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Review

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Pathophysiology of liver cirrhosis and risk correlation between immune status and the pathogenesis of hepatocellular carcinoma

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Abstract

Chronic liver disease (CLD) and cirrhosis are leading contributors to global morbidity and mortality, with hepatocellular carcinoma (HCC) frequently arising in patients with advanced liver damage. This review explores the interplay between immune dysfunction and the progression of cirrhosis to HCC, emphasizing the pivotal role of immune status in HCC pathogenesis. Chronic inflammation, cirrhosis-associated immune dysfunction syndrome (CAIDS), and immunosenescence create a permissive environment for tumorigenesis by impairing immune surveillance and promoting hepatocyte stress. Key mechanisms include T cell exhaustion, dysregulated cytokine signaling, and gut-liver axis dysfunction, which collectively drive malignant transformation. Emerging immune biomarkers, such as PD-1/PD-L1, LAG-3, TIGIT, and soluble CD14/CD163, offer promise for refining HCC risk stratification and improving early detection. Integrating these biomarkers into existing surveillance protocols could enhance screening efficacy, particularly in high-risk populations such as the elderly and immunocompromised. Current guidelines recommend biannual ultrasound and alpha-fetoprotein testing for cirrhotic patients, but adherence remains suboptimal, and late diagnoses are common. A personalized approach combining clinical risk

factors, immune markers, and patient demographics may improve surveillance outcomes. Future research should focus on validating immune biomarkers in large cohorts, exploring novel therapeutic targets like LAG-3 and TIGIT, and developing tools to quantify immune dysfunction for risk stratification. By addressing immune dysregulation as a critical factor in HCC development, this review highlights the potential for improved HCC screening adherence and early detection for better patient outcomes through immune-based strategies.

Keywords: Liver cirrhosis, hepatocellular carcinoma (HCC), risk stratification, immune dysfunction in liver cirrhosis, chronic inflammation in liver cirrhosis, cirrhosis-associated immune dysfunction syndrome (CAIDS), tumor microenvironment, surveillance

INTRODUCTION

Chronic liver disease (CLD) is a leading global health concern, contributing significantly to mortality and affecting the quality of life of millions worldwide. Liver cirrhosis, the advanced stage of CLD, is a silent yet progressive disease that can remain asymptomatic for years, often leading to significant morbidity and mortality[1]. In 2019, cirrhosis accounted for 2.4% of global deaths, ranking as the 14th most common cause of death and a significant contributor to disability-adjusted life years (DALYs)[2]. The pathogenesis of cirrhosis typically involves prolonged inflammation, ultimately resulting in hepatic fibrosis, vascular distortion, and increased liver stiffness. Patients with cirrhosis progress from an asymptomatic compensated phase to a symptomatic decompensated phase, marked by complications such as ascites, jaundice, hepatic encephalopathy, and variceal bleeding[3]. These complications signify worsening liver function and often coexist with an increased risk of hepatocellular carcinoma (HCC)[4].

HCC, the most common primary liver malignancy, is a leading cause of cancer-related deaths worldwide. With an annual incidence of 2%-5% in cirrhotic patients, HCC remains a major burden, particularly in individuals with chronic liver injury[5]. Unfortunately, most cases are diagnosed at advanced stages, precluding curative interventions like surgical resection or liver transplantation. This late detection contributes to a poor 5-year survival rate of less than 15%[6]. The global burden of HCC is expected to rise due to increasing rates of obesity and metabolic-associated steatotic liver disease (MASLD), further underscoring the importance of early detection and prevention strategies[7].

Despite clinical practice guidelines recommending HCC screening for high-risk populations, adherence remains poor, with less than 25% of eligible patients receiving regular surveillance[8]. The limitations of current screening modalities, such as ultrasound and alpha-fetoprotein testing, further compound this challenge, often leading to late-stage diagnoses[9]. While advanced imaging techniques and novel biomarkers hold promise for improving early detection, their high costs and limited accessibility pose barriers, particularly in resource-limited settings[10]. These challenges highlight the need for more robust risk stratification tools that incorporate key factors influencing HCC development.

