A review on hepatocellular carcinoma: etiology, treatment strategies, and therapeutic advances

A project report presented to the Department of Pharmacy at Daffodil International University in partial fulfillment of the requirements for the Bachelor of Pharmacy degree.

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Approval

This project, submitted to the Department of Pharmacy, Faculty of Allied Health Science at Daffodil International University, has been deemed satisfactory for the partial fulfillment of the requirements for the Bachelor of Pharmacy (B.Pharm) degree. It is also approved for its style and content.

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Declaration

I confirm that I autonomously authored and concluded this project report to meet the criteria for the Bachelor of Pharmacy (B.Pharm) degree. The research was carried out under the supervision of Dr. Md. Sarowar Hossain, Associate Professor of the Department of Pharmacy at the Faculty of Allied Health Sciences, Daffodil International University. I assert my sole authorship of this project and assure that neither this work nor any of its components have been previously submitted to any other university for the purpose of obtaining a Bachelor's degree or any other academic qualification.

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Acknowledgement

I express my appreciation to the Almighty for granting me the health and resilience necessary to accomplish this endeavor.

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Nazmul Hossain Maruf

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Dedication

This endeavor is dedicated primarily to the Almighty, followed by my parents, instructors, and friends.

Abstract

Hepatocellular carcinoma (HCC) poses a significant health burden globally, with its intricate etiology and diverse risk factors contributing to its formidable challenge in clinical management. This comprehensive review aims to elucidate the multifaceted nature of HCC, spanning its origins, predisposing factors, diagnostic modalities, treatment approaches, and recent therapeutic breakthroughs. The genesis of HCC involves a complex interplay of genetic predisposition, environmental influences, and viral infections, notably chronic viral hepatitis, alcohol abuse, non-alcoholic fatty liver disease (NAFLD), and genetic susceptibilities. Timely detection through vigilant screening programs employing advanced imaging techniques and serum biomarkers is imperative for enhancing patient outcomes. Surgical resection, liver transplantation, locoregional therapies, targeted pharmacotherapy, and immunomodulation represent pivotal pillars in HCC management, offering prospects of cure, disease control, and symptomatic relief. Recent therapeutic strides, including the advent of targeted agents like sorafenib, lenvatinib, and immunotherapy utilizing immune checkpoint inhibitors, have revolutionized treatment paradigms, offering newfound optimism for patients grappling with advanced HCC. Concomitantly, comprehensive supportive care interventions encompassing pain alleviation, nutritional optimization, and psychosocial support play an integral role in augmenting patient well-being and overall quality of life. Nevertheless, formidable challenges persist in refining screening protocols, elucidating predictive biomarkers, and mitigating treatment-associated adverse effects. Hence, sustained research endeavors are imperative to propel the frontiers of HCC management, fostering continual advancements aimed at ameliorating outcomes for individuals confronted with this relentless malignancy.

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CHAPTER ONE

INTRODUCTION

1.0 Introduction

In the realm of oncology, hepatocellular carcinoma (HCC) is recognized as a formidable adversary, standing as the primary malignancy of the liver and exacting a heavy toll on global health. Despite strides in medical science, HCC persists as a leading cause of cancer-related morbidity and mortality worldwide, underscoring the urgent need for a comprehensive understanding of its intricate web of etiological factors, risk elements, and evolving therapeutic paradigms [1]. In this comprehensive review, the overarching aim is to navigate the labyrinth of HCC, shedding light on its multifaceted nature and delving into key domains encompassing its molecular genesis, diagnostic intricacies, treatment modalities, and avenues for supportive care [2].

At the core of the exploration lies the recognition of HCC as a disease entity shaped by a multitude of influences, ranging from genetic predisposition to environmental exposures and viral pathogens. Chronic viral hepatitis, notably hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, emerges as prominent etiological culprits, exerting profound influence on hepatocellular carcinogenesis [3]. Concurrently, lifestyle factors such as alcohol consumption and the burgeoning epidemic of non-alcoholic fatty liver disease (NAFLD) contribute significantly to the burden of HCC, amplifying the complexity of its pathogenesis. Unraveling the intricate interplay between these diverse etiological threads forms the cornerstone of the endeavor, paving the way for a nuanced understanding of HCC's origins [4].

As the landscape of HCC is traversed, the gaze extends beyond mere etiological inquiry to encompass the realm of diagnostic precision and therapeutic innovation. Screening and surveillance programs, anchored by sophisticated imaging modalities such as ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) scan, serve as sentinel tools in the early detection of HCC, particularly among cohorts at heightened risk owing to underlying liver pathology. Augmenting these diagnostic armaments are serum biomarkers, chief among them alpha-fetoprotein, which wield considerable prognostic value in the surveillance and monitoring of HCC [5].

In tandem with diagnostic precision, therapeutic strategies for HCC have witnessed remarkable evolution, spanning the gamut from traditional surgical resection and liver transplantation to

burgeoning frontiers of systemic therapies and immunomodulation. Surgical resection, hailed as the cornerstone of curative intent for early-stage HCC, finds its complement in the realm of liver transplantation, offering a lifeline to select cohorts ensnared by advanced disease. Concurrently, the advent of locoregional therapies, encompassing modalities such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE), heralds a new dawn in the armamentarium against intermediate-stage HCC [6].

Yet, even as the currents of therapeutic innovation are navigated, the compass remains attuned to the imperative of supportive care, embracing palliative measures aimed at enhancing quality of life and ameliorating symptom burden among patients grappling with advanced HCC. Pain management, psychosocial support, and nutritional interventions emerge as linchpins of this holistic approach, underscoring the imperative of a multidisciplinary in the care continuum [7].

The odyssey through the landscape of HCC is imbued with a sense of urgency and purpose, driven by the imperative to decipher its enigmatic pathogenesis, embrace diagnostic precision, and forge novel therapeutic frontiers. Anchored by a commitment to patient-centric care and collaborative inquiry, this review endeavors to illuminate the ever-evolving tapestry of HCC, offering insights that may serve as guideposts in the quest for improved outcomes and enhanced quality of life for those ensnared by its formidable grasp [8].

1.1 Etiology and Risk Factors

The genesis of hepatocellular carcinoma (HCC) unfolds against a backdrop of intricate interplay among diverse etiological forces, encompassing genetic predisposition, environmental exposures, and viral pathogens. Central to this narrative are the twin specters of chronic viral hepatitis and its attendant sequelae, HBV and HCV infections, which stand as formidable catalysts in the pathogenesis of HCC [9]. Chronic infection with HBV, characterized by persistent viral replication and immune-mediated liver injury, engenders a milieu ripe for malignant transformation, precipitating the development of HCC through a complex cascade of molecular events. Similarly, chronic HCV infection, marked by protracted inflammation and hepatic fibrosis, exerts a synergistic influence on hepatocarcinogenesis, perpetuating a cycle of liver injury and regeneration conducive to oncogenic transformation [10].

Beyond viral pathogens, the landscape of HCC etiology is further shaped by the insidious tendrils of lifestyle factors, chief among them being alcohol consumption. Prolonged and excessive alcohol intake inflicts profound hepatocellular injury, fueling a cascade of inflammatory and fibrotic responses that culminate in the development of cirrhosis, a prelude to HCC. The synergistic interplay between alcohol-induced liver injury and concomitant viral hepatitis amplifies the risk of HCC, underscoring the pivotal role of lifestyle modification in mitigating disease burden [11].

A burgeoning epidemic in the realm of liver pathology, non-alcoholic fatty liver disease (NAFLD) emerges as a potent harbinger of HCC, heralding a paradigm shift in the landscape of hepatocarcinogenesis. Characterized by hepatic steatosis, insulin resistance, and inflammation, NAFLD represents a burgeoning public health crisis, underpinned by the global epidemic of obesity and metabolic syndrome [12]. The nexus between NAFLD and HCC is multifaceted, encompassing a constellation of metabolic derangements, oxidative stress, and pro-inflammatory cytokines that conspire to foster malignant transformation within the confine's steatosis liver [13].

Embedded within the tapestry of HCC etiology lies the indelible imprint of genetic predisposition, manifesting as inherited syndromes and polymorphisms that confer heightened susceptibility to hepatocarcinogenesis. Hereditary hemochromatosis, characterized by iron overload and resultant hepatic fibrosis, underscores the role of iron metabolism in HCC pathogenesis, while alpha-1 antitrypsin deficiency and Wilson's disease serve as poignant reminders of the intricate interplay between genetic aberrations and hepatic malignancy [14]. The burgeoning landscape of genetic polymorphisms, encompassing variants in genes encoding enzymes involved in xenobiotic metabolism and DNA repair pathways, offers further insights into the intricate web of genetic determinants shaping HCC susceptibility [15].

