AUCTORES
Globalize your Research

Journal of General Medicine and Clinical Practice
Victoria Ferguson *

Open Access

Review Article

Progression from Hepatitis C to Hepatocellular Carcinoma (HCC)

Victoria Ferguson *, James Keane, Leonard B. Goldstein

Resonant Medicine, Omer, Israel.

***Corresponding Author:** Victoria Ferguson, Resonant Medicine, Omer, Israel.

Received date: June 11, 2025; Accepted date: July 02, 2025; Published date: July 14, 2025

Citation: Victoria Ferguson, James Keane, Leonard B. Goldstein, (2025), Progression from Hepatitis C to Hepatocellular Carcinoma (HCC), *J. General Medicine and Clinical Practice,* 8(7); **DOI:10.31579/2639-4162/281**

Abstract

Cirrhosis and hepatocellular carcinoma (HCC) are potentially fatal complications of chronic hepatitis C virus (HCV) infection. Hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) progresses with a highly multicentric occurrence, even after radical hepatectomy. Despite efforts to clarify the pathogenesis, the underlying molecular mechanism remains elusive.

Kew Words: hepatocellular; carcinoma; chronic; hepatitis C virus

Introduction

Cirrhosis and hepatocellular carcinoma (HCC) are potentially fatal complications of chronic hepatitis C virus (HCV) infection. Hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) progresses with a highly multicentric occurrence, even after radical hepatectomy. Despite efforts to clarify the pathogenesis, the underlying molecular mechanism remains elusive.

Hepatocellular Carcinoma (HCC) is the most common primary liver cancer and the third leading cause of cancer-related deaths worldwide [1, 2]. HCC is also the fifth most common solid tumor [3]. It is induced by alcohol intake, obesity, and chronic liver illness, particularly viral hepatitis B or hepatitis C virus (HCV) [4].

Hepatitis C Virus (HCV) is widespread globally, and all individuals, regardless of race, sex, or age are susceptible to this virus. Despite the availability of curative treatment, beginning in 2020, there were an estimated 56,800,000 viremic HCV infections globally [5]. The World Health Organization (WHO) estimates that each year 399,000 people die from HCV related cirrhosis and hepatocellular carcinoma [6]. Certain populations are particularly impacted by the burden of HCV, including people who inject drugs (PWID), men who have sex with men (MSM), incarcerated individuals, and those of lower socioeconomic status (7). By expanding awareness of the progress of HCV to HCC among physicians and other providers, such vulnerable populations will receive improved and more effective care. Cancer-related research has recently focused on chemokines and microRNAs (miRNAs) discovered as tumor indicators in tissues and the blood [8, 9]. This article will focus on the progression from hepatitis C to Hepatocellular Carcinoma (HCC).

Discussion:

Transmission

HCV is a bloodborne viral illness spread via blood transfusions, organ transplantation, unsafe needle and sexual practices, and vertical transmission in the perinatal period. Prior to the implementation of blood screening practices in 1992, HCV was most commonly transmitted via blood transfusions. The ubiquity of advanced blood product screening techniques in developed nations has drastically decreased the incidence of transfusion-transmitted HCV to one in a million per unit of transfused blood (0.0001%) (10). However, around 2004, clinicians and public health professionals were met with a new challenge as the opioid epidemic accelerated the transmission of HCV. Currently, the primary mode of transmission of HCV is via shared needles, syringes and other objects used to prepare and inject drug products (11). The opioid epidemic prompted public health officials to broaden screening practices for HCV to include all adults at least once per lifetime, regardless of risk assessment. Previous screening guidelines were risk-based and limited to only those with specific risk factors including PWID, MSM, individuals who received tattoos and/or blood transfusions prior to 1992, and/or those undergoing hemodialysis.

Screening The United States Preventive Services Task Force (USPSTF) classifies HCV screening in all adults aged 18 to 79 as a Grade B recommendation. Per USPSTF grading criteria, Grade B designation means the service is recommended to provide moderate benefit with high certainty (12). The USPSTF acknowledges that the aforementioned populations who exhibit high risk factors should be screened more than once per lifetime. Furthermore, the guidelines as per recommendations from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend screening these populations at least annually (13). Additionally, the Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists recommend all pregnant individuals be screened for HCV during every pregnancy, regardless of risk profile (14). Women of childbearing age have an increased prevalence of HCV compared to the general population. Therefore, it's vital to screen women during the perinatal period, regardless of participation in risk factors, given the vertical transmission pattern of HCV. The rationale for screening individuals with ongoing risk factors more frequently than the general population is based on the importance of identifying new infections quickly in the era of high-

efficacy treatment modalities. The process of screening begins with an anti-HCV antibody test, which if positive is followed by a nucleic acid test (NAT) for HCV ribonucleic acid (RNA) as a method of quantitative analysis [15].