Emerging evidence suggests that immune dysfunction plays a pivotal role in the progression of liver cirrhosis and the development of HCC. Cirrhosis-associated immune dysfunction syndrome (CAIDS) is characterized by systemic inflammation and impaired immune surveillance, creating an environment conducive to malignant transformation. Chronic inflammation, mediated by dysregulated cytokines and immune cell exhaustion, drives hepatocyte stress and genetic alterations that promote tumorigenesis. However, the role of immune dysfunction in HCC risk stratification and screening remains underexplored, particularly in elderly and immunocompromised populations[11,12]. This review article aims to discuss the impact of immune dysfunction on cirrhosis and HCC progression. Integrating immune status, emerging

immune biomarkers, and other relevant factors may improve HCC risk prediction and pave the way for improved outcomes in high-risk populations.

MAIN TEXT

Immune dysregulation in cirrhosis

Liver cirrhosis represents an advanced stage of CLD, characterized by profound alterations in liver architecture and immune function. Major etiological factors include chronic hepatitis B (HBV) and hepatitis C (HCV) infections, alcohol consumption, MASLD, and other causes. Cirrhosis is pathologically defined by the formation of regenerative hepatic nodules separated by fibrotic septa, leading to significant vascular distortion[13].

The liver comprises parenchymal cells (hepatocytes) and non-parenchymal cells, including liver sinusoidal endothelial cells (LSECs) and Kupffer cells (KCs). Both cell types contribute to the onset and progression of liver fibrosis and cirrhosis[14].

Hepatocytes are primary targets of various hepatotoxic agents, such as hepatitis viruses, alcohol metabolites, and bile acids. These agents induce hepatocyte damage and subsequent release of reactive oxygen species (ROS) and damage-associated molecular patterns (DAMPs), which activate KCs and hepatic stellate cells (HSCs)[15]. ROS-Activated KCs secrete proinflammatory cytokines, such as CCL2, which recruit monocytes and intensify the inflammatory response. This cascade triggers HSC activation - a key process in hepatic fibrosis. Upon activation, HSCs transdifferentiate into myofibroblasts, leading to excessive deposition of extracellular matrix (ECM) proteins, including collagen, fibronectin, and laminin[15]. This pathologic ECM imbalance contributes to liver cirrhosis, the most advanced stage of liver fibrosis, contributing to portal hypertension and organ dysfunction[16,17].

However, cirrhosis also induces a paradoxical immune suppression referred to as CAIDS. This clinical state features both immune activation and immune paralysis, with the degree of dysfunction correlating with liver failure severity, bacterial translocation, and multiorgan failure[11]. CAIDS captures the paradoxical coexistence of systemic inflammation and immunosuppression in advanced liver disease[18,19]. Patients with CAIDS exhibit elevated levels of proinflammatory cytokines, yet key immune cells - neutrophils, monocytes, T cells, and NK cells - demonstrate compromised functionality. Bacterial translocation from the gut, facilitated by intestinal barrier dysfunction and altered gut-associated lymphoid tissue (GALT), further amplifies immune dysregulation. Consequently, cirrhotic patients become more susceptible to infections and may fail to mount effective antitumor responses[19,20].

CAIDS is driven by a complex interplay of molecular mechanisms and cell-cell interactions. Bacterial translocation and toll-like receptor (TLR) signaling play a central role, as gut-derived pathogens and PAMPs activate KCs and HSCs, triggering proinflammatory cytokine release and oxidative stress. Immune cell dysfunction is another hallmark, with neutrophils, monocytes, T cells, and NK cells exhibiting impaired functionality. T cell exhaustion, marked by upregulation of inhibitory checkpoints (e.g., PD-1, CTLA-4, LAG-3), further compromises antitumor immunity. Additionally, a cytokine imbalance - elevated IL-6 and TNF-α alongside increased IL-10 and TGF-β - creates a tolerogenic environment conducive to tumorigenesis. Dysregulation of the gut-liver axis, including intestinal dysbiosis and GALT alterations, exacerbates systemic immune dysfunction, increasing susceptibility to HCC[18,21,22].