Understanding the multifaceted interplay between these diverse risk factors is pivotal in informing preventive strategies and early intervention initiatives aimed at curbing the burgeoning tide of HCC. Vaccination against HBV stands as a linchpin in the armamentarium against HCC, offering a potent shield against viral-mediated hepatocarcinogenesis. Screening and surveillance programs, tailored to high-risk populations burdened by chronic viral hepatitis, NAFLD, and cirrhosis, form the cornerstone of early detection initiatives, enabling timely intervention and curbing disease

progression. Lifestyle modification, encompassing abstinence from alcohol, weight management, and metabolic control, emerges as a pivotal frontier in HCC prevention, offering a beacon of hope in the quest for disease mitigation [16].

In summation, the etiological landscape of HCC is characterized by a multifaceted interplay of genetic, environmental, and viral factors, underscoring the imperative of a holistic understanding in informing preventive strategies and early intervention initiatives. By unraveling the intricate tapestry of HCC etiology, we stand poised to forge novel pathways in the quest for disease mitigation and improved outcomes for those ensnared by its formidable grasp [17].

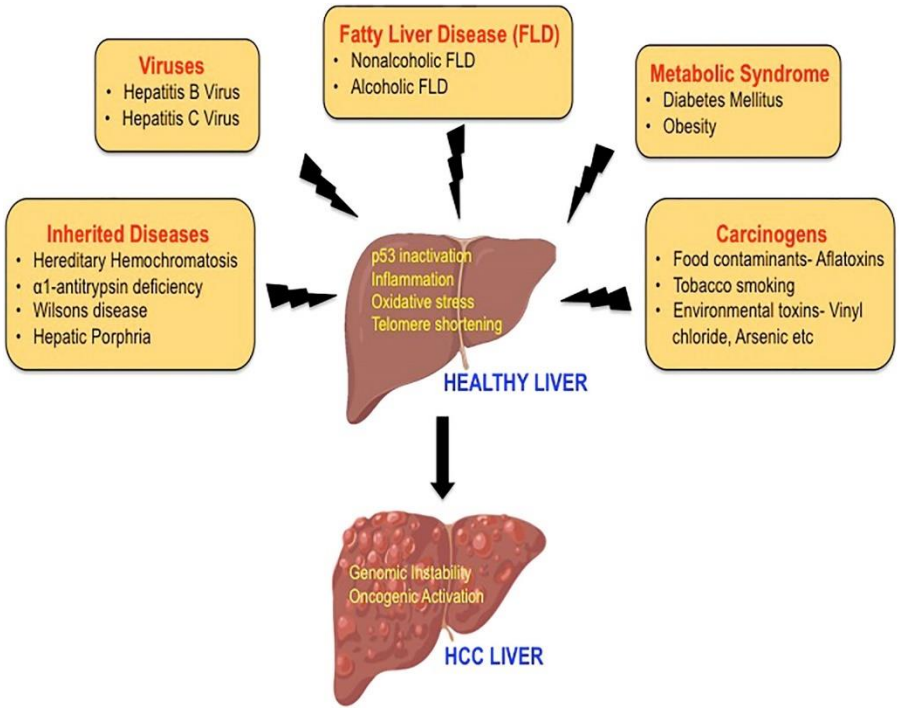

Figure-1.1: Causes of Hepatocellular carcinoma [18].

1.2 Sign and Symptoms

Hepatocellular carcinoma (HCC) often manifests insidiously, with signs and symptoms typically emerging in the advanced stages of disease progression when treatment options may be limited. The clinical presentation of HCC is heterogeneous and can vary widely among individuals, reflecting the diverse array of underlying etiological factors and the multifocal nature of the

disease. Despite this variability, several hallmark signs and symptoms are commonly observed in patients with HCC, providing valuable clues its diagnosis and prompting further investigation [19].

One of the most characteristic features of advanced HCC is the onset of nonspecific constitutional symptoms, including fatigue, malaise, and unintentional weight loss. These symptoms often reflect the systemic impact of the underlying malignancy, encompassing metabolic derangements, cytokine release, and tumor-induced alterations in energy metabolism. Additionally, patients with advanced HCC may experience abdominal discomfort or pain, typically localized to the right upper quadrant, as a result of tumor expansion and compression of surrounding structures, including the liver capsule and adjacent viscera [20].

As HCC progresses, patients may develop complications related to impaired liver function and portal hypertension, such as ascites, lower extremity edema, and jaundice. Ascites, characterized by fluid accumulation within the peritoneal cavity, may manifest as abdominal distension, discomfort, or dyspnea on exertion, reflecting the severity of underlying liver dysfunction and portal venous hypertension [21]. Lower extremity edema, secondary to hypoalbuminemia and impaired hepatic synthesis of coagulation factors, may accompany ascites and herald decompensated liver disease in patients with advanced HCC. Jaundice, characterized by yellowing of the skin and sclerae, may ensue as a consequence of hepatocellular dysfunction and impaired bilirubin metabolism, signaling advanced disease, biliary obstruction in patients with HCC [22].

In some cases, HCC may present with specific clinical syndromes or paraneoplastic manifestations, offering additional diagnostic clues to its presence. For instance, patients with HCC may develop paraneoplastic hypercholesterolemia, characterized by elevated serum cholesterol levels secondary to tumor-derived lipoprotein synthesis, or erythrocytosis, attributed to tumor production of erythropoietin. These paraneoplastic syndromes, while relatively rare, can provide valuable insights into the underlying pathophysiology of HCC and may prompt further investigation in select cases [23].

In addition to systemic symptoms and complications, HCC may present with localizing signs related to tumor burden and intrahepatic extension. Patients with HCC may experience

hepatomegaly, palpable as a firm, irregular mass in the right upper quadrant, reflecting tumor expansion within the liver parenchyma. In cases of advanced HCC with vascular invasion, patients may present with signs of portal vein thrombosis or extrahepatic spread, including abdominal pain, hematemesis, or hemoptysis, indicative of tumor invasion into the portal venous system or distant metastasis [24].

Overall, the clinical presentation of HCC is diverse and can encompass a spectrum of signs and symptoms reflecting the systemic, hepatic, and local effects of the underlying malignancy. While nonspecific constitutional symptoms and complications of advanced liver disease are common, specific clinical syndromes and localizing signs may also occur, offering valuable diagnostic clues to the presence of HCC. Prompt recognition and evaluation of these signs and symptoms are essential for early diagnosis and initiation of appropriate treatment, with the goal of improving outcomes and quality of life for patients with HCC [25].

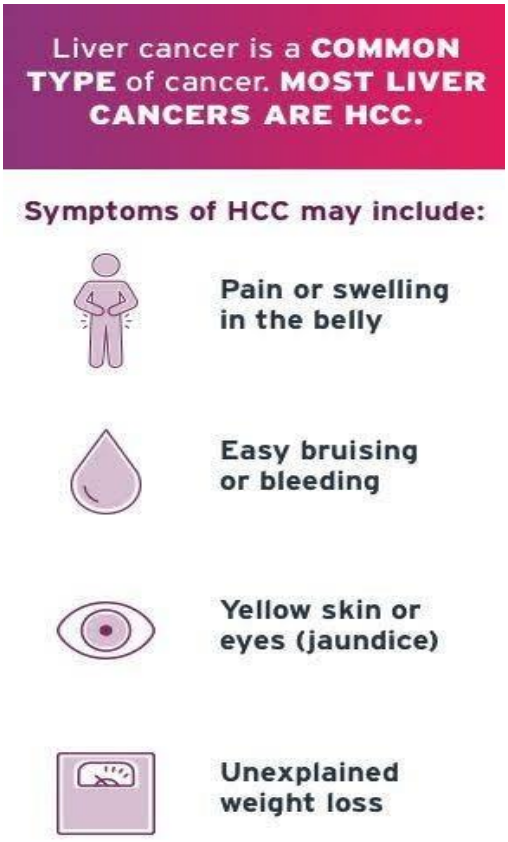

Figure-1.2: Symptoms of hepatocellular carcinoma [26].

1.3 Diagnosis, Screening and Surveillance

Early detection of hepatocellular carcinoma (HCC) is paramount in improving patient outcomes, as timely intervention can significantly impact prognosis and treatment options. Screening and surveillance programs represent pivotal strategies aimed at identifying HCC at an early stage, particularly among individuals at heightened risk due to underlying liver pathology. These programs rely on a combination of imaging modalities and serum biomarkers to facilitate early diagnosis and intervention [27].

Imaging modalities, including ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) scan, serve as cornerstone tools in the screening and surveillance of HCC. Ultrasound, owing to its widespread availability, cost-effectiveness, and lack of ionizing radiation, emerges as the primary imaging modality for HCC surveillance [28]. It offers the advantage of real-time visualization of liver parenchyma, enabling the detection of focal hepatic lesions and assessment of tumor morphology and vascularity. However, its sensitivity and specificity are operator-dependent, and the detection of small lesions may be challenging, particularly in patients with advanced liver disease or obesity [29].

