A SYSTEMATIC REVIEW ON HCV EXTRAHEPATIC MANIFESTATIONS IN THE ASIAN POPULATION

BY

FAMIYAH BINTI ABDUL HAMID

A dissertation submitted in fulfillment of the requirement for the degree Master of Medical Sciences

Kulliyyah of Medicine
International Islamic University Malaysia

JUNE 2025

ABSTRACT

The primary manifestation of hepatitis C is usually hepatotropic; however, it is also associated with a wide range of extrahepatic manifestations, which may affect certain specific organs or multiple organ systems. The symptoms, including metabolic problems, autoimmune illnesses, lymphoproliferative ailments, renal and cardiovascular consequences, and dermatological concerns, significantly increase the total disease burden of hepatitis C. This complicates clinical care and needs a comprehensive and individualized therapeutic strategy to address afflicted individuals' various and linked health issues. HCV extrahepatic manifestations are well-known in Western countries and other developed countries; however, the prevalence of extrahepatic diseases in Southeast Asia is still limited. This systematic review initially investigated the prevalence and patterns of extrahepatic manifestations in HCV-infected individuals in Southeast Asia. However, there was limited literature on the topic in the region; therefore, the scope was widened to include East Asia. The systematic literature review was guided by PRISMA and formulated by PICO: 'P' for Problem or Population, 'I' for Interest, 'Co' for Context, and 'O' for Outcome. After a comprehensive identification and screening of articles, 12 cohort studies, 7 case reports, and one cross-sectional study were selected from Taiwan, Japan, China, Korea, and other multiple countries. The total sample size of the selected article is 255,340 HCV patients, of whom 11,955 exhibited extrahepatic manifestations. Data on the prevalence, disorder, and specific manifestations of extrahepatic manifestations of hepatitis C were analyzed. The analysis focused on the prevalence, disorder, and specific manifestations of extrahepatic manifestations of hepatitis C. The overall prevalence of extrahepatic manifestations stands at 21.69%. Hypertensive cardiovascular disease affected 4,616 HCV patients, showing a prevalence rate of approximately 38.61%. This was followed by hyperlipidemia at 25.39%, diabetes at 23.22%, and chronic kidney disease at 14.60%. A large number of reports originated from Taiwan; however, there is a significant lack of data from Southeast Asia, which highlights a critical gap in regional research that needs to be addressed. Additionally, the data indicates that men (4624) exhibited a greater propensity for developing extrahepatic complications compared to women (4098). Factors that may be associated include underlying disease, smoking, sex, and body mass index. However, there is a lack of information regarding HCV genotype in relation to EHM. In conclusion, this review underscores the systemic impact of HCV infection and should be considered in the evaluation of the disease within clinical management practices. The geographical and gender disparities in the data highlight the necessity for additional research focused on underrepresented populations, especially in Southeast Asia, to enhance our understanding and treatment strategies for HCV-related complications.

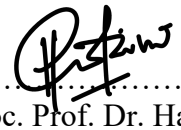
ملخص البحث

عادة ما يكون المظهر الأساسي لالتهاب الكبد سي موجهًا للكبد؛ لذلك فهو يرتبط أيضًا بمجموعة واسعة من مظاهر خارج الكبد، والتي قد تؤثر على أعضاء معينة أو أجهزة أعضاء متعددة. وتؤدي الأعراض، بما في ذلك المشاكل الأيضية، وأمراض المناعة الذاتية، وأمراض تكاثر الخلايا الليمفاوية، والعواقب الكلوية والقلبية والأوعية الدموية، والمخاوف الجلدية، إلى زيادة العبء الإجمالي لمرض التهاب الكبد الوبائي سي بشكل كبير. وهذا يعقد الرعاية السريرية ويحتاج إلى استراتيجية علاجية شاملة وفردية لمعالجة القضايا الصحية المختلفة والمترابطة لدى الأفراد المصابين .إن مظاهر فيروس التهاب الكبد الوبائي سي خارج الكبد معروفة جيداً في الدول الغربية وغيرها من الدول المتقدمة؛ ومع ذلك، فإن انتشار الأمراض خارج الكبد في جنوب شرقي آسيا لا يزال محدوداً. تم توجيه المراجع المنهجية للأدبيات بواسطة **PRISMA** وتم صياغتها بواسطة 'P' :**PICO**' للمشكلة أو السكان، و 'I' للاهتمام، 'Co' للسياق، و 'O' للنتيجة. وبعد تحديد وفحص شامل للمقالات، تم اختيار **12** دراسة أترابية و**7** تقارير حالة ودراسة مقطعية واحدة من تايوان، واليابان، والصين، وكوريا، ودول متعددة أخرى. ويبلغ إجمالي حجم العينة للمقالة المختارة **255,340** مريضًا بفيروس التهاب الكبد الوبائي سي، منهم **11,955** أظهروا مظاهر خارج الكبد. تم تحليل البيانات المتعلقة بانتشار واضطراب والمظاهر المحددة للمظاهر خارج الكبد لالتهاب الكبد الوبائي سي. ركز التحليل على مدى انتشار واضطراب ومظاهر محددة للمظاهر خارج الكبد لالتهاب الكبد سي. ويبلغ معدل الانتشار الإجمالي للمظاهر خارج الكبد **21.69%**. وأثرت أمراض القلب والأوعية الدموية الناجمة عن ارتفاع ضغط الدم على **4,616** مريضًا بفيروس التهاب الكبد الوبائي، مما يدل على معدل

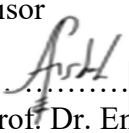
انتشار يبلغ حوالي 38.61%. تتبعها ارتفاع نسبة الدهون في الدم 25.39%، ومرض السكر بنسبة 23.22%، وأمراض الكلى المزمنة بنسبة 14.60%. وقد صدر عدد كبير من التقارير من تايوان؛ على الرغم من ذلك، فإن هناك نقص كبير في البيانات من جنوب شرقي آسيا، مما يسلط الضوء على فجوة حرجة في البحث الإقليمي تحتاج إلى معالجة. إضافة إلى ذلك، تشير البيانات إلى أن الرجال (4624) أظهروا ميلًا أكبر للإصابة بمضاعفات خارج الكبد مقارنة بالنساء (4098). تشمل العوامل التي قد تكون مرتبطة بالمرض الأساسي، والتدخين، والجنس، ومؤشر كتلة الجسم. ولذلك، هناك نقص في المعلومات المتعلقة بالنمط الجيني لفيروس التهاب الكبد الوبائي سي فيما يتعلق بـ EHM. وفي الختام، تؤكد هذه المراجع على التأثير الجهازي لعدوى فيروس التهاب الكبد الوبائي وينبغي أخذها في الاعتبار عند تقييم المرض.

APPROVAL PAGE (MASTER'S DEGREE)

I certify that I have supervised and read this study and that in my opinion, it conforms toacceptable standards of scholarly presentation and is fully adequate, in scope and quality,as a dissertation for the degree of Master of Medical Sciences.



……
Assoc. Prof. Dr. Hairul Aini Hamzah
Supervisor



……
Asst. Prof. Dr. Engku Nuraishah Huda E. Zainudin
Co-Supervisor

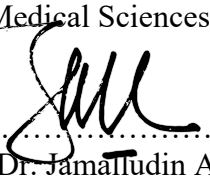
I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Master of of Medical Sciences.

……
Asst. Prof. Dr. Hanan Hamimi Wahid
Internal Examiner

This dissertation was submitted to the Department of Basic Medical Sciences and is accepted as a fulfilment of the requirement for the degree of Master of Medical Sciences.

……
Asst. Prof. Dr. Yusoff Sharizal Yusoff Azmi Merican
Head, Department of Basic Medical Sciences

This dissertation was submitted to the Kulliyyah of Medicine and is accepted as a fulfillment of the requirement for the degree of Master of Medical Sciences.



……
Prof. Dr. Jamalludin Ab Rahman
Dean, Kulliyyah of Medicine

DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Famiyah binti Abdul Hamid

Signature …… Date 27 May 2025

INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA

DECLARATION OF COPYRIGHT AND AFFIRMATION OF FAIR USE OF UNPUBLISHED RESEARCH

A SYSTEMATIC REVIEW ON HCV EXTRAHEPATIC MANIFESTATIONS IN THE ASIAN POPULATION

I declare that the copyright holder of this dissertation are jointly owned by the student and IIUM.

No part of this unpublished research may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without prior written permission of the copyright holder except as provided below

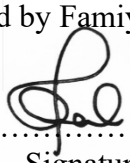
1. Any material contained in or derived from this unpublished research may only be used by others in their writing with due acknowledgement.

2. IIUM or its library will have the right to make and transmit copies (print or electronic) for institutional and academic purpose.

3. The IIUM library will have the right to make, store in a retrieval system and supply copies of this unpublished research if requested by other universities and research libraries.

By signing this form, I acknowledged that I have read and understand the IIUM Intellectual Property Right and Commercialization policy.

Affirmed by Famiyah binti Abdul Hamid



…… 27 May 2025

Signature Date

ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude to Allah SWT for His countless blessings, guidance, and strength throughout my Master's degree journey. Without His mercy and grace, none of this would have been possible. Alhamdulillah, for giving me the patience and perseverance to reach this milestone.

To my parents, thank you for your unconditional love, support, and endless prayers. Your sacrifices and encouragement have been the foundation upon which I have built this achievement. I am forever grateful for everything you have done for me, and I owe so much to your constant belief in me.

To my family, I extend my heartfelt appreciation for always being there for me, offering your support and encouragement in countless ways. Your love and understanding helped carry me through the challenges, and I am blessed to have such a strong and supportive family.

To my special person, I cannot thank you enough for your unwavering support, patience, and belief in me. You have been my pillar of strength throughout this journey, sharing in both the struggles and the triumphs. Thank you for being by my side and for your understanding during the most difficult times.

I would also like to extend my sincere thanks to my supervisor, Assoc Prof Dr Hairul Aini Binti Hamzah for your guidance, insight, and encouragement throughout my studies. Your support and feedback have been invaluable, and I am deeply appreciative of the time and effort you dedicated to helping me grow and succeed.

I also like to thank to my co-supervisor, Dr. Engku Nuraishah Huda binti E. Zainudin, whose assistance and collaboration made this study possible. Last but not least, I would like to thank Dr Hanan Hamimi binti Wahid, all of the lecturers, staffs and supporting members who contributed their time, energy, and assistance to this project.

This achievement is a reflection of the support and love I have received from all of you. I am truly blessed and forever grateful. Once again, we praise Allah for His unending mercies on us, one of which is allowing us to successfully complete the efforts of writing this thesis. Alhamdulillah

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

APA	American Psychological Association
BCCDC	BC Centre For Disease Control
CDC	U.S Centres for Disease Control and Prevention
CHC	Hepatocellular Carcinoma
DAAs	Direct-Acting Antivirals
DCV/ASV	Daclatasvir (DCV)/Asunaprevir (ASV)
EHM	Extrahepatic manifestations
EMC	Essential Mixed Cryoglobulinemia
GN	Glomerulonephritis
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
ICD-9 CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IR	Insulin Resistance
ISGs	Interferon-Stimulated Genes
JBI	Joanna Briggs Institute
MC	Mixed Cryoglobulinemia
MPGN	Membranoproliferative Glomerulonephritis
NHI	National Health Insurance
NHL	Non-Hodgkin's Lymphomas
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RNA	Ribonucleic Acid
SEA	Southeast Asia
SLR	Systematic Literature Review
T2DM	Type 2 Diabetes

WHO	World Health Organization
AST	Aspartate Aminotransferase
ALT	Alanine Transaminase
eGFR	estimated Glomerular Filtration Rate
DCP	des-γ-carboxy prothrombin
AFP	serum Alpha-Fetoprotein

CHAPTER ONE

INTRODUCTION

1.1 HEPATITIS C

Hepatitis C is a liver infection caused by hepatitis C virus (HCV) which can be acute (less than 6 months) or chronic. It is a bloodborne infection that is mostly acquired from unsafe injection procedures, hazardous medical treatment, unscreened blood transfusions, injectable drug usage, and sexual activities (WHO, 2024). Comprehending the global burden of Hepatitis C is essential for understanding its transmission modes, which is critical for developing effective prevention strategies.

Worldwide, around 50 million individuals are affected by chronic hepatitis C, with approximately 1.0 million new infections happening each year. WHO estimates that over 242,000 people died from hepatitis C in 2022; most of the fatalities were ascribed to cirrhosis and hepatocellular cancer (WHO, 2024). Hepatitis C's geographic spread exposes significant incidence of the disease in Eastern Mediterranean and certain areas of Africa. With a startling 12 million individuals suffering from chronic illness, the Eastern Mediterranean Region has the highest burden of disease. Whereas the Region of the Americas has a rate of five million (WHO, 2024), the African Region boasts a chronic infection rate of eight million people. As seen in Figure 1, chronic infections also affect people in Southeast Asia (9 million), Europe (9 million), and the Western Pacific (7 million). Mostly from cirrhosis and hepatocellular carcinoma (HCC), there were around 290,000 deaths globally linked to HCV in 2019. HCV was responsible for 15.3 million global disability-adjusted life years (DALYs), with acute hepatitis, cirrhosis, and liver cancer contributing 1.7%, 79.5%, and 18.8% to DALYs attributed to HCV, respectively. In the countries of the WHO Western Pacific Region (WPR), HCV was responsible for 26% of all liver cancer deaths and 27% of deaths attributed to liver cirrhosis and other chronic liver diseases (CLD) (Coalition for Global Hepatitis Elimination (2021), WHO (2024). In 2019, 25% of the top 20 countries worldwide for HCV-related deaths were located within the WHO Western Pacific Region (Coalition for Global Hepatitis Elimination (2021), WHO (2024).

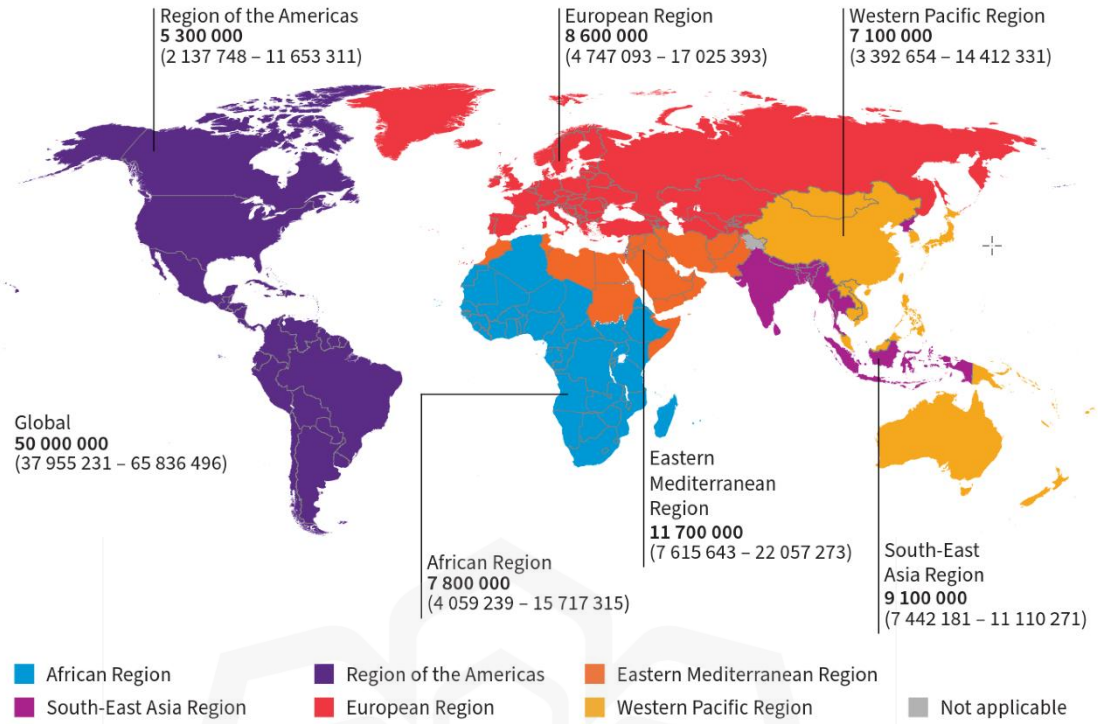


Figure 1. The world map shows the prevalence of chronic HCV globally in 2022. While HCV is prevalent throughout the world, the Eastern Mediterranean region exhibits the highest prevalence (WHO, 2024).

Transmission is less often via sexual behaviours and from an infected mother to her unborn child. In addition, HCV may be vertically transmitted from mother to child during pregnancy (Ohto et al., 1994). Hepatitis C is not transmitted by breast milk, food, water, or casual contact, such as embracing, kissing, or sharing food or beverages with an infected individual (WHO, 2024). Consistent with the viewpoint of, the Centres for Disease Control and Prevention (2025) states that HCV cannot be transmitted through casual contact, breastfeeding, or the sharing of food or drinks. In addition, Transfusions, transplantation, injectable drug use, dangerous therapeutic injections, occupational blood exposure, and unprotected sex with an infected partner are the primary risk factors for HCV transmission (Talić Alter et al., 2025). The predominant mode of transmission varies among industrialized, developing, and underdeveloped nations. Thus, injection drug use, receiving transfusions prior to donor screening, and engaging in high-risk sexual activity have been responsible for the majority of the HCV-related disease burden in developed nations. In contrast, receiving unsafe therapeutic injections and contaminated blood is linked to the disease burden in developing nations (Alter & Fabiani, 2007).

The enzyme immunoassay used to detect the antibody to HCV (anti-HCV), and seroconversion typically occurs 8–11 weeks after exposure. In contrast, HCV RNA is typically detectable within 1–2 weeks of exposure. Approximately 30% of individuals infected with HCV are able to spontaneously eliminate the virus within six months of infection without the need for treatment. This category of individuals would demonstrate anti-HCV antibody positivity but be negative for HCV RNA, and they are likely to be asymptomatic. HCV RNA was detected in the serum of the remaining 70% of individuals with HCV, indicating that they would develop chronic infection. Chronic HCV infection frequently goes undiagnosed until decades later, when symptoms arise from the consequences of HCV-related complications, including chronic liver disease, liver cirrhosis, and HCC (WHO, 2024).