Cirrhosis and the risk of HCC

Role of cirrhosis on HCC risk

Available evidence underscores a strong association between cirrhosis and HCC. The etiology and the duration of the cirrhotic process significantly influence the risk of HCC. For example, HCC is a leading

cause of mortality in patients with compensated cirrhosis. Conversely, approximately 10% to 20% of HCC cases occur in patients without cirrhosis, underscoring the role of additional risk factors in hepatocarcinogenesis[23]. Malignancy often follows liver cell dysplasia, which involves cellular enlargement affecting both the nucleus and cytoplasm. Dysplastic cells exhibit nuclear pleomorphism, multinucleation, and occasional mitotic activity, reflecting early carcinogenic transformation. Chronic liver injury, regardless of its etiology, establishes a proinflammatory microenvironment that modifies immune and stromal cell interactions within the liver.

This altered environment promotes chronic inflammation and hepatocellular changes, ultimately leading to HCC development[24]. CLD is further characterized by deregulation of the hepatic immune network, leading to cellular stress, apoptosis, and hepatocyte proliferation. These events are accompanied by epithelial-to-mesenchymal transition (EMT), a process in which epithelial cells lose their polarity and adhesion properties, acquiring a mesenchymal phenotype. EMT, coupled with genetic mutations and epigenetic changes, is a pivotal driver of hepatocarcinogenesis[25]. The inflammatory microenvironment in CLD exacerbates hepatocellular stress through various mechanisms, including mitochondrial dysfunction, epigenetic modifications, DNA damage, and chromosomal alterations. Mitochondrial injury impairs cellular energy metabolism, while persistent oxidative stress damages DNA and proteins, further promoting genomic instability. Additionally, epigenetic changes, such as DNA methylation and histone modifications, lead to aberrant gene expression, ultimately facilitating malignant transformation[26].

Key molecular drives of HCC

HCC development is driven by a combination of genetic and epigenetic alterations, chronic inflammation, and immune dysfunction. Key molecular drivers include:

1. *TP53*: Mutations in the *TP53* gene (occurring in 30% of HCC cases) hinder cell cycle arrest and apoptosis, thereby facilitating tumor survival[27].

2. TERT: Telomerase reactivation via TERT promoter mutations (e.g., occurring in > 60% of HCC cases) abrogates cellular senescence and enables the indefinite replication of injured hepatocytes[28].

3. DNA Methylation: Aberrant methylation of tumor suppressor genes frequently occurs in HCC, potentially linked to chronic inflammation and oxidative stress[29].

These molecular events synergize with immune dysfunction, promoting the escape of precancerous hepatocytes from immune surveillance and propelling the progression toward HCC.

Immune mechanisms driving HCC

Immune responses in HCC (Innate, adaptive, and immune checkpoints)

Both the innate and adaptive arms of the immune system are critical for anticancer immunity. Cytotoxic CD8+ T cells, which are part of the adaptive immune system, are the most effective effector cells in eliminating cancer cells. These T cells rely on transcription factors, cytokines, and chemokines to regulate their differentiation and function. CD4+ T helper cells play a complementary role by sustaining CD8+ T cell activity and preventing their exhaustion.

Immune checkpoints are regulatory molecules that modulate the activation and function of the immune system. While these pathways are essential for maintaining immune homeostasis and preventing autoimmunity, cancer cells exploit them to suppress antitumor immunity. Immune checkpoint inhibitors

(ICIs), such as anti-CTLA-4 and anti-PD-1/PD-L1 therapies, block these pathways to restore immune function and enhance the immune response against cancer. Emerging checkpoint pathways, such as LAG-3 and TIGIT, are being investigated for their potential therapeutic synergy with existing ICIs.

Tumor microenvironment: immune escape and evasion

The immune system plays a fundamental role in both the prevention and progression of cancer. Cancer cells, which arise from normal cells, develop mechanisms to evade immune detection through a process known as immune escape. This evasion disrupts the immune system's natural function of immunosurveillance. Tumors evade immune recognition through several pathways[30,31].