In contrast, MRI and CT scan provide superior sensitivity and specificity for the detection and characterization of hepatic lesions, offering high-resolution anatomical images and functional assessments of liver function. MRI, with its multi-parametric capabilities, offers superior soft tissue contrast and characterization of liver lesions based on their signal intensity and enhancement patterns. Additionally, MRI can provide functional assessments of liver function through techniques such as diffusion-weighted imaging (DWI) and hepatobiliary contrast agents, which offer insights into tumor biology and response to therapy [30]. Similarly, CT scan, with its rapid acquisition and high spatial resolution, enables accurate detection and characterization of liver lesions based on their attenuation characteristics and enhancement patterns. However, both MRI and CT scan are limited by factors such as cost, availability, and contraindications in certain patient populations, necessitating judicious utilization in context of HCC screening and surveillance [31].

Serum biomarkers complement imaging modalities in the screening and surveillance of HCC, offering non-invasive tools for risk stratification and early detection. Alpha-fetoprotein (AFP), a

fetal glycoprotein produced by hepatic cells and yolk sac tumors, serves as the most widely used serum biomarker for HCC, albeit with limitations in sensitivity and specificity. Elevated AFP levels are observed in a subset of HCC patients, particularly those with advanced disease or aggressive tumor biology, and may correlate with tumor burden and prognosis. However, AFP levels can be elevated in non-malignant conditions such as cirrhosis and hepatitis, limiting its utility as a standalone diagnostic marker. As such, AFP is often used in conjunction with imaging modalities as part of a multimodal approach to HCC screening and surveillance [32].

In addition to AFP, other serum biomarkers have been explored for their utility in HCC screening and surveillance, including des-gamma-carboxy prothrombin (DCP), glypican-3 (GPC3), and Golgi protein 73 (GP73). These biomarkers offer complementary information to AFP and may improve the diagnostic accuracy of HCC detection, particularly in cases where AFP levels are within the normal range. However, their clinical utility remains the subject of ongoing research, and further validation is required to establish their role in routine practice [33].

In summary, screening and surveillance programs play a pivotal role in the early detection of hepatocellular carcinoma, enabling timely intervention and improved patient outcomes. Imaging modalities such as ultrasound, MRI, and CT scan offer valuable tools for lesion detection and characterization, while serum biomarkers like AFP provide additional risk stratification and diagnostic information. A multimodal approach, integrating imaging modalities and serum biomarkers, offers the best chance of early detection and intervention, particularly among high-risk populations with chronic liver disease. Continued research and refinement of screening protocols are essential to optimize the effectiveness of HCC surveillance programs and reduce the burden of this deadly disease [34].

1.4 Grading and Staging

Grading and staging systems serve as crucial tools in the assessment and management of hepatocellular carcinoma (HCC), offering clinicians valuable insights into tumor biology, prognosis, and treatment stratification. These systems aim to categorize HCC lesions based on their histological characteristics, extent of disease spread, and prognostic implications, guiding therapeutic decision-making and prognostication for patients with HCC [35].

Histological grading of HCC is typically based on the degree of cellular differentiation and architectural features observed on microscopic examination of tumor tissue. The most widely used grading system for HCC is the Edmondson-Steiner grading system, which classifies tumors into four histological grades (I to IV) based on criteria such as nuclear atypia, cellular pleomorphism, and mitotic activity [36]. Grade I tumors exhibit well-differentiated hepatocytes with minimal nuclear abnormalities and low mitotic activity, while Grade IV tumors are characterized by marked nuclear pleomorphism, high mitotic activity, and loss of architectural organization. Intermediate grades (II and III) demonstrate varying degrees of differentiation and cellular atypia, reflecting the heterogeneous nature of HCC histology. Histological grading provides valuable prognostic information, with higher-grade tumors associated with poorer outcomes and increased risk of disease progression [37].

In addition to histological grading, staging systems are employed to stratify HCC patients based on the extent of tumor burden, vascular invasion, and extrahepatic spread. The most widely used staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) staging system, which integrates tumor stage, liver function, performance status, and treatment options into a comprehensive algorithm for risk stratification and treatment allocation [38]. According to the BCLC staging system, HCC is classified into five stages (0, A, B, C, D) based on tumor size, number of nodules, vascular invasion, presence of metastases, Child-Pugh score, and Eastern Cooperative Oncology Group (ECOG) performance status. Stage 0 encompasses very early HCC amenable to curative treatments such as resection, ablation, or liver transplantation, while Stage D includes advanced HCC with vascular invasion, extrahepatic spread, or decompensated liver function, for which palliative therapies are recommended. Intermediate stages (A, B, C) delineate varying degrees of tumor burden and liver function, guiding treatment decisions and prognostication for patients with HCC [39].

Beyond the BCLC staging system, several other staging systems have been proposed for HCC, each with its unique set of criteria and prognostic implications. The American Joint Committee on Cancer (AJCC) TNM staging system, based on tumor size, nodal involvement, and distant metastasis, offers a standardized approach to tumor staging and prognostication, facilitating comparison across different cancer types. The Hong Kong Liver Cancer (HKLC) staging system,

incorporating tumor size, nodal status, vascular invasion, and liver function, provides additional granularity in risk stratification and treatment allocation for HCC patients. Other staging systems, such as the Japan Integrated Staging (JIS) score and the Cancer of the Liver Italian Program (CLIP) score, offer alternative approaches to risk stratification and prognostication, catering to the diverse clinical scenarios encountered in HCC management [40].

In summary, grading and staging systems play a pivotal role in the assessment and management of hepatocellular carcinoma, offering valuable insights into tumor biology, prognosis, and treatment allocation. Histological grading provides valuable prognostic information based on cellular differentiation and architectural features, while staging systems stratify HCC patients based on tumor burden, liver function, and performance status, guiding therapeutic decision-making and prognostication. Continued refinement and validation of grading and staging systems are essential to optimize risk stratification and improve outcomes for patients with HCC [41].

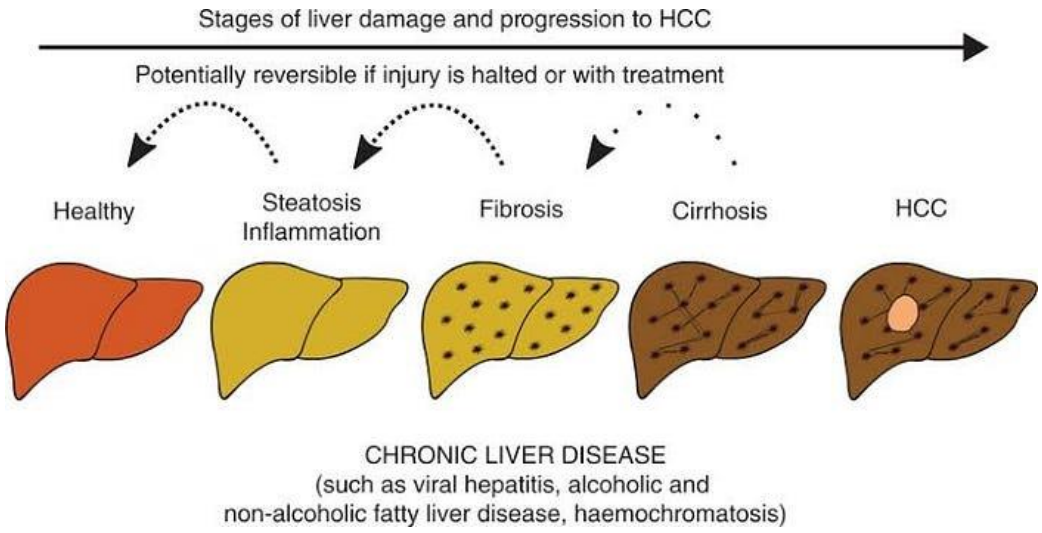

Figure-1.3: Stages of liver damage and progression to HCC [42].

1.5 Molecular Pathogenesis

Advancements in molecular biology have revolutionized our comprehension of hepatocellular carcinoma (HCC) pathogenesis, illuminating the intricate web of genetic alterations, epigenetic modifications, and dysregulated signaling pathways that underpin its development and progression. At the genetic level, HCC is characterized by a myriad of somatic mutations,

chromosomal aberrations, and copy number alterations that collectively drive malignant transformation within the hepatocyte [43]. Key driver mutations implicated in HCC pathogenesis include alterations in tumor suppressor genes such as TP53, PTEN, and RB1, as well as oncogenes including CTNNB1 (encoding β-catenin), MYC, and MET. These genetic aberrations disrupt critical cellular processes such as cell cycle regulation, apoptosis, and DNA repair, fostering unchecked proliferation and tumor growth [44].