The current recommendations from the Centres for Disease Control and Prevention (CDC) propose first doing an HCV antibody (Ab) test for HCV testing. If nonreactive, further testing is unnecessary. If the patient is Ab positive, reflex testing must be conducted with an HCV RNA assay (CDC, 2025). Upon detection of HCV RNA in a patient with a positive anti-HCV result, a diagnosis of chronic HCV infection is established, necessitating the patient's referral for evaluation of liver disease and the subsequent commencement of antiviral medication (CDC, 2025). The first two weeks post-infection are marked by the previremic period, during which HCV RNA levels progressively rise in the bloodstream, detectable alone by very sensitive diagnostic tests (Glynn et al., 2005). Detection in the acute phase is inconsistent, since RNA levels may vary (Glynn et al., (2005)and Busch & Page Shafer, (2005). Nucleic acid testing (NAT) is the optimal method for detection at this stage; yet, it is constrained by its elevated cost and prolonged turnaround time (Tharakan et al., 2022). RNA levels reach a maximum of one million copies per mL between 6 to 10 weeks .RNA levels may decrease to undetectable levels in self-resolving instances and in patients receiving DAA medication after six months (Mulrooney-Cousins & Michalak, 2024).

After six months, the RNA levels in patients receiving DAA medication and self-resolving instances may decrease to undetectable levels (Mulrooney-Cousins & Michalak, 2024). Viral load monitoring tests are required in these situations in order to assess the disease's state. The expression of the HCV core antigen parallels that of HCV-RNA, although with a little temporal lag. Consequently, HCV core antigen has been shown to be a substitute for RNA testing(Y. Wang et al., 2021). Anti-HCV antibody levels may be detectable during both acute and chronic infections. These characteristics may complicate diagnosis, since anti-HCV-based testing might overlook people with acute HCV and fail to distinguish between those who have recovered and those with a chronic infection (Mulrooney-Cousins, P. M., & Michalak, T. I., (2024) and Y. Wang et al. (2021).

Zilouchian et al., (2025) extensively elaborate on the current detection methods of Hepatitis C infection, including serological assays (enzyme immunoassay (EIA) and rapid immunoassays), *molecular and nucleic acid-based detection (*polymerase chain reaction (PCR)-based tests, branched DNA assays (bDNA), and transcription-mediated amplification (TMA)), and lastly, *non-invasive and point-of-care testing (*dried blood tests and point-of-care NAAT testing). This study also discussed new and possible ways to find HCV, like isothermal amplification-based tests, loop-mediated isothermal amplification (LAMP), surface plasmon resonance-based testing, microfluidics, electrochemical-based sensing, and CRISPR (clustered regularly interspaced short palindromic repeats (Zilouchian et al., (2025).

The natural history of hepatitis C starts from the initial infection which can be asymptomatic to potentially progress to long-term liver complications, depending on the immune response of the patients, age, sex, presence of comorbidities such as HIV or alcohol use and treatment. Symptoms of acute hepatitis C infection include fatigue, jaundice, and nausea (Evon et al., 2018). Patients who are undiagnosed earlier or untreated can develop liver complications in the long term, such as cirrhosis, liver carcinoma and liver failure. Furthermore, patients with chronic infection may be presented with extrahepatic complications such as mixed cryoglobulinemia, lymphoproliferative disorders, and renal disease. Upon diagnosis of the disease, the principal treatment for hepatitis C is directly targeting the virus either in the host's circulation or in the liver using drugs known as direct-acting antivirals (DAAs). DAAs are highly effective, with cure rates exceeding 90-95% (Asselah et al., 2016). Some of the commonly used DAAs include sofosbuvir, ledipasvir, veltapatasvir and glecaprevir/pibrentasvir.

In countries like Malaysia, Singapore, and Thailand, where healthcare infrastructure is relatively well-developed, governments have increased efforts to make hepatitis treatment more accessible. The goal in these countries is to move towards the World Health Organization's objective of eliminating hepatitis C as a public health threat by 2030. However, there are still supply and demand barriers impeding the expansion of treatment among people living with HCV in Malaysia (Chan et al., 2022). Chan et al., (2022) discussed people living with HCV have limited access to health facilities, life pressure that prevent them getting free therapy, gaps in delivering HCV care and lastly, pharmaceutical treatment is not commonly accepted among HCV patients.

Additionally, concerns have been raised about the potential effects on extrahepatic cancer risk in HCV-infected patients treated with DAAs attributed to the "unmasking effect". The "unmasking effect" refers to a notable phenomenon in which some patients receive a cancer diagnosis shortly after initiating treatment with DAA for HCV. This is thought to occur because the rapid clearance of HCV allows for the detection of pre-existing malignancies previously masked by the chronic inflammatory state associated with the infection. The chronic presence of the virus frequently compromises the immune system, which may mask the signs of malignancy prior to DAA treatment. Upon the virus's effective suppression, the immune system may become more adept at identifying and diagnosing these malignancies, resulting in a perceived rise in cancer cases (Conti et al., 2016). Consequently, a study review on extrahepatic cancer risk associated with DAAs treatment does not suggest a notable risk, but the authors demand ongoing surveillance and research since newer DAAs are in the pipeline of clinical trials. DAAs have fundamentally transformed the way that HCV is treated with their low adverse effects and excellent cure rates (>95%). Although DAAs have significantly improved liver-related outcomes, there is a continuous debate on their impact on extrahepatic cancer risk. Some studies suggest that DAA medication may reduce the incidence of extrahepatic cancers; other studies detect no appreciable change. Confounding factors and short follow-up periods complicate these outcomes (Tani et al., 2024).

1.2 HCV GENOME AND GENOTYPES

HCV is a single-stranded RNA genome enclosed in a lipid bilayer classified under the hepacivirus genus belonging to the *Flaviviridae* family. Unlike the other thirteen (Yellow Fever virus, Dengue virus, Zika virus, West Nile virus, Japanese Encephalitis virus, Tick-Borne Encephalitis virus, Kyasanur Forest virus, Alkhurma virus and Omsk virus) species which infect a range of vertebrates, HCV only infects humans. The genome of HCV is approximately 9.6 kb in size and encodes three structure proteins and seven non-structure proteins as presented in Figure 2. These proteins are arranged in the following order: 5'UTR-C-E1-E2-P7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-3'UTR (Peter Simmonds, 2004; Zhang et al., 2017). The virus comprises an open reading frame around 3000 base pairs, a 5′ noncoding region (NCR), a site of internal ribosome entrance (IRES), and a 3′ NCR. The vital step of internal ribosome entrance for viral protein synthesis emphasizes the significance of the 5′ NCR in viral replication (Niepmann & Gerresheim, 2020). Structural proteins consisted of core proteins and enclosure glycoproteins E1 and E2. Core proteins are nucleocapsid proteins that are highly conserved and are essential for the assembly of the viral particle (Pascut et al., 2021a). Meanwhile, the enclosure glycoproteins E1 and E2 are proteins that reside on the viral surface and facilitate the entrance of the virus into host cells. They have considerable sequence variability, which may influence immune recognition (Romero-López & Berzal-Herranz (2009) and Pascut et al. (2021). Additionally, non-structural proteins, consisting of NS1 – NS5 proteins, play critical roles in viral propagation and assembly (Dubuisson & Fabiani, 2007; Pascut et al., 2021b; Tomei et al., 1993). NS3 is a serine protease essential for the digestion of the HCV polyprotein (Li et al., 2018), whereas NS5B is an RNA-dependent RNA polymerase required for viral RNA replication (Dubuisson & Fabiani, 2007; Pascut et al., 2021b; Tomei et al., 1993).

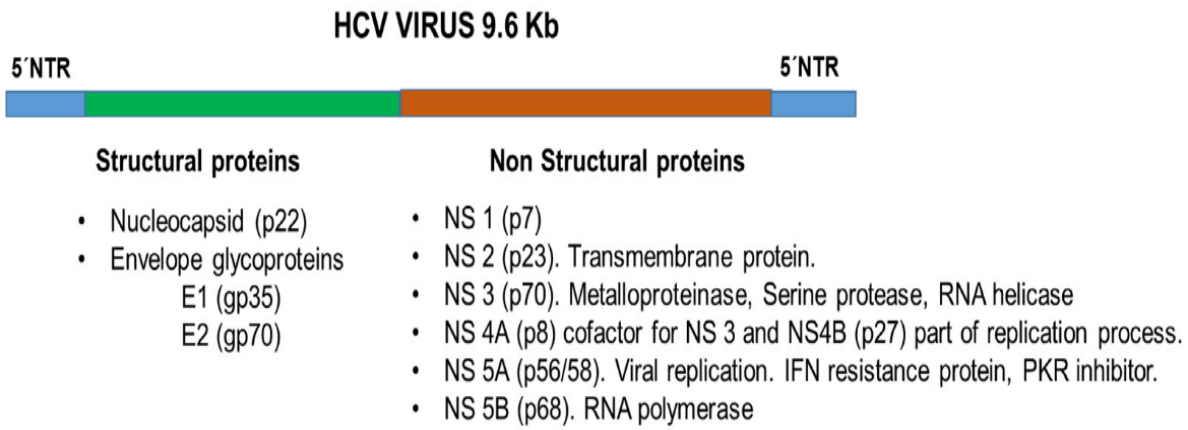


Figure 2. HCV genomic virus structure and viral proteins (Adapted from Medina et al., (2023): A Synopsis of Hepatitis C Virus Treatments and Future Perspectives)

Phylogenetically, HCV is grouped into six main genotypes which vary from each other by more than 30% nucleotide mutations. Eight primary HCV genotypes have been found globally. These genotypes may be further classified into up to 100 subtypes based on phylogeny and sequencing studies (Gower et al., 2014; Messina et al., 2014). Interestingly, the seventh HCV genotype was found originating in central Africa (Murphy et al., 2015) and in 2018, HCV genotype 8 was discovered in Punjab, India by (Borgia et al., 2018a). Globally, genotype 1 of HCV is the most prevalent (46.2%) (Borgia et al., 2018b) , followed by genotype 3 (30.1%) (Hissar et al., 2006). A smaller proportion (22.8%) of all HCV infections are caused by genotypes 2, 4, and 6. The genotype 6 is widespread in southern China and SEA, including Vietnam, Thailand, Malaysia, and Cambodia (Wasitthankasem et al., 2015). Studies have shown that the Southeast Asian immigrant groups are most commonly infected with HCV genotype 6, which became prevalent after the year 2000 (Irekeola et al., 2021). It is unclear if infection by certain viral genotypes is predilected to certain host factors or significantly contributes to disease complications including extrahepatic syndromes. However, viral genotyping has been used to identify the source of infection and helps in the treatment decision-making by physicians. With HCV genotypes 1, 2, 4, 5, and 6 treated with a 12-week combination of sofosbuvir and velpatasvir, ASTRAL 1 and ASTRAL 2 trials revealed great effectiveness and tolerability in patients from the UK, Australia, and New Zealand. With a similar safety profile, ASTRAL 3 research revealed 95% viral clearance in individuals with genotype 3 infection after a 24-week regimen of sofosbuvir and velpatasvir. With >80% efficacy and <20% serious adverse effects, ASTRAL 4 research verified the safety and effectiveness of this combination in patients with decompensated liver disease (Guntipalli et al., 2021).

Previous studies were done by (Machado Mariana V. & Cortez-Pinto Helena, 2009) and (Mihm et al., 1997) reported that the distribution of steatosis in chronic HCV infection differs depending on the viral genotype with hepatic steatosis being more common in individuals with HCV type-3 infections in insulin resistance subjects. In addition, serum lipid levels in HCV type-3 infections are considerably lower than in HCV non-type-3 infections. As a result, HCV type-3-related steatosis is often accompanied with hypolipoproteinaemia (Negro & Sanyal, 2009).

1.3 EXTRAHEPATIC MANIFESTATIONS

Hepatocytes are the primary location of HCV replication. The virus could remain cell-associated and prevent hepatocyte death but results in liver complications later in life. Liver damage is generated by a cell-mediated immune response against infected liver cells, which leads to hepatitis, cirrhosis and hepatocellular carcinoma after a long-term infection. In the host's defense against HCV infection, the cellular innate immune response is of crucial significance, with natural killer (NK) cells being among the most critical effectors of early antiviral immunity. About 30–50% of the total lymphocyte count in the liver are NK cells, which highlight their major importance in immunosurveillance and antiviral defense in this organ (Corado et al., 1997). The expression patterns of the surface markers CD16 and CD56 define these cells mainly in terms of their functional characteristics. Whereas CD16 − CD56bright NK cells have a largely immunoregulatory and cytokine-producing phenotype, NK cells expressing CD16 + CD56 dim are mostly cytotoxic and demonstrate significant effector capabilities including direct target cell lysis. Many studies have shown how viral infections impair NK function, which was also seen in individuals with HCV. Particularly CMV, Epstein-Barr virus, and herpes virus have been linked to a decrease in natural NK cell cytotoxic function. Either the direct infection of NK cells by the viruses or the release of soluble substances from infected cells that control the natural cytotoxicity of NK cells might be the cause of this noted reduction in cytotoxic response (Corado et al., 1997).

A non-structural protein, NS5A, is responsible for the overexpression of cyclooxygenase-2, which in turn promotes the production of prostaglandins and thromboxane A2 and the release of matrix-metalloproteinases. Ultimately, this process results in inflammation, fibrosis, and carcinogenesis, regardless of the viral load (Núñez et al., 2004) . Furthermore, the activation of hepatic and extrahepatic inflammatory cells perpetuates these effects. Interleukin-1beta and tumour necrosis factor-alpha (TNF-alpha) are produced at an elevated level by liver macrophages and stellate cells (Zampino et al., 2013).

Extrahepatic manifestations are hepatitis-related disorders that develop outside the liver. In the course of chronic HCV infection, patients may have one or more extrahepatic manifestations which rates may reach up to 70 (Mazzaro et al., 2021) %. The classification of extrahepatic manifestations in chronic hepatitis C disease is based on the afflicted organ, system or disease process (Figure 1). In addition to the well-known long-term consequences of chronic hepatitis C such as liver cirrhosis and hepatocellular carcinoma, it mediates other systemic illnesses through immune-related dysregulation, metabolic (glucose and lipid) modification that leads to neuropsychiatric disorders, renal damage and cardiovascular disease (Mazzaro et al., 2021). Examples of HCV-related extrahepatic manifestations include glucose and lipid metabolic disorders, insulin resistance, type 2 diabetes, mixed cryoglobulinemia, atherogenic disease, lymphoproliferative disorders, renal disease, sicca syndrome, rheumatoid arthritis-like polyarthritis, and autoimmune disease (Fabrizi et al., 2017), which are often linked to a wide range of extrahepatic symptoms.

In addition, a meta-analysis revealed a high frequency of HCV infection in patients with B-cell non-Hodgkin's lymphoma (B-NHL), with a gradient from north to south (Dal Maso & Franceschi, 2006; De Sanjose et al., 2008; Gisbert et al., 2003) HCV linked to diffuse big B-NHL (OR 2.24) and marginal zone NHL (odds ratio (OR 2.47). More often seen was a serum monoclonal gammopathy based on IgMk (Andreone et al., 1998). A reduced cumulative incidence of lymphoma formation in individuals who eliminated the virus verifies this link and implies that HCV therapy might be a preventive approach (Kawamura et al., 2007). Whereas a viral relapse was followed by lymphoma recurrence, SVR-induced NHL regression (Saadoun et al., 2005). After antiviral treatment, splenic lymphoma positive for HCV showed villous cells regressed (Livier et al., 2002). In addition, the mean reported prevalence of HCV infection in patients with non-Hodgkin’s lymphomas (NHL) also depends on geographical region, which ranges from 8.9 to 37.1%, with the odds ratio (OR) ranging from 2.6 to 4.3. B-cell NHL is strongly associated with chronic hepatitis C, which the virus infection is known as one of the aetiologies of NHL. A study in Indonesia showed that the positivity rate of HCV expression in NHL samples was 34.9% (Saputra et al., 2024).

Mixed cryoglobulinemia (MC) is a rare disorder defined by the presence of cryoglobulins in the blood, which are immune complexes that clump together at 4 °C and deposit on blood vessels causing inflammation, but reversible at normal body temperature while mixed cryoglobulinemia syndrome (MCS) describes the clinical manifestations associated with these cryoglobulins, particularly a systemic vasculitis. Essentially, mixed cryoglobulinemia is the serological finding (the presence of the specific cryoglobulins), and MCS is the clinical picture resulting from the presence of these cryoglobulins. It is commonly manifested in patients staying in the four seasonal countries. In 42 MC patients, HCV RNA was found in 86% of the patients (Ferri et al., 1991). Studies show that the risk is further increased with underlying co-infection with *Streptococcus aureus* (Reinberg et al., 2024) and hepatitis B virus (Morrone et al., 2024). The incidence of HCV-associated MC is higher in southern Europe (over 60%) compared to northern Europe (10%-50%). On the other hand, the prevalence of HCV-associated mixed cryoglobulinaemic syndrome is less than 1% in North America and ranges from 2% to 5% in some southern European nations. The prevalence of MC and mixed cryoglobulinaemic syndrome among persons was 64.5% and 2.9%, respectively, falling within the stated range (Cheng et al., 2020). MC syndrome was diagnosed by the presence of serum cryoglobulins in at least two determinations over 12-week intervals (De Vita et al., 2011). Scarpato et al. (2020) showed that rituximab (RTX) improves the health and immune systems of HCV patients with MC. Because of this, it has been suggested that people with severe peripheral motor sensory neuropathy should consider about consuming RTX before starting antiviral therapy to get a quick and effective response to treatment. In 40% of individuals with HCV-related MC and nephropathy, DAAs help to lower creatinine levels and moderate proteinuria. Clinically, this should be relevant as renal involvement in MC is linked to poor prognosis (Mazzaro et al., 2000). Treatment with RTX or apheresis has been demonstrated to be beneficial in improving both immunological and renal function in individuals with nephropathy without clinical response to antiviral medication (Saadoun et al. (2005) and Fabrizi et al., (2019).

Type 2 diabetes mellitus (T2DM) is one of the most common extrahepatic symptoms linked to hepatitis C virus (HCV) infection, and prediabetes occurs four times more commonly in HCV patients (Nevola et al., 2021). The pathogenetic mechanism via which HCV develops T2DM is complex, mostly associated with the onset of insulin resistance, seen in up to 70% of cases, particularly involving virus genotypes 1 and 4 and HCV RNA levels. HCV replicates in pancreatic β-cells, inducing stress that diminishes the β-cell reserve (Nevola et al., 2021). HCV, via its structural and non-structural proteins, particularly the core protein, directly influences insulin signalling pathways, including IRS-1 and IRS-2 (Nevola et al., 2021). Indirect mechanisms of insulin resistance (IR) involve hepatitis C virus (HCV)-induced oxidative stress, fatty liver, the release of inflammatory cytokines such as tumour necrosis factor-α, insulin receptor substrate 1, phosphorylation, protein kinase B, and the upregulation of gluconeogenic genes including glucose 6-phosphatase and phosphoenolpyruvate carboxykinase 2 (Adinolfi et al., 2013). Insulin interacts with insulin receptors located on the cell surface, leading to the autophosphorylation of the receptor's cytoplasmic domains. This process activates insulin receptor substrates 1 and 2, which subsequently stimulate downstream enzymatic activity. When this happens, glucose transporter 4 (GLUT 4) moves from inside cells to the plasma membrane. This makes it easier for skeletal muscle and fat cells to take in glucose (Hammerstad et al., 2015a). Insulin inhibits hepatic glucose output through the reduction of gluconeogenesis. Insulin resistance leads to an increase in hepatic glucose production while simultaneously decreasing protein and glycogen synthesis. Furthermore, insulin promotes triglyceride synthesis and suppresses lipolysis (Hammerstad et al., 2015b). Figure 3 illustrates the mechanisms as follows.