Acute vs Chronic Acute HCV infection is delineated as the six-month period following exposure. During the acute phase, there is an estimated 20-40% possibility of spontaneous clearance (16). Factors that influence the likelihood of spontaneous clearance include female sex, genetic factors, and viral genotype. Regardless, early treatment with direct acting antivirals (DAAs) has been shown to be highly effective and cost-effective (17). The process of identifying an acute HCV infection is difficult for two main reasons. Firstly, upon exposure to HCV, there is a one-to-two-week window period in which the virus is undetectable as viral RNA replicates. Secondly, approximately 80% of individuals with acute HCV are asymptomatic. The silent nature of acute HCV allows progression to chronic HCV unknowingly. Most individuals with chronic HCV do not exhibit symptoms until significant hepatic damage has occurred (18). In 2023, the Centers for Disease Control (CDC) estimated that 75% of individuals living with HCV were unaware of their infection status (19). Those who are symptomatic experience generalized malaise, jaundice, nausea, vomiting, diarrhea, fever, right upper quadrant abdominal pain, and/or dark urine. Neuropsychiatric symptoms such as depression, irritability, cognitive impairment, and/or poor concentration "cluster" with the insidious somatic symptoms further hindering quality of life [20]. The proposed mechanisms of neuroinvasion, immune-mediated damage, neurotransmitter alterations, and cryoglobulinemia have been hypothesized as etiologies of such extrahepatic symptoms of HCV.

Progression from hepatitis C to HCC pathophysiology:

Chronic HCV is the leading cause of hepatocellular carcinoma (HCC) and liver-related deaths in the Western world. The basis of progression from chronic HCV to HCC lies in the turbulent and persistently inflamed hepatic environment created by chronic HCV. The synergistic effects of chronic inflammation, hepatic steatosis, oxidative stress, and disrupted cell signaling pathways accumulate and create a supportive tumor microenvironment. When chronic HCV is left untreated, fibrotic and cirrhotic changes occur. Once cirrhosis has been established the annual risk of developing HCC increases by 1-5% (21). Chronic HCV induces a state of hepatic steatosis. As lipids accumulate within hepatocytes, stress and oxidative changes occur [22]. Oxidative stress is known to trigger tumorigenesis via DNA damage and genomic instability. Such changes are accompanied by the production of reactive oxygen species (ROS), which upregulate cell proliferation and survival pathways including Wnt/beta-catenin, NF-kappaB, and p53 [23]. Immune-mediated pathways involving dendritic, Langerhans, and B cells and macrophages contribute to hepatic injury [24].

Dendritic Cells Dendritic cells play a vital role in regulating the immune system by capturing and processing pathogens and damaged cells via endocytosis, phagocytosis, and receptor-mediated uptake (25). The processed pathogens, now referred to as antigens, are presented to T cells to initiate an adaptive immune response. As part of the adaptive immune response, dendritic cells contribute to cytokine and chemokine production. In the acute phase of HCV there is an initial increase in both circulating and intrahepatic dendritic cells, followed by a reduction in circulating dendritic cells. Chronic HCV hinders normal functioning of dendritic cells directly leading to immune invasion and viral persistence (26). Dendritic cells in both the acute and chronic phases of HCV display an immature and defective phenotype, characterized by impaired T cell stimulation, altered cytokine production, and increased apoptosis.

Macrophages As a key component of the innate immune system, macrophages play an important role in immune surveillance via phagocytosis. During the acute phase of HCV, macrophages are involved in pathogen clearance and tissue repair. However, chronic activation of macrophages in cases of untreated HCV leads to prolonged inflammation and subsequent hepatic fibrosis. As fibrotic changes progress, macrophages create a pro-tumorigenic environment by interacting with hepatic stellate cells [27]. Tumor-associated macrophages (TAMs) promote tumor growth and invasion further promoting the progression towards HCC. Once HCC is established, macrophages undergo a metabolic shift supporting immune suppression and tumor progression [28].

