy doktorskiej.

Oświadczenia współautorów

Dorota Zarębska-Michałuk,
Zakład Chorób Zakaźnych i Alergologii
Uniwersytet Jana Kochanowskiego
Kielce

Kielce, 21.01.2026

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients with chronic hepatitis C**”, Jakub Janczura, Michał Brzdęk, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdęk, Piotr Rzymiski, Dorota Zarębska-Michałuk, World Journal of Hepatology, 2025 mój udział polegał na:

- opracowaniu koncepcji pracy
- analizie i interpretacji danych
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu
- pełnieniu funkcji autora korespondencyjnego

A wkład autorski wyniósł 10%

Prof. dr hab. med. Dorota Zarębska-Michałuk
lekarz chorób wewnętrznych
specjalista chorób zakaźnych
hepatolog 2284330



Podpis

Dorota Zarębska-Michaluk,
Zakład Chorób Zakaźnych i Alergologii
Uniwersytet Jana Kochanowskiego
Kielce

Kielce, 21.01.2026

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease and chronic viral hepatitis**”, Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdęk, Kinga Brzdęk, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michaluk, *Clinical and Experimental Hepatology*, 2025 mój udział polegał na:

- opracowaniu koncepcji pracy
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 12%

*Prof. dr hab. med. Dorota Zarębska-Michaluk
lekarz chorób wewnętrznych
specjalista chorób zakaźnych
hepatolog 2284330*

D. Michaluk

Podpis

Dorota Zarębska-Michaluk,
Zakład Chorób Zakaźnych i Alergologii
Uniwersytet Jana Kochanowskiego
Kielce

Kielce, 21.01.2026

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michaluk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- opracowaniu koncepcji pracy
- zbieraniu danych
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 10%

Prof. dr hab. med. Dorota Zarębska-Michaluk
lekarz chorób wewnętrznych
specjalista chorób zakaźnych
hepatolog 2284330

D. Michaluk

Podpis

Piotr Rzymiski,
Katedra Medycyny Środowiskowej
Uniwersytet Medyczny w Poznaniu
Poznań

Poznań, 21.01.2026

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients with chronic hepatitis C**”, Jakub Janczura, Michał Brzdęk, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdęk, Piotr Rzymiski, Dorota Zarębska-Michaluk, World Journal of Hepatology, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- analizie i interpretacji danych
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 5%



.....
Podpis

Piotr M. Stępień,

Katedra Chorób Zakaźnych i Alergologii

Uniwersytet Jana Kochanowskiego

Kielce

Kielce, 21.01.2026

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease and chronic viral hepatitis**”, Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdęk, Kinga Brzdęk, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michałuk, *Clinical and Experimental Hepatology*, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 2%

Piotr M. Stępień
Lekarz
specjalista chorób zakaźnych
certyfikat hepatologia PT110pat
2619000

Piotr M. Stępień

Podpis

Iwona Gorczyca-Głowacka,

Katedra Psychiatrii

Uniwersytet Jana Kochanowskiego

Kielce

Kielce, 22/01/2026 r.

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease and chronic viral hepatitis**”, Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdęk, Kinga Brzdęk, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stepień, Dorota Zarębska-Michałuk, *Clinical and Experimental Hepatology*, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 2%

Iwona Gorczyca-Głowacka

Podpis

Robert Pleśniak,

Klinika Chorób Zakaźnych z Oddziałem Hepatologii

Wydział Lekarski Uniwersytetu Rzeszowskiego

Rzeszów

Janów, 22/01/2026

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michałuk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- zbieraniu danych
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 2%

dr n.zmed. Robert Pleśniak
Specjalista chorób zakaźnych
7060477

Podpis

Małgorzata Wajdowicz,

Klinika Chorób Zakaźnych z Oddziałem Hepatologii

Wydział Lekarski Uniwersytetu Rzeszowskiego

Rzeszów

Brzadz, 22.01.2026

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michaluk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- zbieraniu danych
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 3%

Małgorzata Wajdowicz

Podpis

Małgorzata Wajdowicz,

Klinika Chorób Zakaźnych z Oddziałem Hepatologii

Collegium Medicum Uniwersytetu Rzeszowskiego

Rzeszów

Rzeszów, 22.01.2026

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease and chronic viral hepatitis**”, Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdęk, Kinga Brzdęk, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michaluk, *Clinical and Experimental Hepatology*, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 2%