Creating an immunosuppressive tumor microenvironment

Tumor microenvironment (TME) accumulates immunosuppressive cells, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). These cells release cytokines and metabolites that inhibit effector immune cells and create a hostile environment for immune surveillance. Tumors also deplete essential nutrients required by immune cells, further impairing immune function.

Restricting antigen recognition

Cancer cells can downregulate or lose the expression of antigens that are typically recognized by immune cells. This process limits the immune system's ability to identify and target malignant cells.

Inhibiting antigen processing and presentation

Tumors interfere with the function of antigen-presenting cells (APCs), such as dendritic cells and macrophages. APCs normally internalize cancer cell-associated antigens, process them into peptides, and present these peptides on their surface via major histocompatibility complex (MHC)-peptide complexes. Cancer cells can disrupt this process by altering antigen processing machinery or impairing MHC-peptide presentation.

Inducing T cell exhaustion

Chronic antigen exposure leads to sustained expression of inhibitory immune checkpoint molecules, such as PD-1 on T cells, resulting in T cell exhaustion and reduced cytotoxic activity.

Immune biomarkers linked to HCC

Immune biomarkers are pivotal in enhancing the surveillance of HCC by unveiling critical pathways of immune dysregulation and their contribution to disease progression. These biomarkers not only shed light on the immune evasion mechanisms utilized by tumors but also serve as potential targets for therapeutic interventions. Immune checkpoint molecules such as PD-1/PD-L1, CTLA-4, TIM-3, LAG-3, and TIGIT reflect T cell exhaustion and dysfunction, correlating with immune evasion and poor prognosis. MDSCs and enzymes like indoleamine 2,3-dioxygenase (IDO) further suppress T cell activity, promoting advanced disease states. Proinflammatory cytokines, including IL-6 and TNF-α, and immunosuppressive cytokines like TGF-β contribute to chronic inflammation, fibrosis, and tumor progression. Additional markers such as soluble CD14/CD163 and reduced NK cell frequency underscore immune dysregulation, linking immune suppression with higher HCC risk and worse outcomes. Table 1 provides a detailed summary of these immune biomarkers, their clinical relevance, and their associations with HCC risk.

Immunodeficiency, a key player in HCC development

Impaired immunity, whether stemming from genetic defects or acquired conditions, plays a fundamental role in cancer progression and outcomes. However, its status as an independent risk factor for cancer in the

Table 1. Key immune biomarkers and their clinical relevance in HCC surveillance

Key References	Biomarker	Relevance	Association with HCC risk
Yang *et al*. 2023[32]	PD-1/PD-L1	Reflects T cell exhaustion; higher expression suggests immune evasion. Immune checkpoint molecules; targeted in immunotherapy	High expression correlates with advanced HCC and poor prognosis
Walker *et al*. 2013[33] Darmadi *et al*. 2023[34]	CTLA-4	T cell inhibition, immune tolerance. Immune checkpoint molecules; targeted in immunotherapy	High expression correlates with poor prognosis in HCC
Sauer *et al*. 2023[35], Ganjalikhani Hakemi *et al*. 2020[36]	TIM-3	Exhaustion marker; suppresses T cell function. Immune checkpoint molecules; targeted in immunotherapy	High TIM-3 expression linked to T cell dysfunction and poor survival in HCC
Guo *et al*. 2020[37]	LAG-3	Inhibits T cell activation. Immune checkpoint molecules; targeted in immunotherapy	Elevated LAG-3 levels correlate with immune evasion and advanced HCC
Guo *et al*. 2020[38]	TIGIT	Suppresses T cell and NK cell activity. Immune checkpoint molecules; targeted in immunotherapy	High TIGIT expression correlates with T cell exhaustion, immune evasion, and poor prognosis
Ma *et al*. 2021[39]	MDSCs	MDSCs; suppress T cell activity	Elevated MDSC levels correlate with immune evasion and advanced HCC
Eleftheriadis *et al*. 2015[40], Asghar *et al*. 2023[41]	IDO	Enzyme that suppresses T cell activity by depleting tryptophan	High IDO expression linked to immune suppression and poor prognosis
Nenu *et al*. 2023[42], Tan *et al*. 2018[43]	IL-6, TNF-α	Proinflammatory cytokines elevated in chronic liver disease	Elevated levels link to chronic inflammation and tumor growth
Jin *et al*. 2022[44]	TGF-β	Immunosuppressive cytokine; promotes fibrosis and immune evasion	High TGF-β1 levels linked to tumor progression and poor prognosis in HCC
Lee *et al*. 2021[45]	NK Cell Frequency	NK cells provide rapid tumor cell killing	Reduced NK activity is associated with higher HCC incidence
Li *et al*. 2016[46], Kawanaka *et al*. 2023[47]	Soluble CD14/CD163	Markers of monocyte/macrophage activation and CAIDS	Elevated levels reflect ongoing immune dysregulation, tumor progression, and poor prognosis