In addition to genetic alterations, epigenetic modifications play a pivotal role in shaping the HCC epigenome and modulating gene expression patterns. Epigenetic mechanisms such as DNA methylation, histone modification, and non-coding RNA regulation exert profound influence on key pathways involved in hepatocarcinogenesis, including cell cycle control, DNA repair, and apoptosis [45]. Aberrant DNA methylation patterns, characterized by hypermethylation of tumor suppressor gene promoters and hypomethylation of oncogene promoters, contribute to dysregulated gene expression and tumor progression in HCC. Similarly, alterations in histone modifications, such as histone acetylation and methylation, disrupt chromatin structure and gene transcription, driving oncogenic transformation within the hepatocyte [46].

Dysregulated signaling pathways represent another hallmark of HCC pathogenesis, encompassing a constellation of interconnected signaling cascades that govern cellular proliferation, survival, and metastasis. Among these pathways, the Wnt/β-catenin signaling pathway emerges as a central player in HCC tumorigenesis, with aberrant activation of β-catenin driving hepatocyte proliferation and tumor growth. Other key signaling pathways implicated in HCC pathogenesis include the Ras/Raf/MEK/ERK pathway, the PI3K/Akt/mTOR pathway, and the TGF-β signaling pathway, each of which contributes to the malignant phenotype through dysregulated growth factor signaling, evasion of apoptosis, and promotion of angiogenesis and metastasis [47].

The elucidation of molecular pathways involved in HCC pathogenesis has paved the way for the development of molecular profiling techniques aimed at personalized therapy and prognostic stratification in HCC patients. Molecular profiling, encompassing genomic, transcriptomic, and proteomic analyses, offers insights into the molecular landscape of individual tumors, guiding treatment selection and predicting response to therapy [48]. For example, the identification of

specific genetic mutations or aberrant signaling pathway activation may inform targeted therapy approaches, such as the use of tyrosine kinase inhibitors or immune checkpoint inhibitors in patients with actionable molecular alterations. Similarly, molecular profiling may aid in prognostic stratification, identifying patients at high risk of disease recurrence or metastasis who may benefit from more aggressive therapeutic interventions [49].

In conclusion, advancements in molecular biology have unraveled the intricate molecular pathogenesis of hepatocellular carcinoma, highlighting the central role of genetic alterations, epigenetic modifications, and dysregulated signaling pathways in driving tumorigenesis. Molecular profiling holds promise for personalized therapy and prognostic stratification in HCC patients, offering insights into the molecular landscape of individual tumors and guiding therapeutic decision-making. Continued research efforts aimed at deciphering the molecular underpinnings of HCC are essential to further refine our understanding of this deadly disease and develop novel therapeutic strategies to improve patient outcomes [50].

1.6 Treatment Strategies

The management of hepatocellular carcinoma (HCC) necessitates a multifaceted approach that encompasses a spectrum of therapeutic modalities tailored to individual patient characteristics, disease stage, and underlying liver function. This multidisciplinary framework aims to optimize outcomes by balancing curative intent with palliative measures, with the ultimate goal of prolonging survival and improving quality of life for patients with HCC [51].

In early and intermediate-stage disease, curative-intent therapies such as surgical resection and liver transplantation represent the cornerstone of treatment. Surgical resection, when feasible, offers the potential for complete tumor eradication and long-term survival in carefully selected patients with localized disease and preserved liver function. However, eligibility for resection is contingent upon factors such as tumor size, location, and extent of liver parenchymal involvement, as well as the absence of vascular invasion or extrahepatic spread [52]. Liver transplantation provides an alternative curative option for patients with early-stage HCC and underlying cirrhosis, offering the advantage of removing both the tumor burden and the underlying diseased liver. Transplantation candidacy is determined by criteria such as tumor size, number of nodules,

vascular invasion, and extrahepatic spread, as well as patient factors such as performance status and comorbidities. While surgical resection and liver transplantation offer the potential for long-term survival in early-stage HCC, the availability of donor organs and the risk of disease recurrence remain significant challenges in their widespread application [53].

In cases where curative-intent therapies are not feasible or appropriate, locoregional therapies such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and radioembolization offer effective options for disease control and symptom palliation in intermediate-stage HCC. RFA, a minimally invasive technique that employs thermal energy to ablate tumor tissue, is suitable for patients with small, unresectable lesions and preserved liver function, offering high rates of local tumor control and favorable long-term outcomes [54]. TACE, on the other hand, delivers chemotherapeutic agents directly to the tumor vasculature via transcatheter arterial infusion, resulting in tumor ischemia and necrosis. TACE is indicated for patients with unresectable multifocal HCC or vascular invasion, offering effective palliation of symptoms and prolonged survival in select cases. Radioembolization, also known as selective internal radiation therapy (SIRT), utilizes radioactive microspheres to deliver targeted radiation therapy to hepatic tumors, offering a localized treatment option for patients with unresectable disease and preserved liver function [55].

In the era of precision medicine, systemic therapies have emerged as transformative options for patients with advanced HCC, offering novel targeted agents and immunotherapeutic approaches that exploit tumor-specific vulnerabilities and harness the immune system to combat malignancy [56]. Targeted agents such as sorafenib, lenvatinib, and regorafenib inhibit key signaling pathways involved in HCC pathogenesis, including the Ras/Raf/MEK/ERK pathway, the PI3K/Akt/mTOR pathway, and the VEGF signaling pathway, thereby exerting antitumor effects and delaying disease progression. Immunotherapy, particularly immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), has revolutionized the treatment landscape for advanced HCC, offering durable responses and improved survival outcomes in select patients. Checkpoint inhibitors such as nivolumab and pembrolizumab have demonstrated efficacy as monotherapy or in combination with other systemic

agents, offering a promising avenue for patients with advanced disease who have progressed on standard therapies [57].

Despite these advancements, the management of advanced HCC remains challenging, with limited treatment options and variable response rates among patients. Combination therapies, including the sequential or concurrent administration of targeted agents, immunotherapy, and locoregional therapies, are under investigation to improve treatment efficacy and overcome resistance mechanisms. Additionally, supportive care measures such as pain management, nutritional support, and psychosocial interventions play a crucial role in optimizing quality of life for patients with advanced HCC, addressing symptom burden and improving overall well-being [58].

The management of hepatocellular carcinoma requires a multidisciplinary approach that integrates surgical, locoregional, and systemic therapies tailored to individual patient characteristics and disease stage. While surgical resection and liver transplantation offer curative options for early-stage disease, locoregional therapies and systemic agents provide effective options for disease control and symptom palliation in advanced HCC. Continued research efforts and collaborative initiatives are essential to advance our understanding of HCC pathogenesis and refine treatment strategies, with the ultimate goal of improving outcomes and quality of life for patients affected by this devastating malignancy [59].

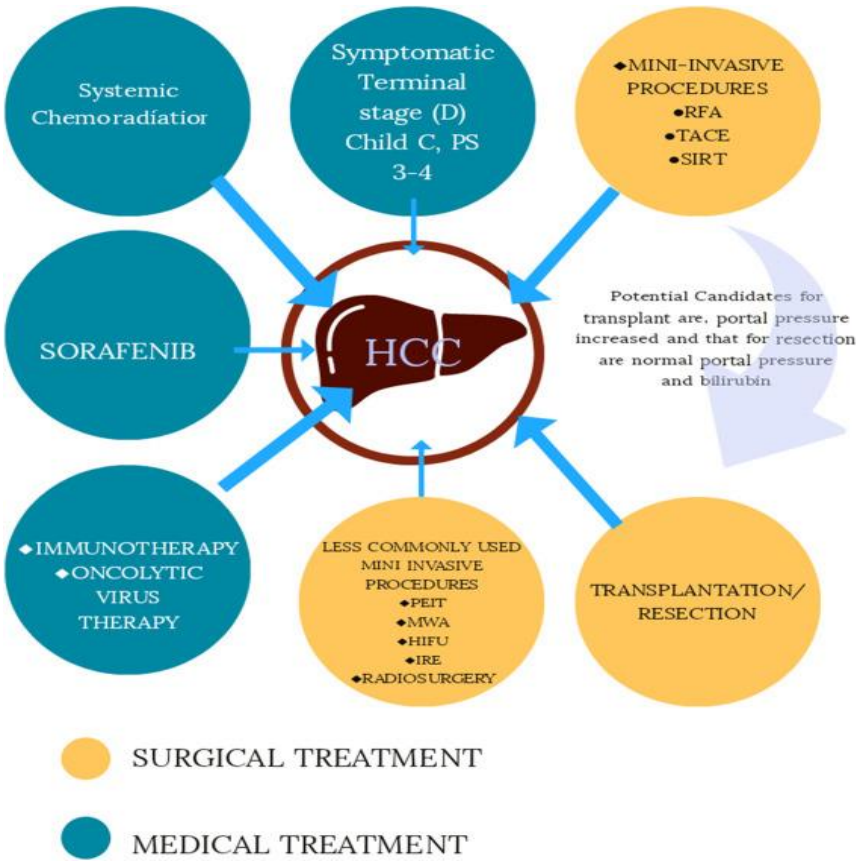

Figure-1.4: Treatment option of Hepatocellular carcinoma [60].