Podpis



Krystyna Dobrowolska,
Collegium Medicum
Uniwersytet Jana Kochanowskiego
Kielce

.....
(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease and chronic viral hepatitis**”, Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdęk, Kinga Brzdęk, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michaluk, *Clinical and Experimental Hepatology*, 2025 mój udział polegał na:

- opracowaniu koncepcji pracy
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 4%

.....
Podpis



PODPIS ZAUFANY
KRYSTYNA
DOBROWOLSKA
22.01.2026 04:35:40 GMT+1
Dokument podpisany elektronicznie
podpisem zaufanym

Krystyna Dobrowolska,
Zakład Chorób Zakaźnych i Alergologii
Uniwersytet Jana Kochanowskiego
Kielce

.....
(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients with chronic hepatitis C**”, Jakub Janczura, Michał Brzdęk, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdęk, Piotr Rzymski, Dorota Zarębska-Michaluk, World Journal of Hepatology, 2025 mój udział polegał na:

- analizie i interpretacji danych
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 5%

.....
Podpis



PODPIS ZAUFANY
KRYSTYNA
DOBROWOLSKA
22.01.2020 04:55:40 GMT+1
Document podpisany elektronicznie
podpisem zaufanym

Krystyna Dobrowolska,
Zakład Chorób Zakaźnych i Alergologii
Uniwersytet Jana Kochanowskiego
Kielce

.....
(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michaluk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- zbieraniu danych
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 4%

.....
Podpis

Kinga Brzdek,

Oddział Reumatologii i Chorób Tkanki Łącznej

Szpital im. Mikołaja Kopernika w Łodzi

Łódź

Łódź 21.01.26

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients with chronic hepatitis C**”, Jakub Janczura, Michał Brzdek, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdek, Piotr Rzymiski, Dorota Zarebska-Michaluk, World Journal of Hepatology, 2025 mój udział polegał na:

- przygotowaniu tabel i figur
- analizie i interpretacji danych
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 5%

Kinga Brzdek

Podpis

Kinga Brzdek,

Collegium Medicum

Uniwersytet Jana Kochanowskiego

Kielce

Lodzi 21.01.

(miejsce, data)

Oświadczenie

Oświadczam, że w pracy „*Steatotic liver disease and chronic viral hepatitis*”, Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdek, Kinga Brzdek, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michaluk, *Clinical and Experimental Hepatology*, 2025 mój udział polegał na:

- przygotowaniu figur
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 4%

Kinga Brzdek

Podpis

Kinga Brzdęk,

Oddział Reumatologii i Chorób Tkanki Łącznej

Szpital im. Mikołaja Kopernika

Łódź

Łódź 28.09.26

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janeczura, Michał Brzdęk, Krystyna Dobrowońska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michaluk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- analizie i interpretacji danych
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 4%

Kinga Brzdęk

Podpis



Michał Brzdęk,

Katedra Gastroenterologii

Uniwersytet Medyczny w Łodzi

92-213 Łódź

.....
(miejscowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michaluk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- analizie i interpretacji danych
- pełnieniu funkcji autora korespondencyjnego
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 8%

.....
Podpis



PODPIS ZAUFANY

MICHAŁ
BRZDĘK

21.01.2026 18:33:19 GMT+1

Document signed electronically
with trusted signature

Michał Brzdek,

Collegium Medicum

Uniwersytet Jana Kochanowskiego

Kielce

.....
(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease and chronic viral hepatitis**”, Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdek, Kinga Brzdek, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michaluk, Clinical and Experimental Hepatology, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu
- przygotowaniu figur

A wkład autorski wyniósł 4%

.....
Podpis



Michał Brzdęk,

Katedra Gastroenterologii

Uniwersytet Medyczny w Łodzi

Łódź

.....
(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients with chronic hepatitis C**”, Jakub Janczura, Michał Brzdęk, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdęk, Piotr Rzymiski, Dorota Zarębska-Michaluk, World Journal of Hepatology, 2025 mój udział polegał na:

- przygotowaniu tabel i figur
- przeprowadzeniu analizy statystycznej
- przygotowaniu manuskryptu do publikacji
- analizie i interpretacji danych
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 5%

Alessandra Mangia,

Liver Unit

Fondazione "Casa Sollievo della Sofferenza"

IRCCS San Giovanni Rotondo

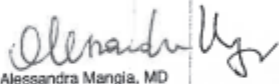
Rotondo

Statement

I declare that in the work "**Steatotic liver disease and chronic viral hepatitis**", Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdęk, Kinga Brzdęk, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michaluk, *Clinical and Experimental Hepatology*, 2025, my contribution consisted of:

- preparing the manuscript
- approving the final version of the manuscript

My contribution amounted to 5%.