Latest Research in Progression from HCV to HCC:

Research has recently focused on components of cell biology as a prognostic tool regarding the progression of HCV to HCC. Micro ribonucleic acids (miRNAs) are non-coding ribonucleic acids (RNAs) responsible for post-transcriptional gene expression. When dysregulated, miRNAs function as oncogenes or tumor suppressors driving various cancers involving the lung(s), breast(s), stomach, and/or colorectal system [29]. By functioning as oncogenes or tumor suppressors, miRNAs are able to influence tumor growth and chemoresistance. Specific miRNA profiles have been identified as potential tumor indicators for HCC. For example, miR-221 and miR-542 have been identified as potential biomarkers for cirrhotic changes and HCC in patients with HCV [30]. miR-122 is significantly elevated in individuals with chronic HCV and can be used as a biomarker to monitor disease progression and treatment response in this population [31]. Therefore, circulating miRNAs can be used to monitor liver disease progression in patients with chronic HCV. Chemokines are proteins that communicate with G-coupled protein receptors (GCPRs) to mediate cell communication. They play a significant role in the pathogenesis of HCV via immune cell recruitment and subsequent hepatic inflammation and fibrosis [32]. Specific chemokines are upregulated in chronic HCV and are involved in the progression of HCV, including CXCL9, CXCL10, CXCL11, CCL3, CCL4, and CCL5 [33]. These chemokines contribute to the immune response and hepatic injury fueling progression to HCC. Studies have shown that plasma CXCL10 levels were higher prior to initiation of antiviral treatment in patients with HCV who did not respond to therapy (34). This indicates that plasma CXCL10 levels may serve as a predictive biomarker for responsiveness to antiviral therapy. This suggests that plasma CXCL10 levels have a predictive ap responsiveness to antiviral therapy [35]. Recent research has shown that certain genetic variations confer a protective advantage against hepatitis C. This includes single nucleotide polymorphisms (SNPs), which are variations of a single nucleotide at a specific site in the genome. Specific SNPs have been identified as advantageous in those with acute HCV in terms of viral clearance and treatment response. For example, the IL-28B SNPs rs12979860 and rs8099917 are more frequently seen in patients with spontaneous clearance of acute HCV (34). There are certain miRNAs that confer anti-HCV activity and are thus referred to as "antiviral miRNA." The let-7 family miRNAs increase cell apoptosis and thus reduce HCV replication by targeting IGF2BP1 required for HCV replication [36].

Treatments: Cure from HCV was achieved in 1998 through the development of pegylated interferon-based therapy. However, significant hematologic, neuropsychiatric and autoimmune adverse reactions called for a safer drug. In 2014, the FDA approved another class of curative treatment with a more favorable side effect profile called direct-acting antivirals (DAAs). This class of medications inhibits various polymerases, proteases, and proteins involved in HCV replication cycle (37). Through the utilization of DAAs, sustained virologic response (SVR) or cure rates are approaching 100% (38).

Barriers to Treatment: Despite the existence of curative treatment options, socioeconomic barriers to treatment impede ubiquitous access. Such barriers include financial, transportation, and fear of stigma and discrimination from

healthcare providers. A retrospective study identified patient-specific factors associated with lower rates of completing DAA treatment. These factors include identifying as Black, experiencing homelessness, recent incarceration, a diagnosis of alcohol use disorder, recent intravenous drug use, co-infection with HIV, and the presence of psychiatric comorbidities (39). The data indicates that the most vulnerable populations are the least likely to receive treatment. The intersectionality of unstable housing, substance use disorder(s), and/or psychiatric comorbidities highlights the importance of expanding access to treatment among such vulnerable populations. This issue has been shown to be ameliorated by initiating treatment at the time of diagnosis, even in non-medical settings, for such marginalized individuals. The No One Waits (NOW) study analyzed the feasibility of initiating treatment at the time of diagnosis in mobile medical van setting designed to reach vulnerable populations. The study involved parking a mobile medical van in an area where PWID were known to gather. A majority of participants were PWID also experiencing homelessness. The results demonstrated that treatment at the time of diagnosis significantly decreased loss to follow-up and further transmission of HCV.

Another barrier to treatment involves insufficient provider knowledge about prescribing DAAs. A cross-sectional survey of healthcare providers in the state of Washington identified that approximately 33% of primary care providers reported treating HCV themselves, while the rest referred patients to specialists for treatment (40). This exacerbates the potential for patient attrition during the continuum of care. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) responded by simplifying treatment algorithms for both specialist and non-specialist healthcare providers (41).

Conclusion

The progression from hepatitis C virus (HCV) infection to hepatocellular carcinoma (HCC) is a multifaceted process driven by chronic inflammation, immune system dysregulation, oxidative stress, and genetic and epigenetic factors. While advances in screening and treatment have dramatically improved the prognosis for individuals with HCV, significant barriers to care remain among marginalized populations. This calls for the need for broader awareness and education among healthcare providers at the primary care level. Ongoing research into biomarkers such as miRNAs, chemokines, and SNPs offers the potential for early detection, treatment optimization, and risk stratification. By continuing to integrate molecular knowledge with public health practices, substantial progress toward reducing the burden of HCV-related HCC worldwide can be accomplished.