HCC: Hepatocellular carcinoma; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; TIM-3: T cell immunoglobulin and mucin domain 3; LAG-3: lymphocyte activation gene 3; TIGIT: T cell immunoreceptor with Ig and ITIM domains; MDSCs: myeloid-derived suppressor cells; IDO: indoleamine 2,3-dioxygenase; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; TGF-β: transforming growth factor beta; NK Cells: natural killer cells; CD14: cluster of differentiation 14; CD163: cluster of differentiation 163; CAIDS: chronic activation-induced dysfunctional state.

general population is often underrecognized. This section explores different types of immunodeficiencies - both primary and secondary - and their potential to initiate carcinogenesis[48].

Primary Immunodeficiency

Primary immunodeficiencies (PID), also known as inborn errors of immunity (IEIs), are genetic disorders that compromise immune system function. Individuals with these conditions exhibit increased susceptibility to malignancies due to impaired immune surveillance and dysfunction in pathways critical for tumor suppression[49].

Secondary Immunodeficiency

Secondary immunodeficiencies are acquired conditions that weaken immune function. For instance, human immunodeficiency virus (HIV) infection disrupts the immune system's ability to detect and eliminate tumor cells. Similarly, immunosuppressive therapies, commonly used in organ transplantation or autoimmune disease management, diminish immune defenses and heighten cancer risk. Additionally, chronic immune dysfunction associated with aging - known as immunosenescence - further predisposes individuals to cancer by reducing the efficacy of immune surveillance[50]. Secondary immunodeficiencies are more prevalent than PIDs and are often associated with specific factors such as post-transplantation immune dysfunction, chronic immunosuppressive therapy, and infections like HIV or human T cell

lymphotropic virus (HTLV). These conditions collectively impair the immune system's ability to mount effective antitumor responses[23]. Evidence highlights the substantial cancer risk associated with prolonged immunosuppression, particularly in the context of chronic selective immunosuppressive therapies. While these treatments are essential for preventing graft rejection in transplantation, they are not selective for immune responses targeting the transplanted organ. Consequently, they inadvertently suppress other protective immune functions, including the body's ability to detect and eliminate malignantly transformed cells. This is particularly problematic for tumors driven by viral infections, as the immune system's antiviral surveillance is weakened. Consequently, an increased risk of malignancies, such as post-transplant lymphoproliferative disorders, remains a well-documented adverse effect of long-term immunosuppression[51].

Immunosenescence, another form of secondary immunodeficiency, is characterized by the gradual decline in immune function associated with aging. This process involves structural and functional remodeling of lymphoid organs, leading to significant alterations in the immune response. The aged immune system becomes increasingly dysregulated, with reduced T cell production, impaired antigen presentation, and an accumulation of proinflammatory signals. These changes contribute to a higher susceptibility to infections, autoimmune disorders, and malignancies. The interplay between immunosenescence and tumorigenesis underscores the critical role of immune dysfunction in cancer development among elderly populations[52,53].