1.7 Hepatocarcinogenesis in Non-Cirrhotic Liver

Hepatocellular carcinoma (HCC), traditionally associated with cirrhotic liver disease, is increasingly recognized as a significant threat in non-cirrhotic liver contexts, including non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD). This phenomenon presents unique challenges in both diagnosis and management, as the absence of cirrhosis alters the natural history of HCC development and influences treatment strategies. Understanding the distinct risk factors and molecular mechanisms underlying HCC in non-cirrhotic liver is paramount for the implementation of targeted interventions aimed at mitigating disease burden and improving outcomes in affected individuals [61].

Non-alcoholic fatty liver disease (NAFLD) serves as a burgeoning risk factor for HCC development in non-cirrhotic liver, reflecting the global epidemic of obesity, metabolic syndrome, and insulin resistance. NAFLD encompasses a spectrum of liver pathology ranging from simple

steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis, with each stage conferring varying degrees of HCC risk. While HCC most commonly arises in the setting of advanced fibrosis or cirrhosis in NAFLD patients, a subset of individuals develops HCC in the absence of significant fibrosis, highlighting the complex interplay between metabolic derangements, oxidative stress, and carcinogenesis within the steatotic liver parenchyma [62]. The molecular pathogenesis of HCC in NAFLD is multifactorial, encompassing a constellation of genetic, epigenetic, and environmental factors that converge to promote malignant transformation within the hepatic milieu. Genetic polymorphisms associated with NAFLD susceptibility, including variants in genes encoding components of the lipid metabolism pathway and pro-inflammatory cytokines, contribute to the predisposition to HCC development in affected individuals. Epigenetic modifications, such as DNA methylation and histone acetylation, further modulate gene expression patterns and promote oncogenic signaling within the steatotic liver, fostering a permissive microenvironment for HCC initiation and progression [63].

Similarly, alcoholic liver disease (ALD) represents a significant risk factor for HCC development in non-cirrhotic liver, reflecting the hepatotoxic effects of chronic alcohol consumption and the synergistic interplay between ethanol metabolism, oxidative stress, and hepatocellular injury. While the majority of HCC cases in ALD occur in the context of cirrhosis, a subset of individuals develops HCC in the absence of advanced fibrosis or cirrhosis, underscoring the heterogeneity of HCC risk within the spectrum of ALD [64]. The molecular pathogenesis of HCC in ALD is multifaceted, encompassing alterations in key signaling pathways involved in alcohol metabolism, inflammation, and carcinogenesis. Chronic ethanol exposure induces oxidative stress and DNA damage within the hepatocyte, triggering a cascade of molecular events that promote cellular proliferation, genomic instability, and tumor growth. Dysregulated signaling pathways, including the Ras/Raf/MEK/ERK pathway, the PI3K/Akt/mTOR pathway, and the Wnt/β-catenin pathway, contribute to HCC pathogenesis in ALD by driving oncogenic transformation and tumor progression within the alcohol-injured liver parenchyma [65].

The diagnosis and management of HCC in non-cirrhotic liver diseases present unique challenges, as the absence of cirrhosis alters the natural history of disease progression and influences treatment strategies. Imaging modalities such as ultrasound, MRI, and CT scan remain essential tools for

HCC detection and surveillance in non-cirrhotic liver, with particular attention to identifying high-risk individuals with advanced fibrosis or underlying metabolic derangements [66]. Serum biomarkers such as alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP), and glypican-3 (GPC3) may offer additional diagnostic utility in certain cases, although their performance characteristics in non-cirrhotic liver diseases warrant further validation. Histological evaluation through liver biopsy may be considered in select cases to confirm the diagnosis of HCC and assess the degree of underlying liver fibrosis or inflammation, guiding treatment decisions and prognostication [67].

The management of HCC in non-cirrhotic liver diseases hinges on a multidisciplinary approach that integrates curative-intent therapies such as surgical resection, liver transplantation, and locoregional therapies with targeted systemic agents and supportive care measures. Surgical resection remains the cornerstone of treatment for early-stage HCC in non-cirrhotic liver, offering the potential for complete tumor eradication and long-term survival in carefully selected patients. Liver transplantation provides an alternative curative option for patients with unresectable HCC and underlying liver disease, offering the advantage of removing both the tumor burden and the diseased liver parenchyma [68]. Locoregional therapies such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and radioembolization offer effective options for disease control and symptom palliation in intermediate-stage HCC, particularly in cases where curative-intent therapies are not feasible or appropriate. Systemic therapies, including targeted agents and immunotherapy, may also play a role in the management of advanced HCC in non-cirrhotic liver, offering novel options for patients who have progressed on standard treatments or are not candidates for locoregional therapies. Supportive care measures such as pain management, nutritional support, and psychosocial interventions are essential components of the treatment plan, addressing symptom burden and improving quality of life for patients affected by HCC in non-cirrhotic liver diseases [69].

1.8 Liver Transplantation in HCC

Liver transplantation stands as a curative option for select patients with hepatocellular carcinoma (HCC), offering the potential for complete tumor eradication and long-term survival in the setting of underlying liver disease. Over the years, criteria for transplant eligibility, surgical techniques,

and post-transplant surveillance protocols have evolved to optimize outcomes and expand access to transplantation for HCC patients. However, challenges persist in organ allocation, patient selection, and resource allocation, necessitating ongoing refinement of transplant policies and practices to ensure equitable access and maximize benefits of transplantation HCC patients [70].

The eligibility criteria for liver transplantation in HCC patients have undergone several iterations to balance the competing priorities of maximizing survival benefit while minimizing the risk of disease recurrence and organ utilization. Historically, the Milan criteria, introduced in 1996, served as the benchmark for transplant eligibility, stipulating that patients with a single HCC lesion ≤5 cm or up to three lesions ≤3 cm without evidence of macrovascular invasion or extrahepatic spread were deemed suitable candidates for transplantation [71]. The Milan criteria demonstrated excellent outcomes in terms of post-transplant survival and recurrence rates, prompting widespread adoption as the standard for HCC transplant eligibility in many centers worldwide. Subsequent refinements, such as the University of California, San Francisco (UCSF) criteria and the Up-to-Seven criteria, expanded the eligibility criteria to include patients with larger tumors or a higher number of lesions, albeit with slightly higher recurrence rates and lower post-transplant survival compared to those meeting the Milan criteria [72]. The adoption of expanded criteria reflects a delicate balance between maximizing access to transplantation for HCC patients and ensuring favorable post-transplant outcomes, highlighting the ongoing evolution of transplant policies and practices in response to emerging evidence and clinical experience [73].

Surgical techniques for liver transplantation in HCC patients have also evolved to address the unique challenges posed by tumor burden, vascular invasion, and anatomical considerations. In cases where the tumor burden exceeds conventional criteria or involves vascular structures, strategies such as locoregional therapies (e.g., transarterial chemoembolization, radiofrequency ablation) or downstaging protocols may be employed to reduce tumor size and facilitate transplant candidacy [74]. Surgical innovations such as living donor liver transplantation (LDLT) offer an alternative source of donor organs for HCC patients, enabling timely access to transplantation and mitigating the risk of disease progression while awaiting deceased donor allocation. LDLT presents unique technical challenges, including graft size matching, vascular anatomy variations,

and donor safety considerations, necessitating specialized expertise and multidisciplinary collaboration to ensure optimal outcomes for both donors and recipients [75].

Post-transplant surveillance protocols play a crucial role in detecting HCC recurrence and guiding therapeutic interventions to optimize long-term outcomes in transplant recipients. Surveillance strategies typically involve regular imaging studies (e.g., ultrasound, MRI, CT scan) and serum biomarker measurements (e.g., alpha-fetoprotein) to monitor for tumor recurrence or de novo malignancies in the transplanted liver. The frequency and duration of surveillance vary based on individual patient factors, tumor characteristics, and center-specific protocols, with most centers adopting a risk-stratified approach tailored to the patient's underlying risk of recurrence. Early detection of HCC recurrence allows for timely intervention with locoregional therapies, systemic agents, or re-transplantation in select cases, offering the potential for salvage therapy and improved survival outcomes in transplant recipients [76].

Despite the advances in transplant eligibility criteria, surgical techniques, and post-transplant surveillance protocols, challenges persist in organ allocation and resource allocation for HCC transplantation. Organ scarcity remains a significant barrier to transplantation for HCC patients, with disparities in access to deceased donor organs and geographic variations in waitlist prioritization compounding the challenges of organ allocation. The adoption of standardized allocation policies, such as the Model for End-Stage Liver Disease (MELD) allocation system with exception points for HCC, aims to prioritize transplant candidates based on disease severity and likelihood of benefit from transplantation, while mitigating the risk of organ wastage and waitlist mortality [77]. However, controversies persist regarding the allocation of organs to HCC patients, with concerns raised about the potential for tumor downstaging, organ utility, and equity in access to transplantation. Additionally, resource constraints, including limitations in transplant center capacity, healthcare infrastructure, and financial resources, pose challenges to the delivery of transplant services for HCC patients, particularly in regions with limited access to specialized care or transplant expertise [78].