References:

1. Sung H, Ferlay J, Siegel RL, *et.al.*: (2021). "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries"; *CA Cancer J Clin*; 71: 209-249
2. El-Serag HB, Rudolf KL: "Hepatocellular Carcinoma: Epidemiology and Molecular Carcinogenesis"; *Gastroenterology*; 2007; 132: 2557-2576
3. Altekruse F, McGlynn A, Reichman E: (2009). "Hepatocellular Carcinoma Incidence, Mortality, and Survival Trends in the United States from 1975 to 2005"; *J Clin Oncol;* 27: 1485-1491
4. Bartosch B, Thimme R, Blum E, Zoulim F: "Hepatitis C Virus-Induced Hepatocarcinogenesis"; J Heptol; 2009; 51: 810-820
5. Blach S, Terrault NA, Tacke F, *et.al.*: (2022). "Global Change in Hepatitis C Virus Prevalence and Cascade of Care Between 2015 and 2020: A Modelling Study"; *Lancet Gastro Hepato*; 7: 396-415
6. Roudot-Thoraval F: (2021). "Epidemiology of Hepatitis C Virus Infection"; *Clin Res Hepatol Gastroent;* 45: 101596
7. Mazumder H, Hossain MF, Shrestha P, Mahmud S, Husain M, Ahmed R. Prevalence and associated risk factors of current hepatitis C infection among U.S. general population and injection drug users aged 20-59 years: NHANES 2009-2018. PLoS One. 2024 Aug 26;19(8): e0309345.
8. Lawrie C, Gal s, Dunlop H, *et.al.*: (2008). "Detection of Elevated Levels of Tumor-Associated MicroRNAs in Serum of Patients with Diffuse Large b-cell Lymphoma"; *Br J Haematol*; 14: 672-675
9. Schlosser S, Tumen D, Volz B, *et.al.*: (2022). "HCC Biomarers-State of the Old and Outlook to Future Promising Biomarkers and Their Potential in Everyday Clinical Practice"; *Front Oncol*; 12: 1016952
10. Selvarajah S, Busch MP. (2012). Transfusion transmission of HCV, a long but successful road map to safety. Antivir Ther.;17(7 Pt B):1423-1429.
11. Rogers KJ, Halvorson TS, Krasowski MD, Merrill AE. (2023). Evaluating the utility of a two-assay serological algorithm for hepatitis C screening in a low prevalence population. *Journal of clinical laboratory analysis*. ;37(7): e24887.
12. Grade definitions. (2024.). Grade Definitions | United States Preventive Services Taskforce.
13. Bhattacharya D, Aronsohn A, Price J, Lo Re V; (2023). AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Clin Infect Dis.*
14. Jhaveri R, Broder T, Bhattacharya D, Peters MG, Kim AY, Jonas MM. (2018). Universal Screening of Pregnant Women for Hepatitis C: The Time Is Now. *Clin Infect Dis*.
15. Miller JM, Binnicker MJ, Campbell S, et al. (2018). A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. *Clin Infect Dis*.;67(6): e1-e94.
16. Ghany MG, Morgan TR; (2020). AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology.* Feb;71(2):686-721.
17. Grebely J, Page K, Sacks-Davis R, van der Loeff MS, Rice TM, Bruneau J, Morris MD, Hajarizadeh B, Amin J, Cox AL, Kim AY, McGovern BH, Schinkel J, George J, Shoukry NH, et. all., (2014). InC3 Study Group. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. *Hepatology.* Jan;59(1):109-120.
18. Faccioli J, Nardelli S, Gioia S, Riggio O, Ridola L. (2021). Neurological and psychiatric effects of hepatitis C virus infection. *World J Gastroenterol.* Aug 7;27(29):4846-4861.
19. Hepatitis C (2024). (HCV) - symptoms, causes & treatments. American Liver Foundation. August 18, 2023. Accessed October 21.
20. Faccioli J, Nardelli S, Gioia S, Riggio O, Ridola L. (2021). Neurological and psychiatric effects of hepatitis C virus infection. *World J Gastroenterol*. 7;27(29):4846-4861.

21. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014 Nov;61(1 Suppl): S58-68.
22. Fu N, Yao H, Nan Y, Qiao L. Role of Oxidative Stress in Hepatitis C Virus Induced Hepatocellular Carcinoma. Curr Cancer Drug Targets. 2017;17(6):498-504.
23. Li K, Deng Z, Lei C, Ding X, Li J, Wang C. The Role of Oxidative Stress in Tumorigenesis and Progression. *Cells*. 2024;13(5):441.
24. Fu N, Yao H, Nan Y, Qiao L. Role of Oxidative Stress in Hepatitis C Virus Induced Hepatocellular Carcinoma. Curr Cancer Drug Targets. 2017;17(6):498-504.
25. Balan S, Saxena M, Bhardwaj N. Dendritic cell subsets and locations. Int Rev Cell Mol Biol. 2019; 348:1-68.
26. Nattermann J, Zimmermann H, Iwan A, von Lilienfeld-Toal M, Leifeld L, Nischalke HD, Langhans B, Sauerbruch T, Spengler U. Hepatitis C virus E2 and CD81 interaction may be associated with altered trafficking of dendritic cells in chronic hepatitis C. Hepatology. 2006 Oct;44(4):945-54.
27. Matsuda M, Seki E. Hepatic Stellate Cell-Macrophage Crosstalk in Liver Fibrosis and Carcinogenesis. Semin Liver Dis. 2020 Aug;40(3):307-320..
28. Zhang S, Dong H, Jin X, Sun J, Li Y. The multifaceted roles of macrophages in the transition from hepatitis to hepatocellular carcinoma: From mechanisms to therapeutic strategies. Biochim Biophys Acta Mol Basis Dis. 2025 Mar;1871(3):167676.
29. Melo SA, Esteller M. Dysregulation of microRNAs in cancer: playing with fire. FEBS Lett. 2011 Jul 7;585(13):2087-99.
30. Yasser MB, Abdellatif M, Emad E, Jafer A, Ahmed S, Nageb L, Abdelshafy H, Al-Anany AM, Al-Arab MAE, Gibriel AA. Circulatory miR-221 & miR-542 expression profiles as potential molecular biomarkers in Hepatitis C Virus mediated liver cirrhosis and hepatocellular carcinoma. Virus Res. 2021 Apr 15; 296:198341.
31. Butt AM, Raja AJ, Siddique S, Khan JS, Shahid M, Tayyab GU, Minhas Z, Umar M, Idrees M, Tong Y. Parallel expression profiling of hepatic and serum microRNA-122 associated with clinical features and treatment responses in chronic hepatitis C patients. Sci Rep. 2016 Feb 22; 6:21510.
32. Hughes CE, Nibbs RJB. A guide to chemokines and their receptors. FEBS J. 2018 Aug;285(16):2944-2971.
33. Larrubia JR, Benito-Martínez S, Calvino M, Sanz-de-Villalobos E, Parra-Cid T. Role of chemokines and their receptors in viral persistence and liver damage during chronic hepatitis C virus infection. World J Gastroenterol. 2008 Dec 21;14(47):7149-59.
34. Ferrari SM, Fallahi P, Ruffilli I, et al. Immunomodulation of CXCL10 Secretion by Hepatitis C Virus: Could CXCL10 Be a Prognostic Marker of Chronic Hepatitis C? *Journal of immunology research*. 2019;
35. Cheng M, Si Y, Niu Y, Liu X, Li X, Zhao J, Jin Q, Yang W. High-throughput profiling of alpha interferon- and interleukin-28B-regulated microRNAs and identification of let-7s with anti-hepatitis C virus activity by targeting IGF2BP1. J Virol. 2013
36. Miri HH, Fazeli P, Ali-Hassanzadeh M, Bemani P, Kabelitz D, Kalantar K. Correlation between IL-28 polymorphism and spontaneous clearance in HCV patients: systematic review and meta-analysis. Arch Virol. 2021 Sep;166(9):2469-2478.
37. Kidney Disease: Improving Global Outcomes (KDIGO) Hepatitis C Work Group. KDIGO 2022 Clinical Practice Guideline FOR the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. Kidney Int. 2022 Dec;102(6S): S129-S205.
38. Morris MD, McDonell C, Luetkemeyer AF, Thawley R, McKinney J, Price JC. Community-Based Point-of-Diagnosis Hepatitis C Treatment for Marginalized Populations: A Nonrandomized Controlled Trial. JAMA Netw Open. 2023 Oct 2;6(10): e2338792.
39. Crosby K, Bigelow S, Sachs V, Weakley J, Skaftason H, Hoberecht T. (2022). What barriers delay treatment in patients with hepatitis C? *Journal of Family Practice*;71(7): E22-E24.
40. Cox-North P, Wiggins L, Stockton J, et al. Provider reported implementation barriers to hepatitis C elimination in Washington State. *BMC Primary Care*. 2024;25(1):1-10.
41. Ghany MG, Morgan TR; (2020). AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology.* Feb;71(2):686-721.

DOI:10.31579/2639-4162/281