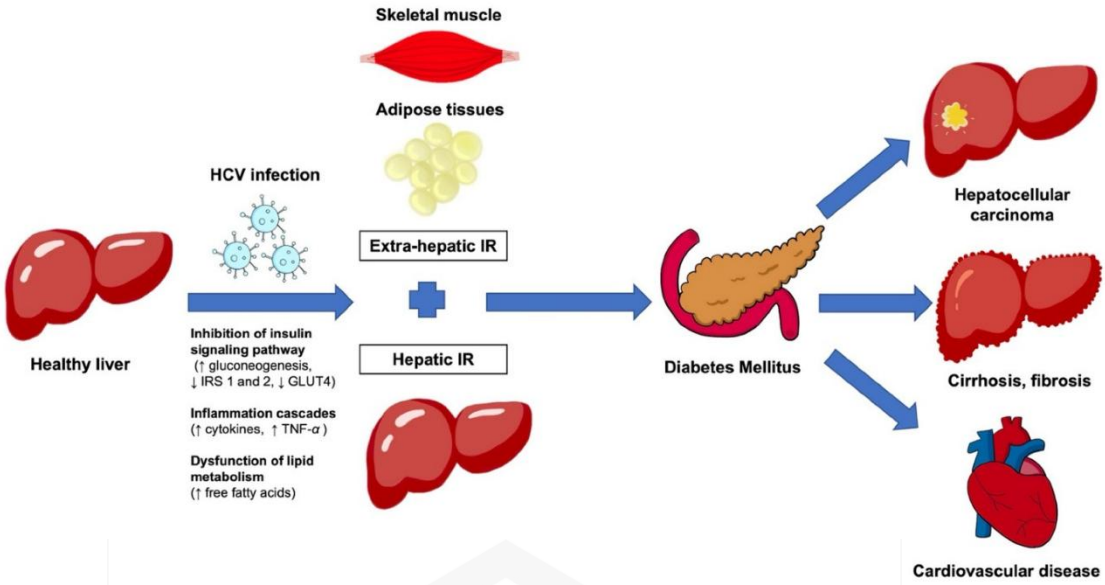


Figure 3: Demonstrates the pathways linked to HCV infections that result in hepatic insulin resistance and extrahepatic insulin resistance in skeletal muscles and adipose tissues, potentially leading to diabetes mellitus and tissue damage related to hyperglycaemia. The persistent inflammation associated Viral infections combined with insulin resistance may result in liver fibrosis, cirrhosis, and hepatocellular cancer. Furthermore, some people manifest cardiovascular illness. HCV refers to the hepatitis C virus; IR denotes insulin resistance (Adapted from Songtanin & Nugent (2023)).

In the last two decades, research links chronic HCV infection to atherosclerosis and cardiovascular disease. Several pro-atherogenic processes, directly or indirectly triggered by the virus, have been hypothesized based on experimental findings. HCV replicates in thrombotic tissue, causing persistent inflammation that contributes to thrombus development and instability (Nevola et al., 2021). HCV entry receptors are expressed by endothelial cells, which facilitate viral replication. Moreover, HCV promotes the migration and proliferation of smooth muscle cells from the tunica media to the intimal surface, therefore changing endothelial permeability and causing cell death and endothelial dysfunction (Adinolfi et al., 2012a).

Thus, it is hypothesized that HCV directly contributes to the development of atherosclerosis by causing vascular damage. HCV has also been implicated in indirect mechanisms of atherosclerosis, including low-grade, chronic systemic inflammation and T helper cell activation through the release of pro-atherogenic cytokines and chemokines (e.g., IL-1β, IL-6, and TNF-α), which in turn cause the expression of VCA M-1 at the endothelial level. This promotes leukocyte transmigration toward the vascular endothelial wall and the development of atherosclerotic plaque by enabling monocytes and T lymphocytes to adhere to the vascular endothelium at the site of atheroma formation (Adinolfi et al., 2012a). Contradictory epidemiological data indicates the link between HCV infection and an elevated risk of cardiovascular illnesses. Previous research has shown that the presence of HCV antibodies in the blood, known as HCV seropositivity, is linked to the development of coronary artery disease. Observational research revealed a noteworthy correlation between elevated HCV RNA levels and the likelihood of developing carotid atherosclerosis.

Treatment and management of extrahepatic symptoms of HCV may potentially impose a financial cost on the nation, as well as on the productivity and quality of life of infected people. As in the report by (Lee et al., 2019), 1.5 million disability-adjusted life years are lost each year, as a result of hepatitis-C-associated cardiovascular illness. The effect is mostly felt in low- and middle-income countries because of direct medical costs (Cacoub et al., 2018) and indirect costs from lost work productivity (Lindgren et al., 2021) and deaths (Z. Younossi et al., 2016a).

1.4 EXTRAHEPATIC REPLICATION OF HCV

Sherman & Sherman (2015) revealed that HCV can replicate in a limited capacity in different organs other than the liver compartment. While these infections comprise a small proportion of the virus load, they may play a substantial role in the formation and control of extrahepatic systemic disease processes. The immunological response to HCV viral proteins might indirectly lead to various immune-mediated processes that may cause damage to distant organs. Furthermore, hepatic replication may have a considerable influence on lipids, hormones, and counter-regulatory peptides, all of which contribute to the systemic illness states associated with the metabolic syndrome. It is consistent with the study done by (Blackard et al., 2006) which demonstrated extrahepatic diseases (mixed cryoglobulinemia, non-hodgkin's lymphoma, cutaneous vasculitis, glomerulonephritis, neuropathy, lymphoproliferative disorder, porphyria cutanea tarda, lichen planus and Sjögren's syndrome) as the result of a virus-induced systemic autoimmune or a direct effect of HCV. *In vitro* and *in vivo* studies have proven the extrahepatic replication of HCV in B-cells the evidence of HCV-RNA presence within the cells. Inokuchi et al., (2012) reported that HCV replication in peripheral blood mononuclear cells (PBMCs), may cause uncontrolled B-cell activation and thus lead to the development of lymphoproliferative and autoimmune disorders, such as non-Hodgkin's lymphoma and mixed cryoglobulinemia, which the diseases are most commonly reported extrahepatic manifestation of chronic HCV infection (Minopetrou et al., 2013).

The discovery of negative-stranded HCV RNA, a hallmark of viral replication, may radically alter our knowledge of HCV replication in multiple respects. The finding shows that HCV may reproduce within a certain cellular environment as steady viral replication relies on the constant synthesis of replicative intermediary components (Sangar & Carroll, 1998). While they cannot distinguish between positive and negative strands, standard viral load assays identify HCV RNA in blood. This makes them less helpful for looking at replication outside of the liver (Blackard et al., 2006).

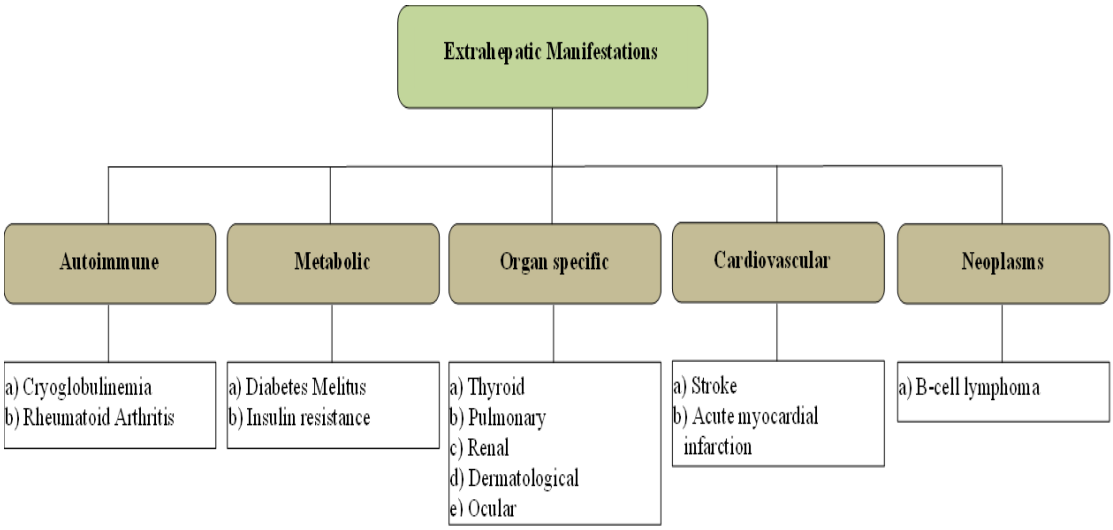


Figure 4: Diagram of Extrahepatic manifestations associated with chronic hepatitis C virus infection. (Adopted from Kuna et al., (2019): HCV extrahepatic infections).

1.5 JUSTIFICATION OF STUDY

Hepatitis C is often considered primarily a liver disease, but it may affect multiple organ systems. Extrahepatic manifestations occur in around 40-75% of patients with chronic HCV (Mazzaro et al., 2021), thus, a comprehensive understanding of the disease helps healthcare providers and researchers gain a holistic understanding of the disease's systemic nature. Despite that there is a large body of literature on HCV extrahepatic manifestations at present in Western countries, the prevalence of extrahepatic diseases in the Asian population, particularly among Southeast Asia is still limited. Understanding the extrahepatic disease improves diagnosis and assists clinicians in identifying less obvious signs of HCV such as fatigue, arthritis or kidney dysfunction. Furthermore, by tailoring treatment to the full spectrum of the disease, it can improve patient outcomes in terms of viral detection and treatment.

Southeast Asia (SEA) is a distinct region; it is multicultural, multiracial, multireligious, and comprises both low- and high-income countries. It consists of Brunei, Cambodia, East Timor, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam. There is a lack of reports on factors associated with the disease and the burden on patients and countries; hence, the treatment and management of HCV extrahepatic manifestations among the local population remain inadequately addressed (Mohamed Shaffril et al., 2021). As a result, the gap in this research was decided to be the relationship between HCV infection and extrahepatic symptoms in Southeast Asians population. However, a preliminary search revealed a very limited study related to extrahepatic manifestation conducted among the countries.

Previously, HCV extrahepatic diseases in East Asian countries were reviewed by (Z. M. Younossi et al., (2019) and worldwide by (Z. Younossi et al., 2016) and (Desbois & Cacoub, 2017) using traditional review methods. The practices of conventional literature reviews have several issues about openness and objectivity. Typically, many authors select articles that support their research (Mohamed Shaffril et al., 2021).

A systematic literature review (SLR) is a structured process that thoroughly identifies relevant research, synthesises it, and employs organised, transparent, and repeatable procedures at every stage of the process. This systematic review is exceptional and robust in two ways. First, a rigorous critical evaluation that determined which papers should be included followed the screening procedure. As a result, bias was removed, and only high-quality (based on risk of bias assessment) research was included in the systematic review. Two, a thorough strategy was used to incorporate the association of extrahepatic diseases with HCV infection outcomes in the study. Nonetheless, this type of review had some limitations, which there is a chance that relevant papers were omitted inadvertently, given only three databases were searched for this systematic review. Additionally, only English-language papers were examined for inclusion in the study.

Considering the limited reports on the topic in the SEA region and a previous non-SLR in the neighbouring region, East Asia, the current study focus was the populations of East Asia and SEA.

This review was guided by three research questions –

1. What is the prevalence of extrahepatic manifestations HCV-related in East Asia and SEA?
2. What are the risk factors of HCV extrahepatic manifestations among the studied population?
3. Is there any association between extrahepatic diseases with host or viral factors?

1.6 OBJECTIVES

Therefore, this study aimed to

1. To determine the prevalence of extrahepatic manifestations among HCV patients in East Asia and SEA.
2. To identify the risk factor between extrahepatic manifestations and HCV infection in the study population.
3. To identify association between specific extrahepatic diseases and viral factors (e.g.: viral genotype).

CHAPTER TWO

METHODOLOGY

2.1 REVIEW PROTOCOL-PRISMA

This systematic review was guided by the PRISMA method, in which the research questions were formulated by applying the PICO method; 'P' for Problem or Population, 'I' for Interest and 'Co' for Context) and 'O' (Outcome) (Lockwood et al., 2015). Following that, a document search technique was devised and implemented into three systematic phases (identification, screening, and eligibility) (Shaffril et al., 2018). Then, using a modified criteria list adapted from Zeng et al. (2015), a quality assessment procedure (Figure 5) was conducted to ensure the integrity of each chosen article included in the review. The chosen papers were then put through several steps, including data extraction and data analysis. The core research topic served as the basis for the data extraction procedure, and the qualitative data synthesis (thematic synthesis) approach was used to analyze the gathered data. Mendeley Desktop 1.19.9 was used as guidance during the writing process. (Abstract, Background, Methods, Results, Discussion, Conclusion).

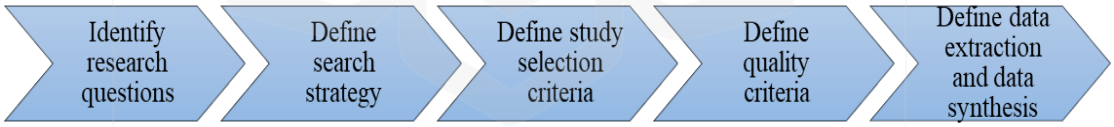


Figure 5: Systematic Literature Review protocol.

2.2 FORMULATION OF THE RESEARCH QUESTION

Two sources were used in the formulation of the study topic. First, concepts from past studies like as by (Z. M. Younossi et al., 2019), (Z. Younossi et al., 2016), and (Desbois & Cacoub, 2017)). Second, using mnemonic of PICO which signifies 'P' (Population or Problem), 'I' (Interest or Exposure), 'C' (Comparison), and 'O' (Outcome) was used as a tool to aid the reviewer in formulating the review's research question (Welty et al., 2012).

The authors based their review on these principles and included four major elements, Asian countries (Population), chronic hepatitis C infection (HCV) (Intervention), non-HCV infected patients (Comparison) and increased risk of extrahepatic manifestations (Outcome).

2.3 IDENTIFICATION

Identification is the process of finding any synonyms, similar phrases, or variations of the study's main keywords. The purpose is to offer more possibilities of similar articles from selected database for the review. First, the suitable keywords are identified. Suitable keywords are obtained from online thesaurus, keywords used in previous studies, keywords suggested from database Scopus, and keywords given by experts. In order to search for related articles and documents for the review, three databases namely PubMed, Scopus and Science Direct were selected as the leading databases. A manual "handpicking" search was conducted through the Google Scholar. To enhance the search process, keywords (Table 1), Boolean operators, truncation, wild cards (special characters), and field code functions were used for the search string. A total of 4187 possible articles were found from the specified databases. The search was carried out electronically on 31st January 2023.

Table 1: Keywords used for searching related articles

MAIN KEYWORDS	ENRICHED KEYWORDS
HCV	HCV = Hepatitis C Virus, HCV infection, HCV, Viral Hepatitis C, Hepatitis C, Hepatitis C virus infection, Hepatitis C antibodies
Extrahepatic manifestations	Extrahepatic manifestations = disease association, outside liver, beyond liver, extrahepatic diseases, extrahepatic appearance, extrahepatic infection, extrahepatic replication, extra-hepatic
Asian	Asian = Asia population, southeast Asia population, Southeast Asian

2.4 SCREENING

The second method was screening, in which publications were either included or omitted from the research (using the database or manually screened by the authors) depending on a defined set of criteria. Several inclusion and exclusion criteria were used in the screening process. To begin with, for literature type, only article journals with empirical data will be selected. In addition, conference proceedings, books, book chapters, newspapers, and review articles were systematically excluded from the analysis. To avoid any confusion about the content, only articles published in English will be chosen. Given the importance of 'research field maturity' as stressed by (Kraus et al., 2020), this study narrowed the screening procedure to publications published between 2017 and 2023. This date was selected because the quantity of published research was adequate to conduct a thorough evaluation. Moreover, this period was chosen to get up-to-date information on HCV extrahepatic symptoms in South East Asian populations. Throughout this phase, 3657 articles were omitted from the review based on exclusion criteria. Consequently, 509 articles remained for consideration in the screening process and 21 articles were included in this review.

Table 2: Inclusion and exclusion criteria of literature

Criterion	Inclusion	Exclusion
Timeline	≥ 2017-2023	< 2017
Literature type	Articles (clinical trials, cross-sectional studies, intervention studies, cohort studies, case - control studies, case series, longitudinal prevalence studies, seroprevalence studies, prevalence surveys)	Meta-analysis, book, newspapers, letters, novels, dissertations, review articles, unpublished reports, and conference papers
Language	English	
Countries and territories	East Asian and SEA countries	

2.4.1 Inclusion and Exclusion Criteria of PICO

2.4.1.1 Population Of Interest

2.4.1.1.1 Inclusion:

Studies that involved susceptible groups (pregnant women, patients with co – infection, patients with chronic disease, animal farm owners, farm workers, veterinary officers, displaced persons, prisoners, homeless, sex workers, illicit drug users, rural dwellers) and non – susceptible groups (healthy general population, healthy blood donors, urban residents) and participants of all age range were included.

2.4.1.1.2 Exclusion

Animal studies, environmental studies, and studies lacking a detailed description of the population were deemed unreliable for this review.

2.4.1.2 Intervention (Exposure)

2.4.1.2.1 Inclusion

Studies that measured the total HCV antibodies (IgG and IgM), IgG only, IgM only, and HCV RNA for the circulating virus genotypes were deemed relevant for this review.

2.4.1.2.1 Exclusion

Studies lacking HCV infection confirmation were disregarded for this study.

2.4.1.3 Context

2.4.1.3.1 Inclusion

This study covered all observational (clinical trials, cross-sectional studies, intervention studies, cohort studies, case-control studies, case series, longitudinal prevalence studies, seroprevalence studies, prevalence surveys) investigations that describe the prevalence of extrahepatic manifestations of HCV infection in the study area with English as the language of publication.

2.4.1.3.2 Exclusion

Animal studies and research published in languages other than English were eliminated. Also omitted were studies on meta-analysis, book, newspapers, letters, novels, dissertations, review articles, unpublished reports, and conference papers.

2.4.1.4 Outcome

Patients diagnosed with hepatitis C manifesting HCV extrahepatic diseases or disorders.