Alessandra Mangia, MD

Signature

Dominika Kukła-Woźnica,

Klinika Chorób Zakaźnych z Oddziałem Hepatologii

Wydział Lekarski Uniwersytetu Rzeszowskiego

Rzeszów

Rzeszów, 23.01.2026

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukła-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michałuk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- zbieraniu danych
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 2%

Dominika Kukła-Woźnica

Podpis

Diana Martonik,

Katedra Chorób Zakaźnych i Hepatologii

Uniwersytet Medyczny w Białymstoku

Białystok

Białystok 23.01.26

(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarebska-Michaluk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- zbieraniu danych
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 2%

Diana Martonik

Podpis

Jakub Janczura,

Collegium Medicum

Uniwersytet Jana Kochanowskiego

Kielce

.....
(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients with chronic hepatitis C**”, Jakub Janczura, Michał Brzdęk, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdęk, Piotr Rzymiski, Dorota Zarębska-Michaluk, World Journal of Hepatology, 2025 mój udział polegał na:

- opracowaniu koncepcji pracy
- analizie i interpretacji danych
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 65%



Podpis

Jakub Janczura,

Collegium Medicum

Uniwersytet Jana Kochanowskiego

Kielce

.....
(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease and chronic viral hepatitis**”, Jakub Janczura, Alessandra Mangia, Krystyna Dobrowolska, Michał Brzdęk, Kinga Brzdęk, Małgorzata Wajdowicz, Iwona Gorczyca-Głowacka, Piotr M. Stępień, Dorota Zarębska-Michaluk, Clinical and Experimental Hepatology, 2025 mój udział polegał na:

- opracowaniu koncepcji pracy
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu
- przygotowaniu figur
- pełnieniu funkcji autora korespondencyjnego
- przygotowaniu manuskryptu do publikacji

A wkład autorski wyniósł 65%



Podpis

Jakub Janczura,

Collegium Medicum

Uniwersytet Jana Kochanowskiego

Kielce

.....
(miejsowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarebska-Michaluk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- przygotowaniu manuskryptu do submisji
- zbieraniu danych
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 60%



Podpis

Robert Flisiak,

Katedra Chorób Zakaźnych i Hepatologii

Uniwersytet Medyczny w Białymstoku

Białystok

 **PODPIS ZAUFANY**
ROBERT FLISIAK
28.01.2026 07:57:20 GMT+1
Dokument podpisany elektronicznie
podpisem zaufanym

Białystok / 10.06
(miejscowość, data)

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients with chronic hepatitis C**”, Jakub Janczura, Michał Brzdek, Robert Flisiak, Krystyna Dobrowolska, Kinga Brzdek, Piotr Rzymski, Dorota Zarębska-Michaluk, World Journal of Hepatology, 2025 mój udział polegał na:

- opracowaniu koncepcji pracy
- analizie i interpretacji danych
- opracowaniu manuskryptu
- zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 5%



Podpis

Robert Flisiak,
Katedra Chorób Zakaźnych i Hepatologii
Uniwersytet Medyczny w Białymstoku
Białystok


(miejsowość, data)

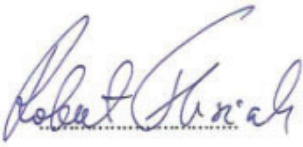

PODPIS ZAUFANY
ROBERT
FLISIAK
28.01.2026 07:54:27 GMT+1
Dokument podpisany elektronicznie
podpisem zaufanym

Oświadczenie

Oświadczam, że w pracy „**Steatotic liver disease in patients treated for chronic hepatitis B**”, Jakub Janczura, Michał Brzdęk, Krystyna Dobrowolska, Robert Flisiak, Diana Martonik, Kinga Brzdęk, Robert Pleśniak, Dominika Kukla-Woźnica, Małgorzata Wajdowicz, Dorota Zarębska-Michaluk, Polish Archives of Internal Medicine, 2025 mój udział polegał na:

- opracowaniu manuskryptu
- opracowaniu koncepcji pracy
- redakcji i zatwierdzeniu ostatecznej wersji manuskryptu

A wkład autorski wyniósł 5%



Podpis

Analiza całego dorobku naukowego

Analiza bibliometryczna publikacji autorstwa Pana Jakuba Janczury*

ORCID ID 0009-0004-7977-9797

I. Oryginalne pełnotekstowe prace naukowe (bez streszczeń zjazdowych i konferencyjnych, prac w suplementach czasopism, listów do redakcji oraz udziału autora wymienionego w dodatku (appendix) jako uczestnika badań wielośrodkowych, recenzji):