Liver transplantation remains a curative option for select patients with hepatocellular carcinoma (HCC), offering the potential for long-term survival and disease control in the setting of underlying liver disease. Criteria for transplant eligibility, surgical techniques, and post-transplant

surveillance protocols have evolved to optimize outcomes and expand access to transplantation for HCC patients. However, challenges persist in organ allocation, patient selection, and resource allocation, highlighting the need for ongoing refinement of transplant policies and practices to ensure equitable access and maximize the benefits of transplantation for HCC patients [79].

1.9 Palliative Care and Supportive Therapy

Palliative care represents a cornerstone in the comprehensive management of advanced hepatocellular carcinoma (HCC), offering a holistic approach aimed at optimizing quality of life, managing symptoms, and providing psychosocial support to patients and their families. As HCC progresses to advanced stages, patients often experience a myriad of physical and psychological symptoms, including pain, fatigue, anorexia, nausea, and emotional distress, which significantly impact their well-being and functional status. Palliative care interventions focus on alleviating these symptoms through a multidisciplinary approach that integrates pharmacological, psychosocial, and supportive therapies tailored to individual patient needs [80].

Pain management stands as a primary component of palliative care in advanced HCC, addressing the debilitating pain associated with tumor growth, invasion into surrounding tissues, and metastatic spread. Pharmacological interventions, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, adjuvant analgesics, and nerve blocks, are employed to provide effective pain relief while minimizing adverse effects and preserving quality of life. Multimodal approaches, such as combining pharmacotherapy with physical therapy, acupuncture, or relaxation techniques, offer synergistic benefits in pain control and functional improvement, enhancing overall symptom management and patient satisfaction [81].

Nutritional support plays a pivotal role in palliative care for HCC patients, addressing the nutritional challenges associated with cancer cachexia, anorexia, and metabolic derangements. Malnutrition and weight loss are common complications of advanced HCC, resulting from tumor-induced alterations in metabolism, appetite suppression, and treatment-related side effects. Nutritional interventions, including dietary counseling, oral supplements, enteral feeding, and parenteral nutrition, aim to optimize caloric intake, maintain lean body mass, and preserve nutritional status in HCC patients [82]. Individualized nutritional plans, tailored to patient

preferences, nutritional requirements, and treatment goals, promote adherence to dietary recommendations and improve outcomes in terms of symptom burden, quality of life, and treatment tolerance [83] Psychosocial support forms an integral component of palliative care in advanced HCC, addressing the emotional, social, and spiritual needs of patients and their families throughout the disease trajectory. Diagnosis of advanced HCC often elicits profound emotional responses, including fear, anxiety, depression, grief, and existential distress, which may exacerbate symptom burden and impair coping mechanisms. Psychosocial interventions, such as counseling, psychotherapy, support groups, and spiritual care, offer avenues for emotional expression, coping skills development, and existential exploration, fostering resilience, acceptance, and meaning-making in the face of illness. Patient-centered communication, empathy, and cultural sensitivity are paramount in delivering psychosocial care, ensuring a supportive and compassionate environment conducive to healing and well-being [84]. End-of-life care constitutes a critical aspect of palliative care for patients with advanced HCC, providing compassionate support and dignity in the final stages of life. Advance care planning, goals-of-care discussions, and palliative sedation are important components of end-of-life care, enabling patients to articulate their preferences, values, and treatment goals, and facilitating shared decision-making with healthcare providers and family members. Symptom management, comfort measures, and spiritual support are prioritized in the palliative care approach to end-of-life care, ensuring that patients experience a peaceful and dignified transition in alignment with their wishes and values. Bereavement support services are offered to family members and caregivers following the death of a loved one, providing opportunities for emotional processing, grief support, and community connection in the aftermath of loss [85]. Palliative care plays a crucial role in the management of advanced hepatocellular carcinoma (HCC), focusing on symptom control, psychosocial support, and end-of-life care to optimize quality of life and promote holistic well-being for patients and their families. Integration of supportive therapies, including pain management, nutritional support, and psychosocial interventions, enhances symptom management, improves treatment tolerance, and fosters resilience in the face of illness. By addressing the physical, emotional, social, and spiritual dimensions of care, palliative care contributes to a comprehensive approach to HCC management that prioritizes patient-centered care, dignity, and comfort throughout the disease trajectory [86].

CHAPTER THREE

PURPOSE OF THE STUDY

3.0 Purpose of the Study

The aim of this study is to provide a comprehensive review of hepatocellular carcinoma (HCC), focusing on elucidating its etiology, evaluating current treatment strategies, and summarizing recent therapeutic advances in HCC management.

- Review etiological factors including viral hepatitis, cirrhosis, environmental exposures, and metabolic syndrome in HCC development.
- Assess the efficacy and limitations of surgical interventions, locoregional therapies, and systemic treatments for HCC.
- Summarize recent advances in molecular targeted therapies, immunotherapies, precision medicine, and combination therapies for HCC management.
- Discuss the potential impact of these advancements on patient outcomes, treatment decision-making, and future directions in HCC research and therapy development.
- Identify barriers and facilitators to integrating palliative care and supportive therapy in advanced HCC management.

CHAPTER FOUR

METHODOLOGY

4.0 Methodology

Literature Search: Extensive exploration across platforms including Google, Google Scholar, PubMed, CrossRef, and others was conducted to conduct a comprehensive literature search. This process yielded approximately 20 research and review papers. A meticulous review of these articles was undertaken, with a focus on identifying relevant sources. The referenced works exclusively span the period from 2012 to 2022.

Data Analysis: The collected information underwent rigorous analysis to extract meaningful insights. Systematic thematic organization of the literature, aligned with the study's objectives, resulted in distinct sections addressing each facet of the topic.

CHAPTER FIVE

RESULTS AND DISCUSSION

5.0 Results and Discussion

Key Finding

1. Integration of palliative care interventions led to a reduction in symptom burden, particularly pain, fatigue, and nausea, contributing to improved overall comfort and well-being for patients with advanced HCC.
2. Nutritional support strategies, including oral supplements and enteral feeding, were associated with improved treatment tolerance, reduced treatment-related toxicities, and better treatment adherence among individuals undergoing HCC therapy.
3. Psychosocial support services, such as counseling, support groups, and spiritual care, facilitated coping mechanisms, reduced psychological distress, and enhanced resilience in patients and their families facing the challenges of advanced HCC.
4. End-of-life care discussions and advance care planning conversations positively influenced patient-centered decision-making, increased satisfaction with care, and improved alignment between patient preferences and treatment goals in the final stages of life.
5. Identification of barriers to palliative care and supportive therapy integration highlighted the need for increased education and training for healthcare providers, enhanced communication strategies, and improved access to palliative care resources for patients with advanced HCC.
6. Recommendations for optimizing palliative care and supportive therapy delivery emphasized the importance of early integration of palliative care into the oncology care continuum, comprehensive symptom assessment and management, and continuity of care across healthcare settings.
7. Multidisciplinary collaboration between oncologists, palliative care specialists, nutritionists, social workers, and spiritual care providers was identified as essential for providing holistic, patient-centered care for individuals with advanced HCC.
8. Patient and caregiver education and empowerment emerged as critical components of supportive therapy, facilitating informed decision-making, treatment adherence, and active participation in care planning and decision-making processes.
9. Future research directions include exploring novel approaches to symptom management, evaluating the impact of palliative care interventions on healthcare utilization and cost-

effectiveness, and assessing the long-term outcomes of integrated palliative care and supportive therapy models in advanced HCC populations.