2.5 SEARCH STRING

After identifying the literature type and PICO, search strings and appropriate Boolean operators were established and optimised to ensure the inclusion of the target study populations.

Table 3: The search string for the four primary databases.

DATABASE	SEARCH STRING
Google Scholar (2570 articles)	(Hepatitis C Virus OR HCV infection OR HCV OR Viral Hepatitis C OR Hepatitis C OR Hepatitis C virus infection OR Hepatitis C antibodies) AND (Extrahepatic manifestation OR Extrahepatic disease OR beyond liver OR outside liver) AND (Southeast Asian OR Asian)
Pubmed (16 articles)	(Hepatitis C Virus OR HCV infection OR HCV OR Viral Hepatitis C OR Hepatitis C OR Hepatitis C virus infection OR Hepatitis C antibodies) AND (Extrahepatic manifestation* OR Extrahepatic disease* OR beyond liver) AND (Southeast Asian OR Asian)
Scopus (1210 articles)	TITLE-ABS-KEY (("Hepatitis C virus" OR "HCV infection" OR "HCV" OR "Viral Hepatitis C" OR "Hepatitis C" OR "Hepatitis C virus infection" OR "Hepatitis C antibodies") AND ("Extrahepatic manifestation*" OR "Extrahepatic disease*" OR "Extra-hepatic" OR "beyond liver" OR "outside liver"))
Science Direct (391 articles)	Title, abstract or author-specified keywords: (Hepatitis C Virus OR HCV OR Hepatitis C virus infection OR Viral Hepatitis C) AND (Extrahepatic manifestation OR Extrahepatic disease) AND (South East Asian OR Asian)

2.6 ELIGIBILITY, QUALITY APPRAISAL AND DATA EXTRACTION

2.6.1 Eligibility

After screening, the retrieved articles were manually reviewed to ensure that all reports met the criteria. This was accomplished by reading the titles and abstracts of the articles or the complete articles to check whether they fit the inclusion criteria. During the title screening phase, 23 articles were deleted, while 409 articles were discarded during the abstract screening phase. 11 further articles were rejected when the authors examined the content of the selected papers. The final number of quality-evaluated articles was 20.

2.6.2 Critical Appraisal Of Relevant Literature

FAH and HAH independently assessed the methodological quality and bias risk of the studies included in the review. Any discrepancies were resolved through consensus and discussion. This assessment was conducted using the JBI Critical Appraisal Checklist for Analytical Cohort Studies (Zeng et al., 2015b) and JBI Critical Appraisal Checklist for Analytical Case Series Studies (Munn et al., 2019). This checklist assesses the methodological quality of studies by evaluating clear research objectives, appropriate study design, measurement tool reliability and validity, and potential biases and confounding factors. Using this technique, we rigorously evaluated each study's methodological quality and bias risk.

The quality evaluation phase was conducted to confirm that the methodology and analysis of the chosen studies had been completed. We used the Joanna Briggs Institute (JBI) critical appraisal tool to assess potential bias in cohort, case reports and cross-sectional studies. We categorized 20 studies based on whether they raised concerns about bias or not.

2.7 STATISTICAL ANALYSIS

This study is systematic review with heterogenous data outcome, in which, making meta-analysis unsuitable. Therefore, statistical analysis was not conducted. Funnel plot analysis was also rendered unnecessary as a result of the incapacity to perform a meta-analysis. Moreover, this study used PRISMA criteria for systematic analysis across various databases in order to reduce publication bias. All cohort, case studies and cross-sectional studies were assessed using JB critical appraisal tool. The risk of bias was ranked as high when the study reached up to 49% of yes scores, moderate when it reached 50 to 69% of yes scores, and low when the study reached more than 70% of yes (Khalish & Gautama, 2025). We conducted a descriptive statistical analysis. To characterize the study cohort, both graphical and tabular descriptive statistical methods were employed, including means, standard deviations (SD), and range, to effectively visualize the data and delineate the empirical distributions.

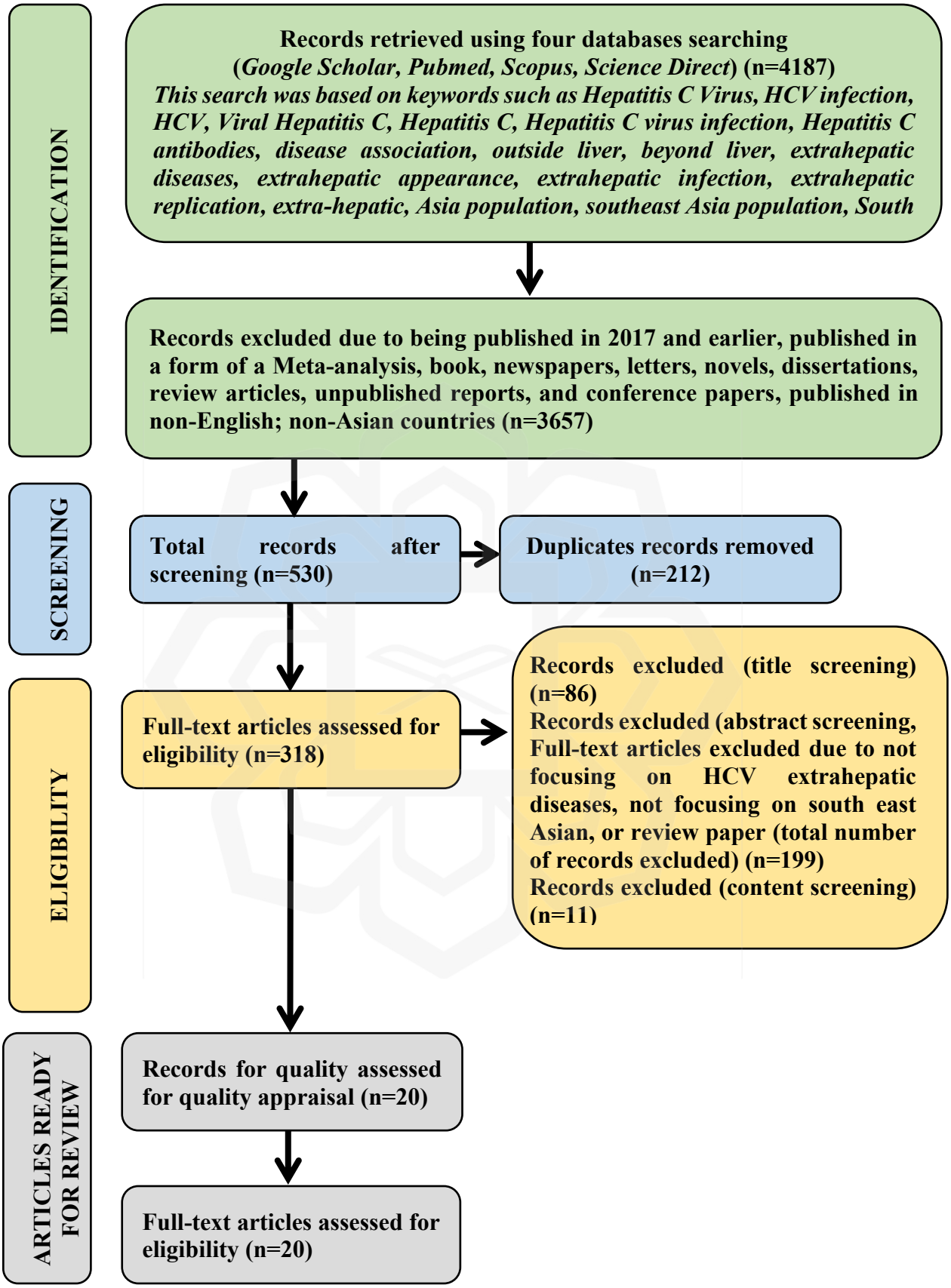


Figure 6: Flow chart shows the systematic screening process.

CHAPTER THREE

RESULTS

3.1 STUDY RESULTS

Based on the PRISMA guidelines, a total of 4187 were identified from Google Scholar, Pubmed, Scopus, and Science Direct by early year 2023. From the 4187 articles, 3657 articles were excluded from the preliminary screening bay criteria of publication in 2017 and earlier, published in the form of a Meta-analysis, book, newspapers, letters, novels, dissertations, review articles, unpublished reports, and conference papers, published in non-English; non-Asian countries. This primary screening leaves 530 articles for screening. 212 duplicates were removed from the screening, leaving 318 articles for eligibility assessment. Based on title screening, 86 articles were excluded, 199 articles did not fulfil the inclusion criteria (not focusing on HCV extrahepatic diseases, not focusing on East Asia or Southeast Asia, or review paper) and 10 articles were excluded during content screening. After exclusion, a total of 21 articles were evaluated on the association between hepatitis C infection and extrahepatic manifestations. Also, those studies used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) in the diagnosis of patients with HCV infection.

3.2 STUDY CHARACTERISTICS

Twenty (20) papers were eligible for review after identification, screening, and quality assessment as shown in Table 4, 5 and 6. Most articles were unequivocally published between 2018 and 2021, with additional papers published in 2019-2020, 2017, and 2022 respectively. Moreover, thirteen articles were distinctly identified from the Scopus database. One study explored the link between paternal HCV and an increased risk of developing various types of cancer. Conversely, multiple studies explained the extrahepatic symptoms of hepatitis C in adults. Collectively, the chosen publications indicated that the frequent locations or systems of extrahepatic replication and manifestation include the lung, kidney, cardiovascular system, psychological impact, blood vessels, skin, and intestines. In addition, only two papers have discussed the usefulness of DAAs treatment for HCV in lowering extrahepatic illnesses.

Based on geographic proximity, Taiwan received the majority of reports, followed by Japan, China, and Korea. The cohort consisted of 12 studies, including 9 studies from Taiwan, Japan (2), and Korea (1). In contrast, there are seven case reports from China (2), Japan (4), and Korea (1), while, one cross sectional study from China. However, the available data displayed ambiguous information on the extrahepatic manifestation's distribution of populations from the Filipino, Southeast Asian, East Asian, and South Asian populations. This review involved 254,334 HCV patients, with more female patients (25,216) than male patients (24,150) with a mean age of 52.12 years old.

3.3 QUALITY ASSESSMENT

Assessment of the 12 cohort studies was assessed using Joanna Briggs Institute (JBI) checklist for cohort studies (Table 4). This tool consists of 11 questions focusing on the selection of the study participants, exposure status, confounding, measurement of the outcome, and statistical analysis, with the option to answer "yes," indicating higher quality; "no," indicating poor quality; or "unclear." The bias risk percentage calculation is done by the amount of “Y” selected in the checklist. When “NA” was selected, this question was not considered in the calculation, according to the guidelines of the Joanna Briggs Institute (Srivastava et al., 2025). The risk of bias was ranked as high when the study reached up to 49% of “yes” scores, moderate from 50 to 69% of “yes" scores, and low more than 70% of “yes" scores (Goplen et al., 2019). Only four cohort studies had moderate bias, while the remaining studies were classified as low bias.

The quality of the included case reports was evaluated using the Joanna Briggs Institute's (JBI) Critical Appraisal Checklist for Case Reports (Table 5). This tool assessed the case report's clarity, appropriateness of treatment, and validity of the findings (Anzali et al., 2025). The risk of bias was categorized based on thresholds: low risk (≥70 % yes scores), moderate risk (50–69 % yes scores), and high risk (<49 % yes scores). (Ghasemi et al., 2025). The quality of all case reports was rated as "low bias”. Additionally, the Joanna Briggs Institute's (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional was used to evaluate one cross-sectional research that had minimal bias (Table 6).

Table 4: JBI risk of bias quality assessment for cohort studies

Authors (Years)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	%YES	RISK*
Sung et al. (2018)	✓	✓	✓	?	?	✓	✓	?	?	?	✓	54	Moderate
T. Y. Jang et al. (2018)	✓	✓	✓	✓	✓	✓	✓	?	?	?	✓	72	Low
Yang et al. (2019a)	✓	✓	✓	✓	✓	✓	✓	✓	?	?	✓	81	Low
Huang et al. (2020)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	90	Low
Sakuraoka et al. (2020)	✓	✓	✓	?	?	✓	✓	?	?	?	✓	54	Moderate
Y. Cheng et al. (2020)	✓	✓	✓	✓	✓	✓	✓	✓	?	?	✓	81	Low
Takahashi et al. (2021)	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✓	72	Low
Chu et al. (2021)	✓	✓	✓	✗	NA	✓	✓	✓	?	?	✓	63	Moderate
Heck et al. (2021)	✓	✓	✓	✓	✓	✓	✓	NA	NA	NA	✓	72	Low
Tung et al. (2022)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
C. E. Huang et al. (2022)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Wang et al. (2022)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100	Low

* The risk of bias was ranked as high when the study reached up to 49% of “yes scores, moderate from 50 to 69% of “yes" scores, and low more than 70% of “yes" scores. ‘✓’ indicates yes, ‘✗’ indicates no, ‘?’ indicates unclear (Goplen et al., 2019), and ‘NA’ indicates not applicable.

Table 5: JBI risk of bias quality assessment for case reports.

Authors (Years)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	%YES	RISK*
Guo et al. (2017)	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Shimada et al. (2017)	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Kamimura et al. (2018)	✓	✓	✓	✓	✓	✓	✗	✓	87	Low
Jang et al. (2018)	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Takakusagi et al. (2018)	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Nagao et al. (2017)	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Xue et al. (2019)	✓	✓	✓	✓	✓	✗	✗	✓	75	Low

*The risk of bias was categorized based on thresholds: low risk (≥70 % yes scores), moderate risk (50–69 % yes scores), and high risk (<49 % yes scores). (Ghasemi et al., 2025)

Table 6: JBI risk of bias quality assessment for cross sectional study.

Authors (Years)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	%YES	RISK*
Yuan et al. (2019)	✓	✓	✓	✓	✗	✗	✓	✓	75	Low

*The risk of bias was categorized based on thresholds: low risk (≥70 % yes scores), moderate risk (50–69 % yes scores), and high risk (<49 % yes scores).

Table 7: Summary of included articles.

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
Sung et al.	2018	Korea	27	100 (27) male=9 female=18	63	Cohort	Division of Hepatology in the Seoul St. Mary's Hospital	17 (Gender is unclear) -fatigue (9) - Type II diabetes (4) - arthralgia (4) - pruritus (3) - depressive mood (3) - chronic kidney diseases (2) - sicca syndrome (1)	- 1a (1) - 1b (21) - 2 (5)	Direct-acting antivirals (DAAs) may alleviate extrahepatic manifestations of hepatitis C virus (HCV) infection by reducing the expression of interferon-stimulated genes (ISGs)

Table 7: Continued.

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
T. Y. Jang et al.	2018	Taiwan	1119	33.33 (373) male=183 female=190	53.6	Cohort	Medical centre in Taiwan	hyperuricemia (n = 191) male: 116 female: 75	- 1 (175) - 2 (164) - mixed 1+2 (22) - others (12)	
Yang et al.	2019	Taiwan	58855	1.22 (11, 771) male=6060 female= 5711	51.61	Cohort	Taiwan's National Health Insurance Research Database (NHIRD)	Atrial Fibrillation - HCV Positive (606) - HCV negative (2045) *Gender is unclear	NR	

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
Huang et al.	2020	Taiwan	617	100% (617) male=261 female:356	62.1	Cohort	Two regional hospitals in Taiwan	cardio-cerebrovascular (4), male	1 (493)	Dyslipidemia occurs after HCV eradication by treatment.
Sakuraoka et al.	2020	Japan	860	n=533	68	Cohort	Second Department of Surgery, Dokkyo Medical University, Japan	Hepatic vein invasion (43) *Gender is unclear as data conflicted with HBV infection.	NR	
Y. Cheng et al.	2020	Taiwan	678	100% (678) male: 348 femlae:330	55.44	Cohort	Taiwan Tertiary Referral Centre	Mixed cryoglobulinemia male=205 female= 232	- 1 (391) - 2 (236) - 3 (18)	

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
Takahashi et al.	2021	Japan	592	45.94% (272) male:130 femlae:142	69.1	Cohort	Multicentre in Japan	diabetes (55) *Gender is unclear	- 1a (6) - 1b (250) - 2a (1) - unknown (15)	Eradication of HCV using DAA therapy improves glycemic control in patients with diabetes.

Table 10: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
Chu et al.	2021	Taiwan	27,141	0.15 (18,094) male: 4865 female: 4182	40	Cohort (Propensity score-matched cohorts)	National Health Insurance (NHI) administrative database, the Cancer Registry Database, and the Death Registry Database,	Esophageal cancer - HCV-Treated (1) - HCV-Untreated (86) - HCV-Uninfected (40) *Gender is unclear	NR	HCV-untreated cohort had the highest incidence of esophageal cancer

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
Heck et al.	2021	Taiwan	127,952	25 (25) male: unclear female: unclear	Age: <11 (gender not available)	Cohort	Taiwan Maternal and Child Health Database, Taiwanese Birth Notification, the Death Registry and the Registry for Beneficiaries of the National Health Insurance Research Database.	- Acute lymphoblastic leukaemia a. HCV-infected father (8) infected child (<5) b. HCV-infected mother (7) infected child (5) - Non-Hodgkin lymphoma a. HCV-infected father (11)	NR	

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
								infected child (<5) b. HCV-infected mother (5) infected child (<5) *Gender is unclear		
Tung et al.	2022	Taiwan	17,166	100 (6369) male: 3569 female: 2800	51.00	Cohort	Taiwan's National Health Insurance Research Database (NHIRD)	Sjögren's syndrome (177) *Gender is unclear	NR	

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
C. E. Huang et al.	2022	Taiwan	3455	52.18 (1803) male:864 femlae:939	61.61	Retrosp-ective and prospect ive	Chang Gung Memorial Hospital, Chiayi, Taiwan.	Thrombocytope nia (205) *Gender is unclear	NR	
Wang et al.	2022	Taiwan	16,743	48.24 (8078) -Cirrhosis Positive (n=1154) male:541 female:613 -Noncirrhosis (n=6924) male:3677 female:3247	44.8	Cohort	Taiwan National Health Insurance (NHI) Research Database (NHIRD).	DM (2717) HCD (4616) CKD (1744) Hyperlipidemia (3035) Lichen Planus (34) Palpable Purpura (220) *Gender is unclear	NR	

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
Yuan et al.	2019	China	128	100 (7) (male=6, female=1)	44.00	Cross sectional	Nanfang Hospital (Southern Medical University, Guangzhou, China)	Glioblastoma (7) male=6 female=1	- 2a (1) - 3a (2) - 1b (2) - 6a (2)	
Guo et al.	2017	China	1	100 (1) (female)	58.00	Case Report	Department of Nephrology of the Second Hospital of Jilin University (Changchun, China)	cryoglobulinemic membranoprolife -rative glomerulonephritis (1)	NR	The combination of prednisolone and interferon alpha has been demonstrated to be highly effective in treating HCV-associated

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
										cryoglobulinemia with MPGN
Shimada et al.	2017	Japan	1	100 (1) (female)	55	Case Report	Department of Cardiology and Nephrology, Hirosaki University Graduate School of Medicine, Zaifu-cho, Hirosaki, Japan	Cryoglobulinemic membranoprolif-erative glomerulonephritis (1)	1b (1)	

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
Kamimura et al.	2018	Japan	1	100 (1) (male)	69	Case Report	Division of Gastroenterology and Hepatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata City, Niigata, Japan	Small-Intestinal Ulcer (1)	1b (1)	Antiviral medication is crucial for treating and preventing B-NHL illnesses linked to HCV
Jang et al.	2018	Korea	1	100 (1) (female)	62	Case Report	Case Report	Lung metastases with HCV (1)	NR	Sorafenib showed a reduction in size of lung

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
										metastases by CT scan
Takakusagi et al.	2018	Japan	1	100 (1) (female)	81	Case Report	Gunma University Hospital, Japan	Renal Disease without Cryoglobulinemia (1)	1b (1)	Combining DCV/ASV therapy improves eGFR and reduces blood creatinine levels in individuals with HCV-related renal impairment

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
Nagao et al.	2017	Japan	1	100 (1) (male)	53	Case Report	Kurume University Hospital (Fukuoka, Japan)	Oral lichen planus (1)	1b (1)	The patient with HCV-associated OLP was treated with IFN-free DAAs, leading to a complete resolution of symptoms.
Xue et al.	2019	China	1	100 (1) (male)	35	Case Report	Dermatology Hospital of Southern Medical University, Guangdong Provincial Dermatology	Necrolytic acral erythema (1)	NR	

Table 7: Continued

First Author	Year	Country	Sample Size	No. of HCV Positive %(n=)	Average age/years old (Mean)	Study Design	Source population	Extrahepatic manifestations, EHM (n=)	Viral genotype (n=)	Treatment Outcome
							Hospital, Guangzhou, China.			