A. W czasopismach z Impact Factor:

Rok	Tytuł czasopisma	Liczba prac	JIF Q	IF	Punkty MNISW
2025	Advances in Medical Sciences	1	Q3	2.6	100
2025	BMC Oral Health	1	Q1	3.1	100
2025	Polish Archives of Internal Medicine	1	Q1	4.7	200
2025	World Journal of Hepatology	1	Q2	2.5	100
Łącznie:		4		12.9	500

B. W czasopismach bez Impact Factor:

Rok	Tytuł czasopisma	Liczba prac	Punkty MNISW
2025	Medycyna po dyplomie	1	5
Łącznie:		1	5

Opisy przypadków:

A. W czasopismach z Impact Factor: 0

B. W czasopismach bez Impact Factor:

Rok	Tytuł czasopisma	Liczba prac	Punkty MNISW
2024	Folia Cardiologica	1	40
Łącznie:		1	40

*Na podstawie zweryfikowanej listy publikacji dostarczonej przez Autora.

Prace poglądowe / przeglądowe:

A. W czasopismach z Impact Factor:

Rok	Tytuł czasopisma	Liczba prac	JIF Q	IF	Punkty MNISW
2026	Archives of Virology	1	Q3	2.5	70
2025	Annals of Pharmacotherapy	1	Q3	2.3	100
2025	Archives of Virology	1	Q3	2.5	70
2025	Clinical and Experimental Hepatology	2	Q3	3.4	40
2025	Current Clinical Microbiology Reports	1	Q3	2.7	20
2025	Egyptian Liver Journal	1	Q4	0.7	20
2025	Journal of Diabetes & Metabolic Disorders	1	Q4	1.6	70
2025	Korean Journal of Family Medicine	2	Q1	5.2	40
2025	Livers	1	Q3	2.4	5
2025	Medical Oncology	1	Q2	3.5	70
2025	Pediatric Investigation	1	Q2	2.0	20
2025	World Journal of Gastroenterology	1	Q1	5.4	100
2024	Expert Opinion on Pharmacotherapy	1	Q2	2.7	100
Łącznie:		15		36.9	725

B. W czasopismach bez Impact Factor:

Rok	Tytuł czasopisma	Liczba prac	Punkty MNISW
2026	Clinical Microbiology Newsletter	1	40
2025	Medical Science Pulse	2	80
2025	Medical Science Review. Hepatologia	1	5
2025	Revista Médica del Hospital General de México	1	20
Łącznie:		5	145

II. Oryginalne pełnotekstowe prace naukowe, w których autor wymieniony jest jako uczestnik badań wieloosrodkowych: 0

III. Monografie naukowe (autorstwo lub współautorstwo):

A. W języku obcym: 0

B. W języku polskim: 0

IV. Rozdziały w monografiach naukowych:

A. W języku obcym: 0

B. W języku polskim: 0

Strona 2 z 3

- V. Redakcja wieloautorskiej monografii naukowej:
- A. W języku obcym: 0
 - B. W języku polskim: 0

- VI. Redaktor naczelny czasopisma o zasięgu:
- A. Międzynarodowym: 0
 - B. Krajowym: 0

Informacje dodatkowe:

VII. Streszczenia pokonferencyjne: 0

VIII. Publikacje naukowe niepunktowane: 0

IX. Publikacje popularnonaukowe: 0

Łączna liczba publikacji: 26

Łączna punktacja Impact Factor: 49.8

Łączna punktacja MNISW: 1 415

Liczba cytowań (Web of Science Core Collection):

sumaryczna liczba cytowań: 44

liczba cytowań bez autocytowań: 32

indeks Hirscha: 4

Liczba cytowań (Scopus):

sumaryczna liczba cytowań: 49

liczba cytowań bez autocytowań: 34

indeks Hirscha: 4

Index Hirscha bez autocytowań: 3

X. Artykuły w druku:

Rok	Tytuł czasopisma	Liczba prac	JIF Q	IF	Przewidywana liczba punktów MNISW
2026	World Journal of Hepatology	1	Q2	2.5	100
Łącznie:		1		2.5	100

Wicedyrektor Biblioteki Uniwersyteckiej
ds. Informacji Naukowej, Integracji i Współpracy

mgr Karolina Wicha

Podpis osoby zatwierdzającej

Strona 3 z 3