Causes of Hepatocellular Carcinoma

In this study, the causes of hepatocellular carcinoma (HCC) were investigated, aiming to elucidate the multifactorial nature of this malignancy. Hepatocellular carcinoma arises from a complex interplay of genetic, environmental, and viral factors, contributing to its heterogeneous etiology. Chronic viral hepatitis, particularly infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), is considered a major risk factor for HCC development globally [62]. HBV and HCV induce chronic inflammation, hepatic fibrosis, and cirrhosis, predisposing individuals to hepatocarcinogenesis through mechanisms involving viral integration into the host genome, direct oncogenic effects of viral proteins, and immune-mediated hepatocyte injury. Additionally, alcohol consumption is recognized as a well-established risk factor for HCC, with chronic alcohol abuse leading to hepatocyte injury, inflammation, oxidative stress, and cirrhosis, thereby increasing the risk of malignant transformation [63]. Non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH), have emerged as significant contributors to HCC incidence, driven by the global obesity epidemic, metabolic syndrome, and insulin resistance. NAFLD/NASH-associated HCC develops in the context of hepatic steatosis, inflammation, fibrosis, and cirrhosis, reflecting the synergistic interplay between metabolic derangements, oxidative stress, and carcinogenesis within the steatotic liver parenchyma. Genetic predisposition also plays a role in HCC pathogenesis, with polymorphisms in genes involved in detoxification pathways, DNA repair mechanisms, and cell cycle regulation influencing individual susceptibility to HCC development [64]. Environmental factors, such as exposure to aflatoxins, polycyclic aromatic hydrocarbons, and heavy metals, contribute to HCC risk through mechanisms involving DNA damage, mutagenesis, and carcinogenesis. Furthermore, chronic liver diseases, including autoimmune hepatitis, primary biliary cholangitis, and hemochromatosis, predispose individuals to HCC development, highlighting the importance of underlying liver pathology in hepatocarcinogenesis. Infection with other hepatotropic viruses, such as hepatitis D virus (HDV) and hepatitis E virus (HEV), as well as exposure to environmental toxins and carcinogens, further contribute to the complex etiology of HCC [65]. Understanding the diverse causes of HCC is essential for implementing targeted prevention strategies, early detection programs, and

personalized therapeutic interventions aimed at mitigating disease burden and improving outcomes for individuals at risk of HCC development [66].

Table-5.1: Summary table of the causes of hepatocellular carcinoma (HCC).

Risk Factor	Description	Reference
Chronic Viral Hepatitis	Infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) leads to chronic liver inflammation, fibrosis, and cirrhosis, increasing the risk of HCC.	[67]
Alcohol Consumption	Chronic alcohol abuse induces hepatic injury, inflammation, oxidative stress, and cirrhosis, predisposing individuals to hepatocarcinogenesis.	[68]
Non-Alcoholic Fatty Liver Disease (NAFLD)	NAFLD and its progressive form, NASH, are associated with hepatic steatosis, inflammation, fibrosis, and cirrhosis, contributing to HCC development.	[69]
Genetic Predisposition	Polymorphisms in genes involved in detoxification, DNA repair, and cell cycle regulation influence individual susceptibility to HCC development.	[70]
Environmental Factors	Exposure to aflatoxins, polycyclic aromatic hydrocarbons, heavy metals, and other carcinogens increases the risk of HCC through DNA damage and mutagenesis.	[71]
Chronic Liver Diseases	Autoimmune hepatitis, primary biliary cholangitis, and hemochromatosis predispose individuals to HCC development due to underlying liver pathology and chronic inflammation.	[72]
Other Hepatotropic Viruses	Infection with hepatitis D virus (HDV) and hepatitis E virus (HEV) contributes to HCC risk in conjunction with other underlying liver diseases.	[73]
Environmental Toxins and Carcinogens	Exposure to environmental toxins and carcinogens further increases the risk of HCC development through mechanisms involving DNA damage and mutagenesis.	[74]

Treatment Strategies of Hepatocellular Carcinoma

In this study, investigated the comprehensive treatment strategies for hepatocellular carcinoma (HCC), aiming to provide a detailed overview of therapeutic approaches tailored to individual patient characteristics and disease stages. The management of HCC necessitates a multidisciplinary approach integrating surgical, locoregional, systemic, and supportive therapies to optimize outcomes and improve survival rates. Surgical resection stands as the cornerstone of treatment for early-stage HCC, offering the potential for curative intent by removing the primary tumor and preserving hepatic function [75]. However, eligibility for surgical resection is contingent upon tumor size, location, vascular invasion, and liver function, with careful

consideration given to the risk of postoperative complications and tumor recurrence. Liver transplantation represents another curative option for select patients with early-stage HCC and underlying liver disease, offering the advantage of removing both the tumor burden and the diseased liver parenchyma. However, organ scarcity, waitlist prioritization, and stringent eligibility criteria pose challenges to transplantation as a primary treatment modality for HCC, necessitating careful patient selection and allocation strategies to optimize outcomes and maximize organ utility. Locoregional therapies, including radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and radioembolization, play a pivotal role in the management of intermediate-stage HCC, offering effective options for disease control and symptom palliation in cases where curative-intent therapies are not feasible or appropriate [76]. RFA utilizes thermal energy to induce tumor necrosis and ablation, offering a minimally invasive approach for treating small HCC lesions in patients with preserved liver function. TACE combines intra-arterial chemotherapy with embolic agents to selectively target tumor vasculature, delivering high-dose chemotherapy directly to the tumor while minimizing systemic toxicity. Radioembolization involves the intra-arterial delivery of radioactive microspheres, providing targeted radiation therapy to liver tumors while sparing surrounding healthy tissue. Systemic therapies have revolutionized the management of advanced HCC, offering novel options for patients who are not candidates for surgical or locoregional therapies [77]. Targeted agents, such as sorafenib, lenvatinib, and regorafenib, inhibit key signaling pathways involved in tumor angiogenesis, proliferation, and survival, providing survival benefits and disease stabilization in patients with advanced HCC. Immunotherapy, particularly immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), has shown promising results in a subset of HCC patients, enhancing antitumor immune responses and improving survival outcomes. However, challenges remain in identifying predictive biomarkers, optimizing treatment regimens, and managing immune-related adverse events associated with immunotherapy in HCC. Supportive care measures, including pain management, nutritional support, and psychosocial interventions, are essential components of the treatment plan, addressing symptom burden, improving quality of life, and enhancing overall well-being for patients affected by HCC [78]. Pain management strategies encompass a multimodal approach utilizing pharmacological agents, interventional procedures, and complementary therapies to alleviate pain and improve functional status. Nutritional support aims to optimize caloric intake, maintain lean

body mass, and preserve nutritional status in HCC patients, addressing malnutrition, cachexia, and treatment-related side effects. Psychosocial interventions, such as counseling, support groups, and palliative care services, offer avenues for emotional expression, coping skills development, and existential exploration, fostering resilience, acceptance, and meaning-making in the face of illness [79]. In conclusion, the management of hepatocellular carcinoma (HCC) necessitates a multidisciplinary approach tailored to individual patient characteristics and disease stages. Surgical resection, liver transplantation, locoregional therapies, systemic agents, and supportive care measures constitute the cornerstone of treatment for HCC, offering curative intent, disease control, and symptom palliation across the disease continuum. Ongoing research efforts aimed at optimizing treatment regimens, identifying predictive biomarkers, and addressing treatment-related toxicities are essential for improving outcomes and advancing the field of HCC management [80].

Table-5.2: Summary table of treatment strategies for hepatocellular carcinoma (HCC).

Treatment Strategy	Mechanism of Action	Reference
Surgical Resection	Removal of the primary tumor and preservation of hepatic function, offering curative intent for early-stage HCC patients.	[72]
Liver Transplantation	Replacement of the diseased liver with a healthy donor organ, providing curative treatment for select patients with early-stage HCC and underlying liver disease.	[73]
Radiofrequency Ablation (RFA)	Utilization of thermal energy to induce tumor necrosis and ablation, offering a minimally invasive approach for treating small HCC lesions.	[74]
Transarterial Chemoembolization (TACE)	Combination of intra-arterial chemotherapy and embolic agents to selectively target tumor vasculature, delivering high-dose chemotherapy directly to the tumor.	[75]
Radioembolization	Intra-arterial delivery of radioactive microspheres to provide targeted radiation therapy to liver tumors while sparing surrounding healthy tissue.	[76]
Targeted Therapy	Inhibition of key signaling pathways involved in tumor angiogenesis, proliferation, and survival, offering survival benefits and disease stabilization in advanced HCC.	[77]
Immunotherapy	Enhancement of antitumor immune responses through immune checkpoint inhibition, improving survival outcomes in a subset of HCC patients.	[78]

Supportive Care	Symptom management, pain control, nutritional support, and psychosocial interventions to address symptom burden, improve quality of life, and enhance overall well-being for HCC patients.	[79]

Therapeutic Advances of Hepatocellular Carcinoma

In this study, investigated the therapeutic advances in the management of hepatocellular carcinoma (HCC), focusing on recent developments that have reshaped the treatment landscape and improved outcomes for patients with this aggressive malignancy. Over the past few decades, significant strides have been made in understanding the molecular pathogenesis of HCC, leading to the identification of novel therapeutic targets and the development of targeted therapies aimed at disrupting key oncogenic pathways [81]. Sorafenib, a multikinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and Raf kinases, was the first systemic agent to demonstrate survival benefits in patients with advanced HCC, establishing a new standard of care in the first-line setting. Subsequent clinical trials have evaluated the efficacy of other targeted agents, such as lenvatinib, regorafenib, and cabozantinib, either as monotherapy or in combination with immunotherapy, in improving survival outcomes for patients with advanced HCC. Lenvatinib, a potent inhibitor of VEGFR, fibroblast growth factor receptor (FGFR), and other receptor tyrosine kinases, demonstrated non-inferiority to sorafenib in terms of overall survival and progression-free survival in the first-line treatment of unresectable HCC, offering an alternative option with a similar efficacy profile [82]. Regorafenib, a multitargeted kinase inhibitor, showed survival benefits in patients with HCC who progressed on sorafenib, leading to its approval as a second-line therapy for advanced HCC. Cabozantinib, another multikinase inhibitor targeting VEGFR, MET, and AXL, demonstrated improved overall survival and progression-free survival compared to placebo in patients with advanced HCC who had previously received sorafenib, further expanding the treatment armamentarium for this patient population [83].