NR, not reported

Table 8: Factors Associated with HCV extrahepatic manifestations.

First Author	Country	Study Design	Extrahepatic manifestations (EHM) (n=)	p value of EHM	Factors associated with EHM (p-value=)
Sung et al. (2018)	Korea	Cohort	(17) - Fatigue (9) - Type II diabetes (4) - Arthralgia (4) - Pruritus (3) - Depressive mood (3) - Chronic kidney disease (2) - Sicca syndrome (1) *Gender is unclear	NR	Age, years Male sex HCV genotype - 1a - 1b - 2 *p-value=NR
T. Y. Jang et al. (2018)	Taiwan	Cohort	Hyperuricemia (191) male: 116 female: 75	NR	BMI (0.003) eGFR (0.02) Serum uric acid level (< 0.001) Age (0.96) Male (0.79) Advanced fibrosis (F3-4) (0.74)

Table 8: Continued

First Author	Country	Study Design	Extrahepatic manifestations (EHM) (n=)	p value of EHM	Factors associated with EHM (p-value=)
					Diabetes (0.24) HCV RNA (log IU/mL) (0.46) HCV genotype 1 (0.54)
Yang et al. (2019a)	Taiwan	Taiwan's National Health Insurance Research Database (NHIRD)	Atrial Fibrillation (2651) HCV Positive (606) HCV negative (2045) *Gender is unclear	0.0002	Sex (1.0000) Age (P Value:1.0000) Hypertension (<0.0001) Diabetes mellitus (<0.0001) Cerebrovascular accident (<0.0001) Acute coronary syndrome (<0.0001) Ischemic heart disease (<0.0001) Peripheral vascular disease (<0.0001) Heart failure (<0.0001) COPD (<0.0001) CKD or ESRD (<0.0001) No treatment (<0.0001)

Table 8: Continued

First Author	Country	Study Design	Extrahepatic manifestations (EHM) (n=)	p value of EHM	Factors associated with EHM (p-value=)
Huang et al. (2020)	Taiwan	Cohort	Cardio-cerebrovascular (4), male	NR	Age (0.007) Smoking (0.027) Follow-up period 138.20 (0.014).
Sakuraoka et al. (2020)	Japan	Retrospective Cohort	Hepatic vein invasion (43) Gender is unclear as data conflicted with HBV infection.	NR	Age (0.49) Gender (0.52) HCV RNA (0.61) Serum DCP (<0.0001) Serum AFP (<0.0001) Portal vein (VP) (<0.0001) Maximum tumor diameter (<0.0001)
Y. Cheng et al. (2020)	Taiwan	Cohort	Mixed cryoglobulinaemia (678) male=205 female= 232	NR	Male (0.004) age 55.44±12.57 (<0.001) BMI 24.87±3.97 (0.162) HCV-RNA level (<0.001) genotype 1 (0.027) genotype 2 (0.173) genotype 1 (0.036)

Table 8: Continued

First Author	Country	Study Design	Extrahepatic manifestations (EHM) (n=)	p value of EHM	Factors associated with EHM (p-value=)
					Liver cirrhosis (%) (<0.001) IFNL3-rs1 (0.02)
Takahashi et al. (2021)	Japan	Cohort	Diabetes (55) *Gender is unclear	NR	NR
Chu et al. (2021)	Taiwan	Cohort	Esophageal cancer HCV-Treated (1) HCV-Untreated (86) HCV-Uninfected (40) *Gender is unclear	0.0292	Male (0.0033) Age ≥49 (0.5049) Liver cirrhosis (0.7315) COPD (0.8057) DM (0.5603) Hypertension (0.818) Dyslipidaemia (0.3909) Stroke (0.6216)

Table 8: Continued

First Author	Country	Study Design	Extrahepatic manifestations (EHM) (n=)	p value of EHM	Factors associated with EHM (p-value=)
Heck et al. (2021)	Taiwan	Cohort	- Acute lymphoblastic leukaemia a. HCV-infected father (8) infected child (<5) b. HCV-infected mother (7) infected child (5) - Non-Hodgkin lymphoma a. HCV-infected father (11) infected child (<5) b. HCV-infected mother (5) infected child (<5) *Gender is unclear	NR (Sample size was too small to estimate associations) NR (Sample size was too small to estimate associations)	NR
Tung et al. (2022)	Taiwan	Retrospec-tive Cohort	Sjögren's syndrome (177) *Gender is unclear	NR	Thyroid disease (0.009) Sex (0.21) Age (0.024)
C. E. Huang et al. (2022)	Taiwan	Retrospec-tive and prospective cohort	Thrombocytopenia n= 205 *Gender is unclear	<0.001	Cirrhosis (<0.001)

Table 8: Continued

First Author	Country	Study Design	Extrahepatic manifestations (EHM) (n=)	p value of EHM	Factors associated with EHM (p-value=)
Wang et al. (2022)	Taiwan	Cohort	DM (2717) HCD (4616) CKD (1744) Hyperlipidemia (3035) Lichen planus (34) Palpable purpura (220)	<0.001	Liver Cirrhosis (<0.001)
Guo et al. (2017)	China	Case Report	Cryoglobulinemic membranoproliferative glomerulonephritis (1), female	NR	NR
Shimada et al. (2017)	Japan	Case Report	Cryoglobulinemic membranoproliferative glomerulonephritis (1), female	NR	NR
Kamimura et al. (2018)	Japan	Case Report	Small-Intestinal Ulcer (1), male	NR	NR
Jang et al. (2018)	Korea	Case Report	Lung metastases with HCV (1), female	NR	NR
Takakusagi et al. (2018)	Japan	Case Report	Renal Disease without Cryoglobulinemia (n=1, female)	NR	NR

Table 8: Continued

First Author	Country	Study Design	Extrahepatic manifestations (EHM) (n=)	p value of EHM	Factors associated with EHM (p-value=)
Nagao et al. (2017)	Japan	Case Report	Oral lichen planus (n=1, male)	NR	NR
Xue et al. (2019)	China	Case Report	Necrolytic acral erythema (n=1, male)	NR	NR
Yuan et al. (2019)	China	Cross sectional	Glioblastoma (n=7) male:6 female:1	NR	NR

NR, not reported

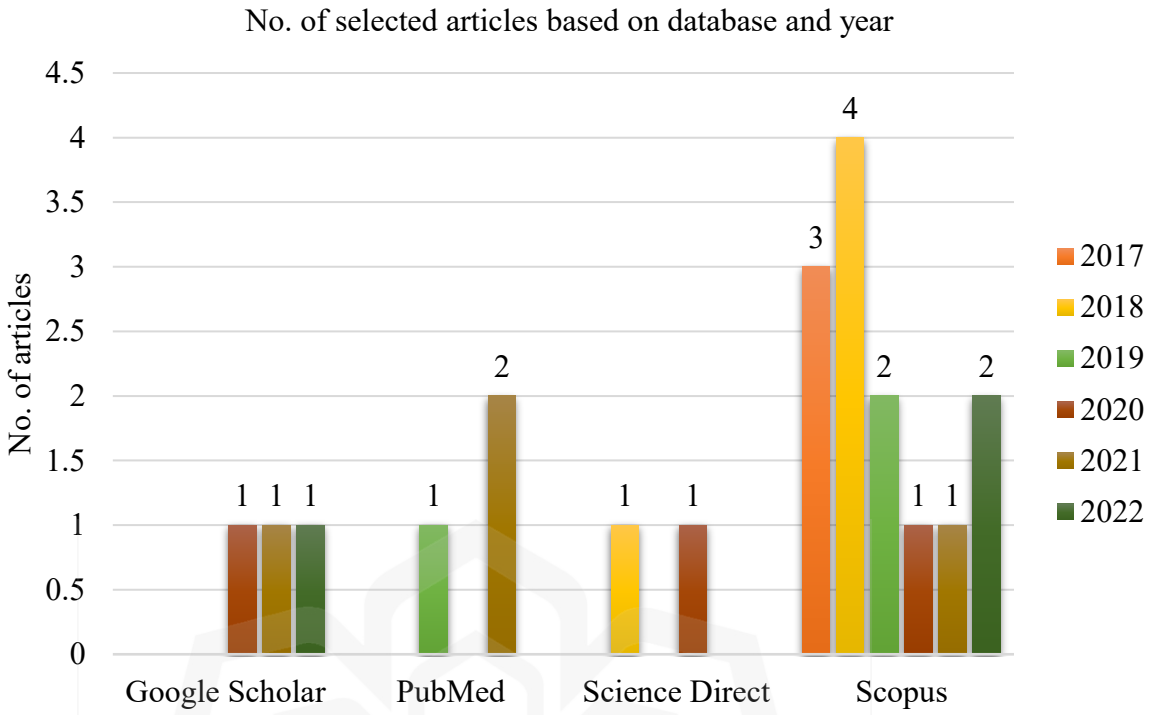


Figure 7: Summary of selected articles based on database and year.

3.4 PREVALENCE OF EXTRAHEPATIC MANIFESTATIONS AMONG HCV PATIENTS IN THE STUDY POPULATION

This review indicates that the overall prevalence of extrahepatic manifestations associated with HCV in the study is approximately 21.69% as shown in Table 9. A prevalence rate of 21.69% is obtained by calculating the total number of HCV patients (55,109) and the number of patients who have extrahepatic symptoms (11,955). The extrahepatic diseases associated with HCV are summarized in Table 7, highlighting the most prevalent conditions observed in patients infected with HCV. In a study conducted by (C. H. Wang et al., 2022), it was observed that 38.61% of patients with Hepatitis C Virus (HCV) exhibited hypertensive cardiovascular disease (HCD). Additionally, hyperlipidemia was reported in 25.39% of the HCV patient cohort, which comprised a total of 3035 individuals. Furthermore, a cumulative total of 2776 individuals diagnosed with HCV, representing 23.22%, subsequently developed diabetes(C. H. Wang et al., 2022) (Takahashi et al., 2021) (Sung et al., 2018). Chronic kidney disease is prevalent in approximately 14.6% of the patient population reported by C. H. Wang et al. (2022) and Sung et al. (2018) . Atrial fibrillation happens in 5.1% of cases (Yang et al., 2019), and mixed cryoglobulinemia is seen in 3.7% of people with HCV (Cheng et al., 2020) Additionally, dermatological conditions such as palpable purpura and lichen planus affect less than 2% of HCV patients.

Table 9: Most frequent HCV-infection-associated extrahepatic disease.

Reported Condition	Total no. of patients	Prevalence Rate (%)
Hypertensive Cardiovascular Disease	4616	38.61%
Hyperlipidemia	3035	25.39%
Diabetes mellitus	2776	23.22%
Chronic Kidney Disease	1746	14.60%
Atrial Fibrillation	606	5.07%
Mixed Cryoglobulinaemia	437	3.66%
Palpable Purpura	220	1.84%
Thrombocytopenia	205	1.71%
Hyperuricemia	191	1.60%
Sjögren's Syndrome	177	1.48%
Esophageal Cancer	127	1.06%
Hepatic Vein Invasion	44	0.37%
Lichen Planus	34	0.28%

3.5 VIRAL GENOTYPE

From Table 7, genotype 1 showed the highest prevalence among the patients. It is primarily isolated from Taiwan (58.22%). Conversely, Japan, Korea, and China isolated 15.23% of Genotype 1b. Additionally, Genotype 2 encompassed 22.26% of the population. Among the others were Genotype 3, Genotype 1a, Genotype 2a, Genotype 3a, and Genotype 6a. Furthermore, Jang et al. (2018) reported that 1.21% of the population is a combination of Genotype 1 and 2. Meanwhile, approximately seven articles contain ambiguous information regarding the association of HCV genotypes with extrahepatic manifestations.

3.6 RISK FACTORS ASSOCIATED WITH HCV EXTRAHEPATIC MANIFESTATIONS

3.6.1 Patient's Characteristics

In summary, 15 out of the 20 studies analysed identified risk factors associated with extrahepatic manifestations as shown in Table 8. Among these studies, 10 reported a p-value of less than 0.05, indicating a significant association between HCV and EHM. The remaining studies did not provide this statistical measure.

Due to the lack of a meta-analysis, this review may only provide brief information on the association of HCV with EHM. A descriptive analysis of three studies revealed a significant association between age and extrahepatic disease in three studies (Y. Cheng et al., 2020; C. F. Huang et al., 2020; Tung & Chen, 2022) for cardio-cerebrovascular, mixed cryoglobulinemia and Sjögren's syndrome respectively. Conversely, three studies (Chu et al., 2021b; T. Y. Jang et al., 2018; Yang et al., 2019) did not demonstrate a significant correlation between age and extrahepatic diseases. Meanwhile, Cheng et al. (2020) and Chu et al. (2021b) showed a significant correlation between male and extrahepatic diseases. Male patients are more likely to develop mixed cryoglobulinemia (Cheng et al., 2020), and according to Chu et al. (2021b), they also have a greater chance of developing extrahepatic diabetes. (T. Y. Jang et al., 2018).

T. Y. Jang et al. (2018) reported a positive association between body mass index (BMI) and hyperuricemia, with a p-value of 0.003. In contrast, Cheng et al. (2020) found no significant relationship between mixed cryoglobulinemia and BMI, as indicated by a p-value of 0.162. Additionally, C. F. Huang et al. (2020) demonstrated a link between smoking and the occurrence of cardiovascular and cerebrovascular diseases in patients with hepatitis C virus (HCV), with a significant p-value of 0.027.

It is noticeable that patients with HCV who have comorbidities exhibited both positive and negative associations with extrahepatic diseases. The study conducted by Yang et al. (2019a) provides compelling evidence that atrial fibrillation in patients with HCV is significantly associated (p-value <0.0001) with a range of comorbidities (chronic obstructive pulmonary disease, chronic kidney disease, diabetes, hypertension, liver cirrhosis, cerebrovascular accident, acute coronary syndrome, ischemic heart disease, peripheral vascular disease, heart failure, and end-stage renal failure). C. H. Wang et al. (2022) showed a significant association (p-value <0.0001) between HCV extrahepatic liver cirrhosis to chronic kidney disease and diabetes.

Additionally, Tung et al. (2022) researched HCV extrahepatic Sjögren's syndrome and found a link to thyroid disease, showing a p-value of 0.009. This review found that hypertensive cardiovascular disease is strongly linked to HCV extrahepatic liver cirrhosis, and there is a very strong association (p-value <0.001) between lichen planus and palpable purpura skin disease in HCV patients (C. H. Wang et al., 2022).

A review of the literature reveals that only two out of twenty studies focused on the treatment of HCV among a substantial cohort of 29,767 patients. Patients who do not receive treatment for HCV are much more likely (p-value < 0.0001) to develop extrahepatic atrial fibrillation (Yang et al., 2019) , but there is also a significant connection (p-value 0.02) between pegylated interferon (IFN) and extrahepatic mixed cryoglobulinemia related to HCV (Cheng et al., 2020). Furthermore, from the Table 11, only one study (Heck et al., 2022) discussing the maternal-infant transmission of HCV. Maternal HCV may be factors to hepatic and non-hepatic cancers in children, however, the sample was too small to estimate associations.

3.6.2 HCV Genotype

In their respective studies (Table 8), only Cheng et al. (2020) and T. Y. Jang et al. (2018) examined the association between HCV genotype and the extrahepatic manifestations associated with HCV. The study conducted by (Cheng et al., 2020) involved the isolation of two HCV genotypes from a cohort of 678 HCV patients. Notably, only genotype 1 demonstrated a significant correlation with mixed cryoglobulinemia among 437 HCV patients, while genotype 2 did not exhibit any significant association, as indicated by a p-value of 0.173. The study conducted by T. Y. Jang et al. (2018) found that there was no significant association between genotype 1 and extrahepatic hyperuricemia. In contrast, the other studies did not report any association with HCV genotypes.

CHAPTER FOUR

DISCUSSION

The findings of the current systematic review highlight the significant load of extrahepatic manifestations among patients with hepatitis C virus infection in Asian population. These manifestations span a broad range of organ systems, indicating the virus infection is not confined to hepatic pathology but also has systemic effects on the host. The geographical distribution included in this study highlights important gaps in the available data. Most of the studies included in this review originate from Taiwan, followed by Japan, China and Korea, suggesting that research on HCV-related complications is concentrated in certain East Asia regions. This concentration of studies likely reflects the higher burden of HCV and the availability of advanced medical research infrastructure in these countries. Among the countries, Taiwan stands out with nine studies, thus making it the focal point for research on this topic in the region. Conversely, there is limited data from SEA and South Asian populations despite their substantial HCV prevalence (WHO,2024), which is a significant gap in the knowledge of extrahepatic manifestations in these populations. While East Asian countries like Taiwan and Japan have contributed extensively to the literature, the absence of comprehensive studies from the Philippines, Malaysia, and Indonesia signifies a lack of a full understanding of how extrahepatic manifestations of HCV affect populations in these regions. This gap could be due to limited research funding, or under-reporting. Moreover, this review included seven case reports from China, Japan and Korea. The case report format often provides valuable insights into rare or severe manifestations but may not fully capture the broader impact epidemiologically, thus offering anecdotal evidence rather than comprehensive trends.