Role of immunity on cirrhosis and HCC pathways

The progression of CLD, whether due to viral hepatitis, alcohol consumption, MASLD, or other risk factors, typically follows one of two distinct pathways [Figure 1]: one leading to HCC and the other to cirrhosis[54]. Cirrhosis, though primarily a structural disorder marked by fibrotic nodules, is heavily influenced by the persistent inflammatory signals and immune deviations that characterize advanced liver disease. Apoptotic hepatocytes release DAMPs, which sustain inflammation and stimulate HSCs. Over time, cumulative genetic and epigenetic insults lead to dysplastic nodules and eventual malignant transformation[55,56]. The compromised immune surveillance - whether due to CAIDS, immunodeficiency, or both - further exacerbates the risk by removing critical mechanisms that suppress tumor outgrowth. Figure 1 illustrates the interconnected processes of chronic liver injury, ongoing fibrosis, and persistent immune dysregulation, highlighting their roles in driving the progression of cirrhosis and the development of HCC.

CONCLUSION

CLD, cirrhosis, and HCC are interconnected through persistent inflammation, immune dysfunction, and tissue remodeling. Hepatocyte apoptosis triggers inflammation and fibrogenesis, which drive progression to cirrhosis. In cirrhosis, "immune paralysis" or CAIDS impairs immune surveillance, fostering a microenvironment conducive to tumorigenesis. Structural changes in cirrhosis, including vascular distortion and sinusoidal capillarization, combined with chronic inflammation, drive hepatocellular stress, epigenetic modifications, and DNA damage, further accelerating HCC development.

The liver's immune response initially defends against injury, but persistent damage leads to scar formation and, ultimately, advanced cirrhosis. Decompensated cirrhosis is characterized by immune exhaustion and a heightened risk of HCC. Impaired cytotoxic CD8+ T cells, critical for antitumor immunity, weaken immune surveillance in this chronic inflammatory environment, enabling tumor progression. HCC risk correlates with cirrhosis due to shared causative factors, including chronic inflammation and immune dysfunction. Cirrhosis exacerbates inflammation, disrupts vascular flow, and exhausts immune mechanisms. Additionally, immunodeficiencies - whether primary, secondary, or age-related - heighten HCC risk, underscoring the critical role of intact immunity in cancer prevention. Addressing the microenvironment in