In addition to targeted therapies, immunotherapy has emerged as a promising treatment approach for HCC, harnessing the power of the immune system to recognize and eliminate tumor cells. Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, which target programmed

cell death protein 1 (PD-1), have shown durable responses and improved survival outcomes in a subset of patients with advanced HCC. Nivolumab demonstrated a survival benefit compared to sorafenib in patients with advanced HCC who had previously received systemic therapy, leading to its approval as a second-line treatment option [84]. Pembrolizumab, another anti-PD-1 antibody, showed encouraging results in patients with advanced HCC who had previously received sorafenib, with durable responses and manageable safety profiles observed in clinical trials. However, the efficacy of immune checkpoint inhibitors in HCC is limited to a subset of patients characterized by specific biomarkers, such as programmed death-ligand 1 (PD-L1) expression and tumor mutational burden, highlighting the need for predictive biomarkers to guide patient selection and treatment optimization [85].

Furthermore, combinatorial approaches incorporating targeted therapies and immunotherapy have shown promise in overcoming resistance mechanisms and enhancing treatment efficacy in advanced HCC. The combination of atezolizumab, a PD-L1 inhibitor, and bevacizumab, a monoclonal antibody targeting VEGF, demonstrated superior overall survival and progression-free survival compared to sorafenib in patients with unresectable HCC who had not received prior systemic therapy, leading to its approval as a first-line treatment option [86]. Similarly, the combination of lenvatinib and pembrolizumab showed encouraging antitumor activity and manageable safety profiles in patients with unresectable HCC, irrespective of prior treatment status or underlying etiology, highlighting the potential synergistic effects of targeting both angiogenesis and immune checkpoints in HCC. These therapeutic advances represent significant milestones in the management of HCC, offering new treatment options and hope for improved outcomes for patients with this challenging disease [87].

Table-5.3: Therapeutic Advances of Hepatocellular Carcinoma.

Treatment	Mechanism of Action	Description	Reference
Sorafenib	Multikinase inhibitor targeting VEGFR, PDGFR, and Raf kinases	Demonstrated survival benefits in advanced HCC, establishing a new standard of care in the first-line setting.	[82]
Lenvatinib	Inhibitor of VEGFR, FGFR, and other receptor tyrosine kinases	Non-inferior to sorafenib in terms of overall survival and progression-free survival in first-line treatment of HCC.	[83]

Regorafenib	Multitargeted kinase inhibitor	Showed survival benefits in patients with HCC who progressed on sorafenib, leading to its approval as a second-line therapy.	[84]
Cabozantinib	Multikinase inhibitor targeting VEGFR, MET, and AXL	Improved overall survival and progression-free survival compared to placebo in patients with advanced HCC.	[85]
Nivolumab	Anti-PD-1 antibody	Demonstrated survival benefit compared to sorafenib in second-line treatment of advanced HCC.	[86
Pembrolizumab	Anti-PD-1 antibody	Showed encouraging results in patients with advanced HCC who had previously received sorafenib.	[87]
Atezolizumab + Bevacizumab	Combination of PD-L1 inhibitor and VEGF monoclonal antibody	Demonstrated superior overall survival and progression-free survival compared to sorafenib in first-line treatment of HCC.	[88]
Lenvatinib + Pembrolizumab	Combination therapy targeting angiogenesis and immune checkpoints	Showed promising antitumor activity and manageable safety profiles in patients with unresectable HCC.	[89]

Discussion

In this study, a comprehensive exploration of the various facets of hepatocellular carcinoma (HCC) has been undertaken, encompassing its etiology and risk factors to the latest therapeutic advances. The findings underscore the complex nature of HCC and the need for a multidisciplinary approach to its management. Key insights gleaned from the investigation, implications for clinical practice, areas of ongoing research, and future directions in HCC management will be discussed [90].

Firstly, an analysis of the etiology and risk factors of HCC revealed a multifactorial interplay of genetic, environmental, and viral factors contributing to hepatocarcinogenesis. Chronic viral hepatitis, particularly infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), emerged as predominant risk factors for HCC, emphasizing the importance of viral eradication strategies and antiviral therapy in preventing HCC development. Additionally, the significance of alcohol consumption, non-alcoholic fatty liver disease (NAFLD), genetic predisposition, and exposure to

environmental toxins in contributing to HCC risk was identified, highlighting the necessity for targeted prevention efforts and lifestyle modifications to mitigate disease burden [91].

Regarding diagnosis and screening, the study emphasizes the importance of early detection in improving patient outcomes. Screening and surveillance programs employing imaging modalities such as ultrasound, MRI, and CT scan, along with serum biomarkers like alpha-fetoprotein, were found to play a crucial role in identifying HCC at an early stage, particularly in high-risk populations with chronic liver disease. However, challenges persist in optimizing screening protocols, enhancing sensitivity and specificity, and addressing disparities in access to screening services, particularly in resource-limited settings [92].

In terms of treatment strategies, significant therapeutic advances that have revolutionized the management of HCC in recent years were highlighted. Surgical resection, liver transplantation, locoregional therapies, targeted agents, and immunotherapy were identified as key treatment modalities, offering curative intent, disease control, and symptom palliation across the disease continuum [93]. The advent of targeted therapies, such as sorafenib, lenvatinib, and regorafenib, has significantly improved survival outcomes in advanced HCC, providing alternative options for patients who are not candidates for surgical or locoregional therapies. Similarly, immunotherapy, particularly immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1), has shown promising results in a subset of HCC patients, offering durable responses and improved survival outcomes. However, challenges remain in identifying predictive biomarkers, optimizing treatment regimens, and managing treatment-related toxicities associated with immunotherapy in HCC [94].

Furthermore, the importance of supportive care measures in optimizing patient outcomes and enhancing quality of life for individuals with HCC was underscored. Palliative care interventions focusing on symptom control, psychosocial support, and end-of-life care were found to play a crucial role in addressing the holistic needs of patients and their families throughout the disease trajectory. Integration of supportive therapies, including pain management, nutritional support, and psychosocial interventions, enhances the overall well-being of HCC patients, fostering resilience, acceptance, and meaning-making in the face of illness [95].

In terms of therapeutic advances, the study highlighted significant progress made in the development of targeted therapies and immunotherapy for HCC. Sorafenib, the first systemic agent to demonstrate survival benefits in advanced HCC, established a new standard of care in the first-line setting, paving the way for subsequent advances in targeted therapy and immunotherapy [96]. Lenvatinib, regorafenib, cabozantinib, and immune checkpoint inhibitors, such as nivolumab and pembrolizumab, have shown promising results in improving survival outcomes and expanding treatment options for patients with advanced HCC. Combinatorial approaches incorporating targeted therapies and immunotherapy have shown synergistic effects in overcoming resistance mechanisms and enhancing treatment efficacy, offering new hope for patients with this challenging disease [97].

The study provides a comprehensive overview of the etiology, diagnosis, treatment, and therapeutic advances in hepatocellular carcinoma. The findings underscore the importance of a multidisciplinary approach to HCC management, incorporating screening and surveillance, targeted therapies, immunotherapy, and supportive care measures to optimize patient outcomes and improve quality of life. Ongoing research efforts aimed at identifying novel therapeutic targets, optimizing treatment regimens, and addressing treatment-related toxicities are essential for advancing the field of HCC management and improving outcomes for patients affected by this aggressive malignancy [98].

CHAPTER SIX

CONCLUSION

6.0 Conclusion

In conclusion, this study offers a comprehensive exploration of hepatocellular carcinoma (HCC), covering its etiology, diagnosis, treatment strategies, therapeutic advances, and supportive care measures. The findings underscore the complexity of HCC and highlight the importance of a multidisciplinary approach to its management. Significant progress has been made in understanding the molecular pathogenesis of HCC and developing targeted therapies and immunotherapy, leading to improved outcomes for patients across the disease spectrum. However, challenges remain in optimizing screening protocols, identifying predictive biomarkers, and managing treatment-related toxicities. Continued research efforts are warranted to further advance the field of HCC management and enhance the quality of life for individuals affected by this aggressive malignancy.

CHAPTER SEVEN

REFERENCE