The review analysed a substantial cohort of 55,109 HCV patients with notable data revealing a slightly higher number of female HCV patients (33,815) compared to males (21,629), which is consistent with other findings that suggested women may have a higher susceptibility to HCV infection due to biological and social factor (Baden et al., 2014). However, among patients with extrahepatic manifestations, there was a higher proportion of males (4,624) compared to females (4,098). This implies that while women may be more frequently infected with HCV, men could be at higher risk of developing extrahepatic complications in these regions. The reasons for gender disparity in extrahepatic outcomes are not fully understood, but a combination of genetic, hormonal, and lifestyle factors may influence it. Therefore, our results were in line with those of prior research conducted by Eliah et al. (2025), which found that the participants' mean age was 62 years old with a standard deviation of 11.2 years, suggesting that the population was mostly older. A notable proportion of the patients were female, representing 62.4% of the total population. Among individuals affected by viral hepatitis, males constituted approximately 80% of the cases. A significant proportion of patients (92.1%) were diagnosed with type 2 diabetes mellitus, the most prevalent form of diabetes and frequently linked to multiple comorbidities, such as viral hepatitis (Eliah et al., 2025).

The mean age of patients with extrahepatic manifestations was 52.12 years, suggesting that these complications tend to occur in middle-aged or older individuals. This is expected, as chronic HCV infection often progresses later in life. The aging population affected by HCV also highlights the importance of early diagnosis and treatment, as delayed management may result in more severe systemic complications as

The analysis of the selected articles revealed a broad spectrum of extrahepatic diseases, disorders and manifestations linked to HCV infection. Cardiovascular conditions rank as the most prevalent extrahepatic diseases affecting 38.61% of HCV patients as shown in Table 9. This highlights the extensive impact of HCV on the cardiovascular system (Figure 8), which is consistent with findings by Petta, (2017). (Rehermann, 2013) reported that HCV infection may result in an elevated cardiovascular risk by promoting oxidative stress and a systemic inflammatory state. Long-lasting inflammation from the body's natural defense and T-helper-1 responses is a common feature in people infected with HCV. Then, this immunological response may result in decreased adiponectin and increased levels of serum TNF alpha and IL-6. Adiponectin is negatively correlated with cardiovascular changes, whereas TNF alpha and IL-6 are directly linked to them (Cua et al., 2007; Petit et al., 2005). Moreover, hepatic steatosis and visceral obesity may contribute to the inflammatory state by increasing the generation of reactive oxygen species and inflammatory cytokines (Adinolfi et al., 2012).

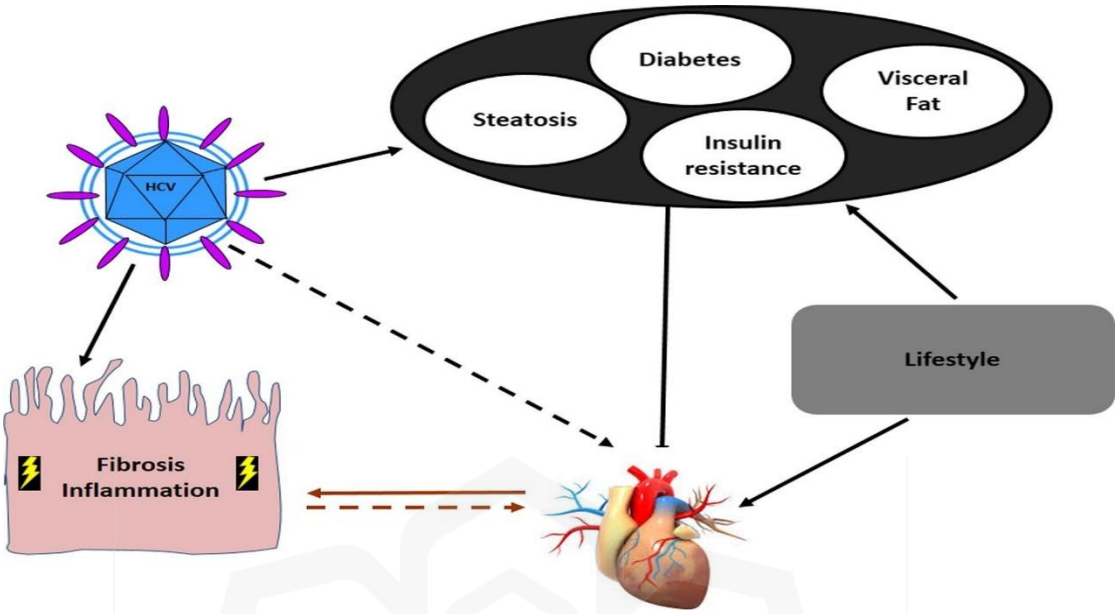


Figure 8: Possible correlations exist between HCV and the risk of cardiovascular disease. HCV directly and indirectly influences glucose and lipid metabolism, resulting in insulin resistance, diabetes, hepatic steatosis, and visceral obesity. Lifestyle and metabolic factors may increase cardiovascular risk in HCV patients. Furthermore, HCV may also induce cardiovascular alterations both directly and indirectly. Proinflammatory and profibrogenic conditions that induce hepatic fibrogenesis may systematically elicit cardiovascular alterations. Nonetheless, one can conjecture the presence of direct viral mechanisms. (Adapted from Petta, (2017)).

Notably, diabetes mellitus was present in over 11% of patients, underscoring the metabolic consequences of chronic HCV infection. The strong association between HCV and diabetes aligns with existing evidence that chronic inflammation of the liver can disrupt glucose metabolism (Andres et al., 2020). The review also identified other manifestations such as palpable purpura, proteinuria and hyperuricemia which though infrequent, are clinically significant and should be monitored to prevent further complications. Furthermore, the review also looked for a link between HCV genotypes with specific extrahepatic manifestations. Genotype 1 appears to be the most common strain in East Asia, especially in Taiwan, however, the findings suggest that there is insufficient clarity on whether different genotypes are more likely to cause extrahepatic conditions.

According to a study by Chu et al. (2021), the group of people who had not been treated for HCV had the highest cumulative incidence of esophageal cancer over 9 years, at 0.174% (95% CI: 0.068–0.395), which is a statistically significant difference ($p = 0.0292$). The overall rate of esophageal cancer was not significantly different between the groups that were treated with HCV (0.019%; 95% CI: 0.002–0.109%) and those that were not infected with HCV (0.035%; 95% CI: 0.007–0.134%) ($p = 0.5964$).

A key finding in this review is the benefit of direct-acting antiviral (DAAs) therapy in improving the extrahepatic manifestation of HCV. The study by Sung et al (2018) and Takashi et al., (2021) demonstrate that DAA therapy not only reduces viral load but also enhances glycaemic control in diabetic patients and mitigates other extrahepatic conditions. This suggests that DAA therapy can have systemic benefits beyond viral clearance, thus improving overall health outcomes for HCV patients. However, the studies also highlight the limited number of studies focused on the impact of antiviral therapy on extrahepatic conditions, pointing to the need for further research in this area.

The findings from this review suggest that clinicians should be vigilant in screening for and managing the extrahepatic manifestations of HCV, particularly cardiovascular and metabolic. This approach will require a multidisciplinary strategy involving hepatologists, cardiologists, endocrinologists, and mental health professionals to ensure that patients receive comprehensive care that addresses both hepatic and extrahepatic complications. Additionally, the role of DAAs in improving extrahepatic manifestations highlights the potential for antiviral therapy to significantly alter the course of HCV-related diseases. This underscores the importance of early detection and timely treatment, not just for hepatic health but also for the overall well-being of HCV patients. In addition, this comprehensive analysis highlights the intricate connections between these health conditions and underscores the importance of monitoring atrial fibrillation in this patient population.

One study by (Heck et al., 2022) discussing the maternal-infant transmission of HCV. The total weighted rate of HCV transmission from mother to newborn is estimated to be between 1.0% and 5.0%. The incidence of mother-to-infant transmission is increased by maternal risk factors such as high maternal viral titre (>10^6 copies/mL), history of intravenous drug use, and coinfection with HIV. Conversely, the rate of mother-to-infant transmission is not substantially influenced by lactation or the mode of delivery (vaginal versus Caesarean-induced). Consistent with this viewpoint, studies by Benova et al. (2014), Bhardwaj et al. (2021) and Roberts & Yeung, (2002) showed that a mother infected solely with HCV has a 5% to 6% chance of transmitting the virus to her baby. However, if she is also infected with HIV, this risk increases to approximately 11%. (Kushner et al., 2022) from Canada found that in 1,780 pregnancies with confirmed HCV RNA, those with a viral load of 10^6 IU/mL or more had much higher rates of transmission. In line with this observation, Malik et al. (2014) and Young et al. (2025) reported that the incidence of hepatitis C virus in children is relatively low and rarely leads to the development of hepatocellular carcinoma (HCC) in the paediatric. Typically, the hepatitis C virus appears to promote neoplastic transformation over an extended period through a distinct mechanism. It operates via chronic inflammation, which results in increased cell turnover. This process ultimately leads to the accumulation of somatic mutations and the progression to HCC.

CHAPTER FIVE

RECOMMENDATIONS & LIMITATIONS

Following a comprehensive review of the selected articles, this study aims to propose several recommendations for consideration by future scholars. Our review faced challenges because the studies we looked at had different designs, populations, and clinical outcomes, and they didn't consistently report important HCV extrahepatic risk factors, making it difficult to compare results and draw strong conclusions. Furthermore, we didn't conduct a systematic meta-analysis, and leaving out many relevant studies during the selection process would weaken our ability to provide complete information on the risk factors for HCV extrahepatic manifestations, including viral genotype. Therefore, we strongly advise future scholars to broaden their focus to the Southeast Asian population and conduct meta-analyses to arrive at a comprehensive conclusion.

CHAPTER SIX

CONCLUSION

In conclusion, this review provides valuable insights into the wide-ranging impact of HCV infection on extrahepatic systems, especially in the East Asian populations. Age, sex, and underlying diseases showed a significant association with HCV extrahepatic diseases. The most common manifestations are cardiovascular and metabolic outcomes. However, evidence linking certain viral characteristics, such as the HCV genotype, to the development of extrahepatic symptoms is lacking. These findings underscore the need for continued research into the systemic effects of HCV and the long-term benefits of antiviral therapy on extrahepatic conditions. The lack of data from the SEA region is concerning, as it limits the generalizability of findings to these regions. Future research should prioritize these underrepresented areas to ensure that the full spectrum of HCV-related extrahepatic manifestations is understood across diverse populations.

REFERENCES

Adinolfi, L. E., Restivo, L., Zampino, R., Guerrera, B., Lonardo, A., Ruggiero, L., Riello, F., Loria, P., & Florio, A. (2012a). Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. *Atherosclerosis*, *221*(2), 496–502. https://doi.org/https://doi.org/10.1016/j.atherosclerosis.2012.01.051

Adinolfi, L. E., Restivo, L., Zampino, R., Guerrera, B., Lonardo, A., Ruggiero, L., Riello, F., Loria, P., & Florio, A. (2012b). Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. *Atherosclerosis*, *221*(2), 496–502. https://doi.org/https://doi.org/10.1016/j.atherosclerosis.2012.01.051

Adinolfi, L. E., Zampino, R., Restivo, L., Lonardo, A., & Loria, P. (2013). *HCV treatment in patients with metabolic syndrome*. Taylor & Francis.

Alter, M. J., & Fabiani, F. L. (2007). Epidemiology of hepatitis C virus infection PREVALENCE AND INCIDENCE. *World J Gastroenterol*, *13*(17), 2436–2441. www.wjgnet.comhttp://www.wjgnet.com/1007-9327/13/2436.asp

Andreone, P., Zignego, A. L., Cursaro, C., Gramenzi, A., Gherlinzoni, F., Fiorino, S., Giannini, C., Boni, P., Sabattini, E., Pileri, S., Tura, S., & Bernardi, M. (1998). Prevalence of Monoclonal Gammopathies in Patients with Hepatitis C Virus Infection. *Annals of Internal Medicine*, *129*(4), 294–298. https://doi.org/10.7326/0003-4819-129-4-199808150-00005

Andres, J., Barros, M., Arutunian, M., & Zhao, H. (2020). Treatment of Hepatitis C Virus and Long-Term Effect on Glycemic Control. In *JMCP Journal of Managed Care & Specialty Pharmacy* (Vol. 26, Issue 6). www.jmcp.org

Anzali, B. C., Javanbakht, A., Rasouli, M., Talebiazar, N., Hashemzadeh, M., & Nazari, M. A. H. S. (2025). Surgical sharp debridement alongside maggot debridement

therapy (MDT) for the treatment of diabetic foot ulcers (DFUs): A systematic review of case reports. In *Surgery in Practice and Science* (Vol. 20). Elsevier Ltd. https://doi.org/10.1016/j.sipas.2024.100270

Asselah, T., Boyer, N., Saadoun, D., Martinot-Peignoux, M., & Marcellin, P. (2016). Direct-acting antivirals for the treatment of hepatitis C virus infection: Optimizing current IFN-free treatment and future perspectives. In *Liver International* (Vol. 36, pp. 47–57). Blackwell Publishing Ltd. https://doi.org/10.1111/liv.13027

Baden, R., Rockstroh, J. K., & Buti, M. (2014). Natural History and Management of Hepatitis C: Does Sex Play a Role? *The Journal of Infectious Diseases*, *209*(suppl_3), S81–S85. https://doi.org/10.1093/infdis/jiu057

Benova, L., Mohamoud, Y. A., Calvert, C., & Abu-Raddad, L. J. (2014). Vertical transmission of hepatitis C virus: Systematic review and meta-analysis. *Clinical Infectious Diseases*, *59*(6), 765–773. https://doi.org/10.1093/cid/ciu447

Bhardwaj, A. M., Mhanna, M. J., & Abughali, N. F. (2021). Maternal risk factors associated with inadequate testing and loss to follow-up in infants with perinatal hepatitis C virus exposure. *Journal of Neonatal-Perinatal Medicine*, *14*(1), 123–129.

Blackard, J. T., Kemmer, N., & Sherman, K. E. (2006). Extrahepatic replication of HCV: Insights into clinical manifestations and biological consequences. *Hepatology*, *44*(1), 15–22. https://doi.org/10.1002/hep.21283

Borgia, S. M., Hedskog, C., Parhy, B., Hyland, R. H., Stamm, L. M., Brainard, D. M., Subramanian, M. G., McHutchison, J. G., Mo, H., Svarovskaia, E., & Shafran, S. D. (2018a). Identification of a novel hepatitis C virus genotype from Punjab, India: Expanding classification of hepatitis C virus into 8 genotypes. *Journal of Infectious Diseases*, *218*(11), 1722–1729. https://doi.org/10.1093/infdis/jiy401

Borgia, S. M., Hedskog, C., Parhy, B., Hyland, R. H., Stamm, L. M., Brainard, D. M., Subramanian, M. G., McHutchison, J. G., Mo, H., Svarovskaia, E., & Shafran, S. D. (2018b). Identification of a novel hepatitis C virus genotype from Punjab, India: Expanding classification of hepatitis C virus into 8 genotypes. *Journal of Infectious Diseases*, *218*(11), 1722–1729. https://doi.org/10.1093/infdis/jiy401

Busch, M. P., & Page Shafer, K. A. (2005). Acute-Phase Hepatitis C Virus Infection: Implications for Research, Diagnosis, and Treatment. *Clinical Infectious Diseases*, *40*(7), 959–961. https://doi.org/10.1086/428583

Cacoub, P., Vautier, M., Desbois, A. C., Saadoun, D., & Younossi, Z. (2018). Direct medical costs associated with the extrahepatic manifestations of hepatitis C virus infection in France. *Alimentary Pharmacology and Therapeutics*, *47*(1), 123–128. https://doi.org/10.1111/apt.14382

CDC (2025) https://www.cdc.gov/hepatitis-c/hcp/diagnosis-testing/index.html (Accessed on 3 May, 2025)

Chan, H. K., Hassali, M. A., Mohammed, N. S., Azlan, A., & Hassan, M. R. A. (2022). Barriers to scaling up hepatitis C treatment in Malaysia: a qualitative study with key stakeholders. *BMC Public Health*, *22*(1). https://doi.org/10.1186/s12889-022-12786-w

Cheng, Y. T., Cheng, J. S., Lin, C. H., Chen, T. H., Lee, K. C., & Chang, M. L. (2020). Rheumatoid factor and immunoglobulin M mark hepatitis C-associated mixed cryoglobulinaemia: an 8-year prospective study. *Clinical Microbiology and Infection*, *26*(3), 366–372. https://doi.org/10.1016/j.cmi.2019.06.018

Chu, Y. Y., Cheng, J. S., Wu, T. S., Chen, C. W., Chang, M. M. L. Y., Ku, H. P., Chien, R. N., & Chang, M. M. L. Y. (2021a). Association between hepatitis c virus infection and esophageal cancer: An asian nationwide population-based cohort

study. *Journal of Clinical Medicine*, *10*(11), 1–11. https://doi.org/10.3390/jcm10112395

Chu, Y. Y., Cheng, J. S., Wu, T. S., Chen, C. W., Chang, M. Y., Ku, H. P., Chien, R. N., & Chang, M. L. (2021b). Association between hepatitis c virus infection and esophageal cancer: An asian nationwide population-based cohort study. *Journal of Clinical Medicine*, *10*(11). https://doi.org/10.3390/jcm10112395

Conti, F., Buonfiglioli, F., Scuteri, A., Crespi, C., Bolondi, L., Caraceni, P., Foschi, F. G., Lenzi, M., Mazzella, G., Verucchi, G., Andreone, P., & Brillanti, S. (2016). Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *Journal of Hepatology*, *65*(4), 727–733. https://doi.org/10.1016/j.jhep.2016.06.015

Corado, J., Toro, F., Rivera, H., Bianco, N. E., Deibis, L., & De Sanctis, J. B. (1997). *Impairment of natural killer (NK) cytotoxic activity in hepatitis C virus (HCV) infection*.