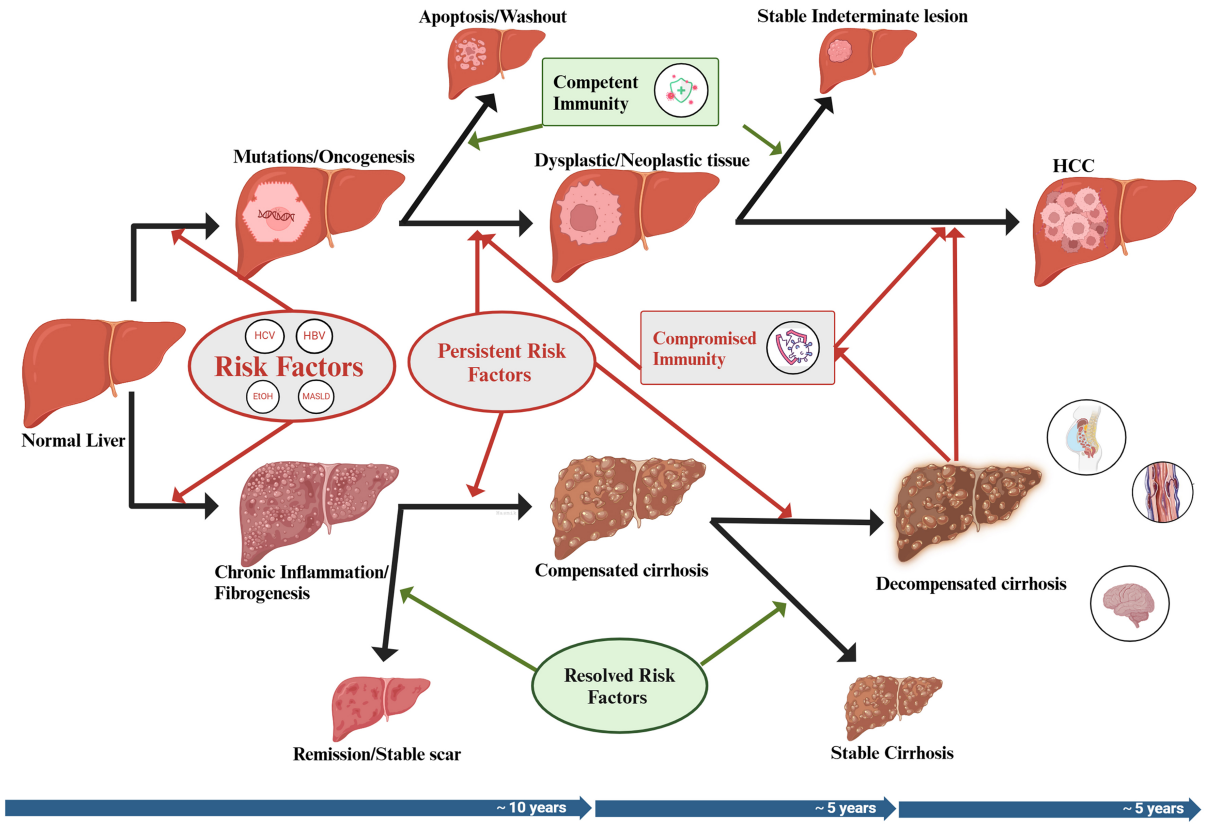

Figure 1. Conceptual Pathway from Chronic Liver Injury to Cirrhosis and HCC. This schematic illustrates how persistent risk factors (e.g., viral hepatitis, alcohol, metabolic dysfunction) drive repeated hepatocyte injury and fibrosis, leading to either stable cirrhosis or decompensated disease. Concurrently, ongoing inflammation and compromised immune surveillance (including CAIDS and Immunodeficiency) propel dysplastic changes that culminate in hepatocellular carcinoma. The diagram underscores how immune dysfunction and persistent risk factors synergize to shape liver disease progression and HCC risk. HCC: Hepatocellular carcinoma; CAIDS: chronic activation-induced dysfunctional state; MASLD: metabolic dysfunction-associated liver disease.

disease progression before cirrhosis develops may slow HCC progression, improve early detection, and optimize patient outcomes.

Immune biomarkers, such as PD-1/PD-L1, CTLA-4, MDSCs, and proinflammatory cytokines like IL-6 and TGF-β, play a pivotal role in HCC surveillance by revealing immune dysregulation and tumor evasion mechanisms. These biomarkers not only highlight immune dysfunction but also offer potential therapeutic targets, linking immune suppression to higher HCC risk and worse outcomes.

Finally, recognizing immune dysfunction as an independent risk factor can guide refined risk stratification and timely HCC surveillance. Incorporating immune status may refine HCC screening and risk stratification, particularly for elderly or immunocompromised patients. Future research should explore immune dysfunction's role in stratifying HCC risk among cirrhotic patients.

DECLARATIONS

Authors' contributions

Concept and design: Alsudaney M, Ayoub W, Kosari K, Koltsova E, Adetyan H, Yalda T, Attia AM, Liu J, Yang JD

Data acquisition, analysis, and/or interpretation: Alsudaney M, Ayoub W, Kosari K, Koltsova E, Abdulhaleem MN, Adetyan H, Yalda T, Attia AM, Liu J, Yang JD
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Final approval and agreement: Alsudaney M, Ayoub W, Kosari K, Koltsova E, Abdulhaleem MN, Adetyan H, Yalda T, Attia AM, Liu J, Yang JD

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Conflicts of interest
Yang JD provides a consulting service for AstraZeneca, Eisai, Exact Sciences, Exelixis, Fujifilm Medical Sciences, and Gilead Sciences. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
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