Cua, I. H. Y., Hui, J. M., Bandara, P., Kench, J. G., Farrell, G. C., McCaughan, G. W., & George, J. (2007). Insulin resistance and liver injury in hepatitis C is not associated with virus-specific changes in adipocytokines. *Hepatology*, *46*(1). https://journals.lww.com/hep/fulltext/2007/07000/insulin_resistance_and_liver_injury_in_hepatitis_c.11.aspx

Dal Maso, L., & Franceschi, S. (2006). Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: A meta-analysis of epidemiologic studies. *Cancer Epidemiology Biomarkers and Prevention*, *15*(11), 2078–2085. https://doi.org/10.1158/1055-9965.EPI-06-0308

De Sanjose, S., Benavente, Y., Vajdic, C. M., Engels, E. A., Morton, L. M., Bracci, P. M., Spinelli, J. J., Zheng, T., Zhang, Y., Franceschi, S., Talamini, R., Holly, E. A.,

Grulich, A. E., Cerhan, J. R., Hartge, P., Cozen, W., Boffetta, P., Brennan, P., Maynadié, M., … Nieters, A. (2008). Hepatitis C and Non-Hodgkin Lymphoma Among 4784 Cases and 6269 Controls From the International Lymphoma Epidemiology Consortium. *Clinical Gastroenterology and Hepatology*, *6*(4), 451–458. https://doi.org/10.1016/j.cgh.2008.02.011

De Vita, S., Soldano, F., Isola, M., Monti, G., Gabrielli, A., Tzioufas, A., Ferri, C., Ferraccioli, G. F., Quartuccio, L., Corazza, L., De Marchi, G., Ramos Casals, M., Voulgarelis, M., Lenzi, M., Saccardo, F., Fraticelli, P., Mascia, M. T., Sansonno, D., Cacoub, P., … Galli, M. (2011). Preliminary classification criteria for the cryoglobulinaemic vasculitis. *Annals of the Rheumatic Diseases*, *70*(7), 1183–1190. https://doi.org/10.1136/ARD.2011.150755

Desbois, A. C., & Cacoub, P. (2017). Diabetes mellitus, insulin resistance and hepatitis C virus infection: A contemporary review. *World Journal of Gastroenterology*, *23*(9), 1697–1711. https://doi.org/10.3748/wjg.v23.i9.1697

Dubuisson, J., & Fabiani, F. L. (2007). Hepatitis C virus proteins. *World J Gastroenterol*, *13*(17), 2406–2415. www.wjgnet.comhttp://www.wjgnet.com/1007-9327/13/2406.asp

Eliah, D. T., Chamba, N. G., Sadiq, A. M., Mwasamwaja, A. O., Kimondo, F. C., Matay, C. D., Nziku, E. B., Mirai, T. E., Muhina, I. A. I., Said, F. H., Gharib, S. K., Lyamuya, F. S., Mkwizu, E. W., Kilonzo, K. G., Maro, V. P., & Shao, E. R. (2025). Seroprevalence and associated factors for hepatitis B and hepatitis C viral infection among patients with diabetes mellitus in Northern Tanzania. *PLoS ONE*, *20*(2 February). https://doi.org/10.1371/journal.pone.0319198

Evon, D. M., Stewart, P. W., Amador, J., Serper, M., Lok, A. S., Sterling, R. K., Sarkar, S., Golin, C. E., Reeve, B. B., Nelson, D. R., Reau, N., Lim, J. K., Reddy, K. R., Di Bisceglie, A. M., & Fried, M. W. (2018). A comprehensive assessment of patient reported symptom burden, medical comorbidities, and functional well

being in patients initiating direct acting antiviral therapy for chronic hepatitis C: Results from a large US multi-center observational study. *PLoS ONE*, *13*(8). https://doi.org/10.1371/journal.pone.0196908

Fabrizi, F., Cerutti, R., Porata, G., Messa, P., & Ridruejo, E. (2019). Direct-acting antiviral agents for HCV-associated glomerular disease and the current evidence. In *Pathogens* (Vol. 8, Issue 4). MDPI AG. https://doi.org/10.3390/pathogens8040176

Fabrizi, F., Donato, F. M., & Messa, P. (2017). Hepatitis C and Its Metabolic Complications in Kidney Disease. *Annals of Hepatology*, *16*(6), 851–861. https://doi.org/10.5604/01.3001.0010.5275

Ferri, C., Greco, F., Longombardo, G., Palla, P., Moretti, A., Marzo, E., Fosella, P. V, Pasero, G., & Bombardieri, S. (1991). *Originalia Antibodies against Hepatitis C Virus in Mixed Cryoglobulinemia Patients*.

Ghasemi, A., Broomand Lomer, N., & Saberi, A. (2025). Is there a link between Hepatitis A virus and Guillain-Barré syndrome? A systematic review of case reports. In *eNeurologicalSci* (Vol. 38). Elsevier B.V. https://doi.org/10.1016/j.ensci.2025.100551

Gisbert, C., Ros, R., De Haro, A., Walker, D. J., Bernal, M. P., Serrano, R., & Navarro-Aviñó, J. (2003). A plant genetically modified that accumulates Pb is especially promising for phytoremediation. *Biochemical and Biophysical Research Communications*, *303*(2), 440–445. https://doi.org/10.1016/S0006-291X(03)00349-8

Glynn, S. A., Wright, D. J., Kleinman, S. H., Hirschkorn, D., Tu, Y., Heldebrant, C., Smith, R., Giachetti, C., Gallarda, J., & Busch, M. P. (2005). Dynamics of viremia

in early hepatitis C virus infection. *Transfusion*, *45*(6), 994–1002. https://doi.org/10.1111/j.1537-2995.2005.04390.x

Goplen, C. M., Verbeek, W., Kang, S. H., Jones, C. A., Voaklander, D. C., Churchill, T. A., & Beaupre, L. A. (2019). Preoperative opioid use is associated with worse patient outcomes after Total joint arthroplasty: A systematic review and meta-analysis. *BMC Musculoskeletal Disorders*, *20*(1). https://doi.org/10.1186/s12891-019-2619-8

Gower, E., Estes, C., Blach, S., Razavi-Shearer, K., & Razavi, H. (2014). Global epidemiology and genotype distribution of the hepatitis C virus infection. In *Journal of Hepatology* (Vol. 61, Issue 1, pp. S45–S57). Elsevier B.V. https://doi.org/10.1016/j.jhep.2014.07.027

Guntipalli, P., Pakala, R., Gara, S. K., Ahmed, F., Bhatnagar, A., Endaya Coronel, M. K., Razzack, A. A., Solimando, A. G., Thompson, A., Andrews, K., Enebong Nya, G., Ahmad, S., Ranaldo, R., Cozzolongo, R., & Shahini, E. (2021). Worldwide prevalence, genotype distribution and management of hepatitis C. *Acta Gastro-Enterologica Belgica*, *84*(4), 637–656. https://doi.org/10.51821/84.4.015

Guo, L., Zhou, L., Zhang, N., Deng, B., & Wang, B. (2017). *Extrahepatic Autoimmune Diseases in Patients with Autoimmune Liver Diseases: A Phenomenon Neglected by Gastroenterologists*. https://doi.org/10.1155/2017/2376231

Hammerstad, S. S., Grock, S. F., Lee, H. J., Hasham, A., Sundaram, N., & Tomer, Y. (2015a). Diabetes and hepatitis C: A two-way association. In *Frontiers in Endocrinology* (Vol. 6). Frontiers Media S.A. https://doi.org/10.3389/fendo.2015.00134

Hammerstad, S. S., Grock, S. F., Lee, H. J., Hasham, A., Sundaram, N., & Tomer, Y. (2015b). Diabetes and Hepatitis C: A Two-Way Association. *Frontiers in Endocrinology*, *6*. https://doi.org/10.3389/fendo.2015.00134

Heck, J. E., Wu, C. K., Huang, X., Chew, K. W., Tong, M., Federman, N., Ritz, B., Arah, O. A., Li, C. Y., Yu, F., Olsen, J., Hansen, J., & Lee, P. C. (2022). Cohort study of familial viral hepatitis and risks of paediatric cancers. *International Journal of Epidemiology*, *51*(2), 448–457. https://doi.org/10.1093/ije/dyab262

Hissar, S. S., Goyal, A., Kumar, M., Pandey, C., Suneetha, P. V, Sood, A., Midha, V., Sakhuja, P., Malhotra, V., & Sarin, S. K. (2006). Hepatitis C virus genotype 3 predominates in North and Central India and is associated with significant histopathologic liver disease. *Journal of Medical Virology*, *78*(4), 452–458. https://doi.org/https://doi.org/10.1002/jmv.20561

Huang, C. E., Chang, J. J., Wu, Y. Y., Huang, S. H., Chen, W. M., Hsu, C. C., Lu, C. H., Hung, C. H., Shi, C. S., Lee, K. Der, Chen, C. C., & Chen, M. C. (2022). Different impacts of common risk factors associated with thrombocytopenia in patients with hepatitis B virus and hepatitis C virus infection. *Biomedical Journal*, *45*(5), 788–797. https://doi.org/10.1016/j.bj.2021.09.001

Huang, C. F., Dai, C. Y., Yeh, M. L., Huang, C. I., Lee, H. C., Lai, W. Ter, Liang, P. C., Lin, Y. H., Hsieh, M. Y., Hou, N. J., Lin, Z. Y., Chen, S. C., Huang, J. F., Chuang, W. L., & Yu, M. L. (2020). Cure or curd: Modification of lipid profiles and cardio-cerebrovascular events after hepatitis C virus eradication. *Kaohsiung Journal of Medical Sciences*, *36*(11), 920–928. https://doi.org/10.1002/kjm2.12275

Inokuchi, M., Ito, T., Nozawa, H., Miyashita, M., Morikawa, K., Uchikoshi, M., Shimozuma, Y., Arai, J., Shimazaki, T., Hiroishi, K., & Imawari, M. (2012). Lymphotropic hepatitis C virus has an interferon-resistant phenotype. *Journal of Viral Hepatitis*, *19*(4), 254–262. https://doi.org/https://doi.org/10.1111/j.1365-2893.2011.01541.x

Irekeola, A. A., Malek, N. A., Wada, Y., Mustaffa, N., Muhamad, N. I., & Shueb, R. H. (2021). Prevalence of HCV genotypes and subtypes in Southeast Asia: A systematic review and meta-analysis. In *PLoS ONE* (Vol. 16, Issue 5 May). Public Library of Science. https://doi.org/10.1371/journal.pone.0251673

Jang, H. jae, Lee, S. A., Seong, S., Kim, S., & Han, G. (2018). Combined Treatment for Lung Metastasis from Hepatocellular Carcinoma: A Case Report. *Explore*, *14*(5), 385–388. https://doi.org/10.1016/j.explore.2017.11.004

Jang, T. Y., Yeh, M. L., Huang, C. I., Lin, Z. Y., Chen, S. C., Hsieh, M. H., Dai, C. Y., Huang, J. F., Huang, C. F., Chuang, W. L., & Yu, M. L. (2018). Association of hyperuricemia with disease severity in chronic hepatitis c patients. *PLoS ONE*, *13*(11). https://doi.org/10.1371/journal.pone.0207043

Jeong, D., Karim, M. E., Wong, S., Wilton, J., Butt, Z. A., Binka, M., Adu, P. A., Bartlett, S., Pearce, M., Clementi, E., Yu, A., Alvarez, M., Samji, H., Velásquez García, H. A., Abdia, Y., Krajden, M., & Janjua, N. Z. (2021). Impact of HCV infection and ethnicity on incident type 2 diabetes: Findings from a large population-based cohort in British Columbia. *BMJ Open Diabetes Research and Care*, *9*(1). https://doi.org/10.1136/bmjdrc-2021-002145

Kamimura, H., Yamagiwa, S., Tomohiro, I., Higuchi, W., Ogata, N., Tsuchiya, A., Kamimura, K., Takamura, M., Kawai, H., & Terai, S. (2018). Bleeding from a small-intestinal ulcer associated with chronic hepatitis C. *American Journal of Case Reports*, *19*, 234–237. https://doi.org/10.12659/AJCR.908594

Kawamura, Y., Ikeda, K., Arase, Y., Yatsuji, H., Sezaki, H., Hosaka, T., Akuta, N., Kobayashi, M., Suzuki, F., Suzuki, Y., & Kumada, H. (2007). Viral Elimination Reduces Incidence of Malignant Lymphoma in Patients with Hepatitis C. *The American Journal of Medicine*, *120*(12), 1034–1041. https://doi.org/https://doi.org/10.1016/j.amjmed.2007.06.022

Khalish, G., & Gautama, M. S. N. (2025). Hand hygiene compliance among hospital visitors: A systematic review and meta-analysis of observational studies. *Journal of Infection Prevention*. https://doi.org/10.1177/17571774251324373

Kraus, S., Breier, M., & Dasí-Rodríguez, S. (2020). The art of crafting a systematic literature review in entrepreneurship research. *International Entrepreneurship and Management Journal*, *16*(3), 1023–1042. https://doi.org/10.1007/s11365-020-00635-4

Kuna, L., Jakab, J., Smolic, R., Wu, G. Y., & Smolic, M. (2019). HCV extrahepatic manifestations. In *Journal of Clinical and Translational Hepatology* (Vol. 7, Issue 2, pp. 172–182). Xia and He Publishing Inc. https://doi.org/10.14218/JCTH.2018.00049

Kushner, T., Djerboua, M., Biondi, M. J., Feld, J. J., Terrault, N., & Flemming, J. A. (2022). Influence of hepatitis C viral parameters on pregnancy complications and risk of mother-to-child transmission. *Journal of Hepatology*, *77*(5), 1256–1264. https://doi.org/10.1016/j.jhep.2022.05.016

Lee, K. K., Stelzle, D., Bing, R., Anwar, M., Strachan, F., Bashir, S., Newby, D. E., Shah, J. S., Chung, M. H., Bloomfield, G. S., Longenecker, C. T., Bagchi, S., Kottilil, S., Blach, S., Razavi, H., Mills, P. R., Mills, N. L., McAllister, D. A., & Shah, A. S. V. (2019). Global burden of atherosclerotic cardiovascular disease in people with hepatitis C virus infection: a systematic review, meta-analysis, and modelling study. *The Lancet Gastroenterology and Hepatology*, *4*(10), 794–804. https://doi.org/10.1016/S2468-1253(19)30227-4

Li, Q., Tong, Y., Xu, Y., Niu, J., & Zhong, J. (2018). Genetic Analysis of Serum-Derived Defective Hepatitis C Virus Genomes Revealed Novel Viral cis Elements for Virus Replication and Assembly . *Journal of Virology*, *92*(7). https://doi.org/10.1128/jvi.02182-17

Lindgren, P., Löfvendahl, S., Brådvik, G., & Weiland, O. (2021). Reduced work absenteeism in patients with hepatitis C treated with second-generation direct-acting antivirals. *Journal of Viral Hepatitis*, *28*(1), 142–146. https://doi.org/10.1111/jvh.13398

Livier, O., Ermine, H., Rançois, F., Efrère, L., Ean -P Ierre, J., Ronowicki, B., Avier, X., Ariette, M., Atayoun, K., Ondeau, J., Irginie, V., Audreau, E. C.-S., Rançoise, F., Alensi, V., Atrice, P., Acoub, C., Hristian, C., Rechot, B., Runo, B., … Roussard, T. (2002). Splenic Lymphoma With Villous Lymphocy Tes And Hepatitis C Virus Regression Of Splenic Lymphoma With Villous Lymphocytes After Treatment Of Hepatitis C Virus Infection A Bstract Background Some epidemiologic studies suggest. In *N Engl J Med* (Vol. 347, Issue 2). www.nejm.org

Lockwood, C., Munn, Z., & Porritt, K. (2015). Qualitative research synthesis: Methodological guidance for systematic reviewers utilizing meta-aggregation. *International Journal of Evidence-Based Healthcare*, *13*(3), 179–187. https://doi.org/10.1097/XEB.0000000000000062

Machado Mariana V., & Cortez-Pinto Helena. (2009). 2009 Insulin resistance and steatosis. *Annals of Hepatology*, *8(1)*, 67–75. https://doi.org/https://doi.org/10.1016/S1665-2681(19)31829-0

Malik, S., Dekio, F., & Wen, J. W. (2014). Liver transplantation in a child with multifocal hepatocellular carcinoma hepatitis C and management of post-transplant viral recurrence using boceprevir. *Pediatric Transplantation*, *18*(2), E64–E68.

Mazzaro, C., Panarello, G., Tesio, F., Santini, G., Crovatto, M., Mazzi, G., Zorat, F., Tulissi, P., Pussini, E., Baracetti, S., Campanacci, L., & Pozzato, G. (2000). Hepatitis C virus risk: A hepatitis C virus related syndrome. *Journal of Internal Medicine*, *247*(5), 535–545. https://doi.org/10.1046/j.1365-2796.2000.00627.x

Mazzaro, C., Quartuccio, L., Adinolfi, L. E., Roccatello, D., Pozzato, G., Nevola, R., Tonizzo, M., Gitto, S., Andreone, P., & Gattei, V. (2021). A review on extrahepatic manifestations of chronic hepatitis c virus infection and the impact of direct-acting antiviral therapy. In *Viruses* (Vol. 13, Issue 11). https://doi.org/10.3390/v13112249

Medina, C., García, A. H., Crespo, F. I., Toro, F. I., Mayora, S. J., & De Sanctis, J. B. (2023). A Synopsis of Hepatitis C Virus Treatments and Future Perspectives. In *Current Issues in Molecular Biology* (Vol. 45, Issue 10, pp. 8255–8276). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/cimb45100521

Messina, J. P., Humphreys, I., Flaxman, A., Brown, A., Cooke, G. S., Pybus, O. G., & Barnes, E. (2014). *Global Distribution and Prevalence of Hepatitis C Virus Genotypes*. https://doi.org/10.1002/hep.27259/suppinfo

Mihm, S., Fayyazi, A., Hartmann, H., & Ramadori, G. (1997). Analysis of histopathological manifestations of chronic hepatitis C virus infection with respect to virus genotype. *Hepatology*, *25*(3), 735–739. https://doi.org/10.1002/hep.510250340

Minopetrou, M., Hadziyannis, E., Deutsch, M., Tampaki, M., Georgiadou, A., Dimopoulou, E., Vassilopoulos, D., & Koskinas, J. (2013). Hepatitis C virus (HCV)-related cryoglobulinemia: Cryoglobulin type and anti-HCV profile. *Clinical and Vaccine Immunology*, *20*(5), 698–703. https://doi.org/10.1128/CVI.00720-12

Mohamed Shaffril, H. A., Samsuddin, S. F., & Abu Samah, A. (2021a). The ABC of systematic literature review: the basic methodological guidance for beginners. *Quality and Quantity*, *55*(4), 1319–1346. https://doi.org/10.1007/s11135-020-01059-6

Mohamed Shaffril, H. A., Samsuddin, S. F., & Abu Samah, A. (2021b). The ABC of systematic literature review: the basic methodological guidance for beginners. *Quality and Quantity*, *55*(4), 1319–1346. https://doi.org/10.1007/s11135-020-01059-6

Morrone, A., Fiorilli, V., Cinti, L., Roberto, P., Ferri, A. L., Visentini, M., Pulsoni, A., Spinelli, F. R., De Santis, A., Antonelli, G., Basili, S., Tosti, M. E., Conti, F., & Casato, M. (2024). Surface antigen serocleared hepatitis B virus infection increases the risk of mixed cryoglobulinemia vasculitis in male patients with chronic hepatitis C. *Frontiers in Immunology*, *15*. https://doi.org/10.3389/fimmu.2024.1411146

Mulrooney-Cousins, P. M., & Michalak, T. I. (2024). Molecular testing in hepatitis virus-related disease. In *Diagnostic Molecular Pathology* (pp. 63–77). Elsevier.

Munn, Z., Barker, T. H., Moola, S., Tufanaru, C., Stern, C., McArthur, A., Stephenson, M., & Aromataris, E. (2019). Methodological quality of case series studies: An introduction to the JBI critical appraisal tool. *JBI Database of Systematic Reviews and Implementation Reports*. https://doi.org/10.11124/JBISRIR-D-19-00099

Murphy, D. G., Sablon, E., Chamberland, J., Fournier, E., Dandavino, R., & Tremblay, C. L. (2015). Hepatitis C virus genotype 7, a new genotype originating from Central Africa. *Journal of Clinical Microbiology*, *53*(3), 967–972. https://doi.org/10.1128/JCM.02831-14

Nagao, Y., Nakasone, K., Maeshiro, T., Nishida, N., Kimura, K., Kawahigashi, Y., Tanaka, Y., & Sata, M. (2017). Successful Treatment of Oral Lichen Planus with Direct-Acting Antiviral Agents after Liver Transplantation for Hepatitis C Virus-Associated Hepatocellular Carcinoma. *Case Reports in Gastroenterology*, *11*(3), 701–710. https://doi.org/10.1159/000484132

Negro, F., & Sanyal, A. J. (2009). Hepatitis C virus, steatosis and lipid abnormalities: Clinical and pathogenic data. In *Liver International* (Vol. 29, Issue SUPPL. 2, pp. 26–37). https://doi.org/10.1111/j.1478-3231.2008.01950.x

Nevola, R., Acierno, C., Pafundi, P. C., & Adinolfi, L. E. (2021). Chronic hepatitis C infection induces cardiovascular disease and type 2 diabetes: mechanisms and management. *Minerva Medica*, *112*(2), 188—200. https://doi.org/10.23736/s0026-4806.20.07129-3

Niepmann, M., & Gerresheim, G. K. (2020). Hepatitis C virus translation regulation. *International Journal of Molecular Sciences*, *21*(7). https://doi.org/10.3390/ijms21072328

Núñez, O., Fernández-Martínez, A., Majano, P. L., Apolinario, A., Gómez-Gonzalo, M., Benedicto, I., López-Cabrera, M., Boscá, L., Clemente, G., García-Monzón, C., & Martín-Sanz, P. (2004). Increased intrahepatic cyclooxygenase 2, matrix metalloproteinase 2, and matrix metalloproteinase 9 expression is associated with progressive liver disease in chronic hepatitis C virus infection: Role of viral core and NS5A proteins. *Gut*, *53*(11), 1665–1672. https://doi.org/10.1136/gut.2003.038364

Ohto, H., Terazawa, S., Sasaki, N., Sasaki, N., Hino, K., Ishiwata, C., Kako, M., Ujiie, N., Endo, C., Matsui, A., Okamoto, H., Mishiro, S., & null null. (1994). Transmission of Hepatitis C Virus from Mothers to Infants. *New England Journal of Medicine*, *330*(11), 744–750. https://doi.org/10.1056/NEJM199403173301103

Pascut, D., Hoang, M., Nguyen, N. N. Q., Pratama, M. Y., & Tiribelli, C. (2021a). Hcv proteins modulate the host cell mirna expression contributing to hepatitis c pathogenesis and hepatocellular carcinoma development. In *Cancers* (Vol. 13, Issue 10). MDPI. https://doi.org/10.3390/cancers13102485

Pascut, D., Hoang, M., Nguyen, N. N. Q., Pratama, M. Y., & Tiribelli, C. (2021b). Hcv proteins modulate the host cell mirna expression contributing to hepatitis c pathogenesis and hepatocellular carcinoma development. In *Cancers* (Vol. 13, Issue 10). MDPI. https://doi.org/10.3390/cancers13102485

Patel, N., Jha, K., Pavethynath, V., Ravi, S., Pendyala, S. K., Shinde, S. M., & Tiwari, R. (2025). Anterior Rehabilitation with Basal Implants in Cleft Cases Systematic Review. *Journal of Pharmacy and Bioallied Sciences*. https://doi.org/10.4103/jpbs.jpbs_373_24

Peter Simmonds. (2004). 2004 Genetic diversity and evolution of hepatitis C. *Journal of General Virology*, *85*, 3173–3188.

Petit, J.-M., Minello, A., Jooste, V., Bour, J. B., Galland, F., Duvillard, L., Verges, B., Olsson, N. O., Gambert, P., & Hillon, P. (2005). Decreased Plasma Adiponectin Concentrations Are Closely Related to Steatosis in Hepatitis C Virus-Infected Patients. *The Journal of Clinical Endocrinology & Metabolism*, *90*(4), 2240–2243. https://doi.org/10.1210/jc.2004-1266

Petta, S. (2017). Hepatitis C virus and cardiovascular: A review. In *Journal of Advanced Research* (Vol. 8, Issue 2, pp. 161–168). Elsevier B.V. https://doi.org/10.1016/j.jare.2016.06.001

Rehermann, B. (2013). Pathogenesis of chronic viral hepatitis: differential roles of T cells and NK cells. *Nature Medicine*, *19*(7), 859–868. https://doi.org/10.1038/nm.3251

Reinberg, C., Vingerhoets, S., Pavlova, O., Guenova, E., Papadimitriou-Olivgeris, M., & Comte, D. (2024). Cryoglobulinemic vasculitis triggered by Staphylococcus aureus endocarditis with chronic hepatitis C virus co-infection: a case report and literature review. *Frontiers in Immunology*, *15*. https://doi.org/10.3389/fimmu.2024.1385086

Roberts, E. A., & Yeung, L. (2002). Maternal-infant transmission of hepatitis C virus infection. *Hepatology*, *36*(S1), S106–S113. https://doi.org/10.1002/hep.1840360714

Romero-López, C., & Berzal-Herranz, A. (2009). A long-range RNA-RNA interaction between the 5′ and 3′ ends of the HCV genome. *RNA*, *15*(9), 1740–1752. https://doi.org/10.1261/rna.1680809

Saadoun, D., Suarez, F., Lefrere, F., Valensi, F., Mariette, X., Aouba, A., Besson, C., Varet, B., Troussard, X., Cacoub, P., & Hermine, O. (2005). *Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity?* https://doi.org/10.1182/blood

Sangar, D. V., & Carroll, A. R. (1998). A tale of two strands: Reverse-transcriptase polymerase chain reaction detection of hepatitis C virus replication. In *Hepatology* (Vol. 28, Issue 5, pp. 1173–1176). https://doi.org/10.1002/hep.510280501

Saputra, L. A., Indrawati, I., Hardianti, M. S., & Anggorowati, N. (2024). Correlation Between the Hepatitis C Virus NS3 Protein and CD30 Expression in Diffuse Large B-cell Lymphoma. *Cureus*. https://doi.org/10.7759/cureus.65108

Scarpato, S., Galassi, G., Monti, G., Mazzaro, C., Mascia, M. T., Scaini, P., Filippini, D., Pietrogrande, M., & Galli, M. (2020). Peripheral neuropathy in mixed cryoglobulinaemia: clinical assessment and therapeutic approach. *Clin Exp Rheumatol*, *38*(6), 1231–1237.

Shaffril, H. A. M., Krauss, S. E., & Samsuddin, S. F. (2018). A systematic review on Asian's farmers' adaptation practices towards climate change. *Science of The Total Environment*, *644*, 683–695. https://doi.org/10.1016/J.SCITOTENV.2018.06.349

Sherman, A. C., & Sherman, K. E. (2015). Extrahepatic Manifestations of Hepatitis C Infection: Navigating CHASM. In *Current HIV/AIDS Reports* (Vol. 12, Issue 3, pp. 353–361). Current Medicine Group LLC 1. https://doi.org/10.1007/s11904-015-0274-8

Shimada, M., Nakamura, N., Endo, T., Yamabe, H., Nakamura, M., Murakami, R., Narita, I., & Tomita, H. (2017). Daclatasvir/asunaprevir based direct-acting antiviral therapy ameliorate hepatitis C virus-associated cryoglobulinemic membranoproliferative glomerulonephritis: A case report. *BMC Nephrology*, *18*(1). https://doi.org/10.1186/s12882-017-0534-5

Songtanin, B., & Nugent, K. (2023). Burden, Outcome, and Comorbidities of Extrahepatic Manifestations in Hepatitis C Virus Infection. In *Biology* (Vol. 12, Issue 1). MDPI. https://doi.org/10.3390/biology12010023

Srivastava, A., Raghav, P., Pradhan, S., Khera, A., Rafique, S., Wadhwa, P., & Saini, R. (2025). Correlating Dose and Time of Prenatal Alcohol, Smoking, and Drug Exposure on Craniofacial Morphology: A Systematic Review. *Cureus*. https://doi.org/10.7759/cureus.78320

Sung, P. S., Lee, E. B., Park, D. J., Lozada, A., Jang, J. W., Bae, S. H., Choi, J. Y., & Yoon, S. K. (2018). Interferon-free treatment for hepatitis c virus infection induces normalization of extrahepatic type i interferon signaling. *Clinical and Molecular Hepatology*, *24*(3), 302–310. https://doi.org/10.3350/cmh.2017.0074

Takakusagi, S., Sato, K., Suzuki, Y., Yamazaki, Y., & Kosone, T. (2018). *Improvement of Proteinuria due to Combination Therapy with Daclatasvir and Asunaprevir in Hepatitis C Virus-associated Renal Disease without Cryoglobulinemia*. 2189–2195. https://doi.org/10.2169/internalmedicine.9624-17

Talić Drlje, I., Šušak, B., Skočibušić, S., Tutiš, B., Jakovac, S., & Arapović, J. (2025). Sociodemographic characteristics, risk factors and genotype distribution of hepatitis C virus in Bosnia and Herzegovina: Single center experience. *Clinical Epidemiology and Global Health*, *31*. https://doi.org/10.1016/j.cegh.2024.101845

Tani, J., Masaki, T., Oura, K., Tadokoro, T., Morishita, A., & Kobara, H. (2024). Extrahepatic Cancer Risk in Patients with Hepatitis C Virus Infection Treated with Direct-Acting Antivirals. In *Microorganisms* (Vol. 12, Issue 9). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/microorganisms12091926

Tharakan, S., Faqah, O., Asghar, W., & Ilyas, A. (2022). Microfluidic Devices for HIV Diagnosis and Monitoring at Point-of-Care (POC) Settings. In *Biosensors* (Vol. 12, Issue 11). MDPI. https://doi.org/10.3390/bios12110949

Tomei, L., Failla, C., Santolini, E., De Francesco, R., & Monica, N. La. (1993). NS3 Is a Serine Protease Required for Processing of Hepatitis C Virus Polyprotein. In *JOURNAL OF VIROLOGY*. https://journals.asm.org/journal/jvi

Tung, C. H., Chen, Y. C., & Chen, Y. C. (2022). Association between Anti-Hepatitis C Viral Intervention Therapy and Risk of Sjögren's Syndrome: A National Retrospective Analysis. *Journal of Clinical Medicine*, *11*(15). https://doi.org/10.3390/jcm11154259

Wang, C. H., Ou, S. F., & Tseng, Y. T. (2022). Long-term impact of certain coexisting extrahepatic unisystem and multisystem manifestations on trends in incidence of liver cirrhosis in treatment-naïve patients with chronic hepatitis C: A nested case-control study. *Medicine (United States)*, *101*(29), E29697. https://doi.org/10.1097/MD.0000000000029697

Wang, Y., Jie, W., Ling, J., & Yuanshuai, H. (2021). HCV core antigen plays an important role in the fight against HCV as an alternative to HCV-RNA detection. In *Journal of Clinical Laboratory Analysis* (Vol. 35, Issue 6). John Wiley and Sons Inc. https://doi.org/10.1002/jcla.23755

Wasitthankasem, R., Vongpunsawad, S., Siripon, N., Suya, C., Chulothok, P., Chaiear, K., Rujirojindakul, P., Kanjana, S., Theamboonlers, A., Tangkijvanich, P., & Poovorawan, Y. (2015). Genotypic distribution of hepatitis C virus in Thailand and Southeast Asia. *PLoS ONE*, *10*(5). https://doi.org/10.1371/journal.pone.0126764

Welty, E., Hofstetter, S., & Schulte, S. J. (2012). *Time to re-evaluate how we teach information literacy Applying PICO in library instruction*. 476–477.

WHO (2024) https://www.who.int/news-room/fact-sheets/detail/hepatitis-c

(Accessed on 3 May, 2025)

Xue, R., Elbendary, A., & Wu, T. (2019). Necrolytic acral erythema in a Chinese patient with hepatitis c and hepatitis b virus coinfection. *Anais Brasileiros de Dermatologia*, *94*(4), 446–448. https://doi.org/10.1590/abd1806-4841.20197257

Yang, Y. H., Chiang, H. J., Yip, H. K., Chen, K. J., Chiang, J. Y., Lee, M. S., & Sung, P. H. (2019). Risk of New-Onset Atrial Fibrillation Among Asian Chronic Hepatitis C Virus Carriers: A Nationwide Population-Based Cohort Study. *Journal of the American Heart Association*, *8*(22). https://doi.org/10.1161/JAHA.119.012914

Young, E. P., O'Neill, A. F., & Rangaswami, A. A. (2025). Pediatric Hepatocellular Carcinoma: A Review of Predisposing Conditions, Molecular Mechanisms, and Clinical Considerations. In *International Journal of Molecular Sciences* (Vol. 26,

Issue 3). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/ijms26031252

Younossi, Z. M., Henry, L., P. Ong, J., Tanaka, A., Eguchi, Y., Mizokami, M., Lim, Y.-S., Dan, Y. Y., Yu, M.-L., & Stepanova, M. (2019). Systematic review with meta-analysis: extrahepatic manifestations in chronic hepatitis C virus-infected patients in East Asia. *Alimentary Pharmacology & Therapeutics*, *49*(6), 644–653. https://doi.org/https://doi.org/10.1111/apt.15131

Younossi, Z., Park, H., Henry, L., Adeyemi, A., & Stepanova, M. (2016a). Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. *Gastroenterology*, *150*(7), 1599–1608. https://doi.org/10.1053/j.gastro.2016.02.039

Younossi, Z., Park, H., Henry, L., Adeyemi, A., & Stepanova, M. (2016b). Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. *Gastroenterology*, *150*(7), 1599–1608. https://doi.org/https://doi.org/10.1053/j.gastro.2016.02.039

Zampino, R., Marrone, A., Restivo, L., Guerrera, B., Sellitto, A., Rinaldi, L., Romano, C., & Adinolfi, L. E. (2013). Chronic HCV infection and inflammation: Clinical impact on hepatic and extra-hepatic manifestations. In *World Journal of Hepatology* (Vol. 5, Issue 10, pp. 528–540). https://doi.org/10.4254/wjh.v5.i10.528

Zeng, X., Zhang, Y., Kwong, J. S. W., Zhang, C., Li, S., Sun, F., Niu, Y., & Du, L. (2015a). The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. In *Journal of Evidence-Based Medicine* (Vol. 8, Issue 1, pp. 2–10). Blackwell Publishing. https://doi.org/10.1111/jebm.12141

Zeng, X., Zhang, Y., Kwong, J. S. W., Zhang, C., Li, S., Sun, F., Niu, Y., & Du, L. (2015b). The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. In *Journal of Evidence-Based Medicine* (Vol. 8, Issue 1, pp. 2–10). Blackwell Publishing. https://doi.org/10.1111/jebm.12141

Zhang, Y., Chen, L. M., & He, M. (2017). Hepatitis C Virus in mainland China with an emphasis on genotype and subtype distribution. In *Virology Journal* (Vol. 14, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s12985-017-0710-z

Zilouchian, H., Faqah, O., Kabir, M. A., Gross, D., Pan, R., Shaifman, S., Younas, M. A., Haseeb, M. A., Thomas, E., & Asghar, W. (2025). Current and Future Diagnostics for Hepatitis C Virus Infection. In *Chemosensors* (Vol. 13, Issue 2). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/chemosensors13020031

APPENDIX I: JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

JBI Critical Appraisal Checklist for Cohort Studies (adopted from Zeng et al., 2015)

Reviewer : _____ Date : _____

Author : _____ Year : _____

Record : _____ Number : _____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	□	□	□	□
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were confounding factors identified?	□	□	□	□
5. Were strategies to deal with confounding factors stated?	□	□	□	□
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	□	□	□	□
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	□	□	□	□
10. Were strategies to address incomplete follow up utilized?	□	□	□	□

11. Was appropriate statistical analysis used? □ □ □ □

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

APPENDIX II: JBI CRITICAL APPRAISAL CHECKLIST FOR CASE REPORTS

JBI Critical Appraisal Checklist for Case Reports (adopted from Munn et al., 2019)

Reviewer : _____ Date : _____

Author : _____ Year : _____

Record : _____ Number : _____

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	□	□	□	□
2. Was the patient's history clearly described and presented as a timeline?	□	□	□	□
3. Was the current clinical condition of the patient on presentation clearly described?	□	□	□	□
4. Were diagnostic tests or assessment methods and the results clearly described?	□	□	□	□
5. Was the intervention(s) or treatment procedure(s) clearly described?	□	□	□	□
6. Was the post-intervention clinical condition clearly described?	□	□	□	□
7. Were adverse events (harms) or unanticipated events identified and described?	□	□	□	□
8. Does the case report provide takeaway lessons?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

_____

_____

APPENDIX III: JBI CRITICAL APPRAISAL CHECKLIST FOR ANALYTICAL CROSS-SECTIONAL STUDIES

JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies (adopted from Patel et al., 2025)

Reviewer : _____ Date : _____

Author : _____ Year : _____

Record : _____ Number : _____

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	□	□	□	□
2. Were the study subjects and the setting described in detail?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were objective, standard criteria used for measurement of the condition?	□	□	□	□
5. Were confounding factors identified?	□	□	□	□
6. Were strategies to deal with confounding factors stated?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was appropriate statistical analysis used?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

_____

_____