Collage of Health Science

School of Medicine

Department of Surgery, Hepatobiliary and Pancreatic Surgery Unit

Clinical Profile and Hepatocellular Cancer Treatment Patterns in Resource Limited Settings- a prospective cross-sectional study at Two Tertiary Referral Teaching Hospitals, Ethiopia

Investigator: Dr. Tebarek Jemal (MD, General Surgeon, HPB Surgery Fellow)

Advisor: Dr. Shimelis Nigussie (MD, Assistant Prof. General and HPB Surgeon)

Co-Advisor: Dr. Henok Teshome (MD, Assistant Prof. General and HPB Surgeon)

A Thesis Proposal to be Submitted to the Department of Surgery, School of Medicine, College Medicine and Health Science for the Partial Fulfillment of the Requirements for Subspecialty in Hepatopancreatic Biliary Surgery.

July, 2025

Addis Ababa, Ethiopia

Abstract

Background: Hepatocellular carcinoma (HCC) exerts a substantial global burden, significantly contributing to worldwide mortality, morbidity, economic costs, and hospitalization rates. A significant treatment gap exists in low- and middle-income countries (LMICs), characterized by a low rate of curative surgical interventions for HCC, making access to effective surgical care for this disease one of the most inequitable aspects of healthcare globally.

Objective: To assess the etiological and treatment patterns of Hepatocellular Carcinoma (HCC) in patients visited to Tikur Anbessa Specialized Hospital (TASH) and St. Paul's Hospital Millennium Medical College (SPHMMC) in Addis Ababa, Ethiopia in 2025.

Methods: A cross-sectional, hospital-based prospective study was conducted to investigate the etiological and treatment patterns of Hepatocellular Carcinoma (HCC). The study included a sample size of 130 HCC patients. To ensure appropriate statistical analysis, the normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed data were described using means and standard deviations, while medians and interquartile ranges were used to summarize skewed data.

Results: Our analysis of 130 Hepatocellular Carcinoma (HCC) patients requiring surgical intervention, Loco-regional, systemic therapy, or supportive care revealed a mean age of 54.5 ± 16.5 years, with a slight male predominance (82/130, 63.1%). A significant proportion of participants (62/130, 47.7%) had a history of hepatitis infection while unidentified risk factor for HCC was alarmingly high (48/130, 37%). Among those with hepatitis, the majority were infected with Hepatitis B Virus (HBV) (45/62, 72.6%), while a smaller proportion had Hepatitis C Virus (HCV) (14/62, 22.6%). The majority of HCC cases presented as either multinodular/multifocal (58/130, 44.6%) or single/solitary (57/130, 44.5%) lesions, with a mean size of 10.0± 4.6cm.In those with imaging features of cirrhosis (58/130), vast majority (29/58, 50%) exhibited Child-Pugh score B. However, a large proportion of patients in our study presented with advanced-stage disease, as evidenced by the Barcelona Clinic Liver Cancer (BCLC) staging system: BCLC stage C was observed in 83 participants (63.8%). Curative Liver resection was performed in only 23 participants (17.7%), while Transarterial Chemoembolization (TACE) was utilized in 27.7% of cases.

Conclusion: Despite advancements in the surgical management of Hepatocellular Carcinoma (HCC), there remain notable challenges in providing access to curative treatments such as liver resection, transplantation, and Radiofrequency Ablation (RFA). These limitations are primarily attributable to deficiencies in highly trained human resource, inadequate infrastructure, and policy gaps, which hinder the effective delivery of potentially life-saving interventions.

Contents

Abstract i
List of Tables and Figures iv
ACRONYMS v
ACKNOWLEDGMENT vi
CHAPTER ONE 1
1. INTRODUCTION 1
1.1. Background 1
1.2. Statement of the problems 3
1.3. Significance of the study 4
CHAPTER TWO 5
2. Literature review 5
2.1. Burden of Hepatocellular carcinoma 5
2.2. Risk factors of HCC 6
2.3. Clinical Profile and Prognostic factors 8
2.4. Treatment of HCC 9
CHAPTER THREE Objectives 12
3.1. General Objective 12
3.2. Specific Objectives 12
CHAPTER FOUR: METHODOLOGY 13
4.1 Study Area 13
4.2 Study Design 14
4.3. Population 14
4.3.1. Source of population 14
4.3.2. Study Population 14
4.4. Study Variables 14
4.5. Sample Size determination and Sampling Technique 14
4.6. Inclusion & Exclusion Criteria 16
4.6.1. Inclusion Criteria 16
4.6.2. Exclusion criteria 16
4.7. Data Collection 16

4.8. Data processing and Analysis 16
4.9. Data Quality Assurance 17
4.10. Ethical Considerations 17
4.11. Term Definitions 17
CHAPTER FIVE: RESULTS 19
5.Results 19
CHAPTER SIX: DISCUSSION AND RECOMMENDATIONS 27
6.1. Discussion 27
6.2. Recommendation 31
Reference 32

List of Tables and Figures

Table 1:Sociodemographic characteristics of patients diagnosed Hepatocellular carcinoma at TASH and Sait Paul, Addis Ababa, Ethiopia 2025 19
Table 2:Clinical profile of patients diagnosed Hepatocellular carcinoma at TASH and Sait Paul, Addis Ababa, Ethiopia 2025 20
Table 3:Diagnosis and prognostic factors for Hepatocellular carcinoma at TASH and Sait Paul, Addis Ababa, Ethiopia 2025 22
Table 4:Stages and management Hepatocellular carcinoma at TASH and Sait Paul, Addis Ababa, Ethiopia 2025..... 24
Table 5:BCLC stage versus Management for HCC at TASH and SPHMMC Addis Ababa, Ethiopia 2025 25
Table 6:ALBI grade versus Management for HCC at TASH and SPHMMC Addis Ababa, Ethiopia 2025 26
Table 7:Drugs used for TACE and systemic management for HCC at TASH and SPHMMC Addis Ababa, Ethiopia 2025 26

List of Figure

Figure 1:Conceptual Framework for Hepatocellular carcinoma at TASH and Sait Paul, Addis Ababa, Ethiopia 2025.....11
Figure 2:Performance status of patients with hepatocellular carcinoma at TASH and SPHMMC Addis Ababa, Ethiopia 2025 21
Figure 3:Location of Hepatocellular carcinoma at TASH and SPHMMC Addis Ababa, Ethiopia 2025..... 23
Figure 4:BCLC stage of Hepatocellular carcinoma at TASH and SPHMMC Addis Ababa, Ethiopia 2025 25

ACRONYMS

AASLD – American Association for the Study of Liver Diseases

AFP – Alfa Fetoprotein

ALBI – Albumin-Bilirubin Index

BCLC – Barcelona Clinic Liver Cancer

CPS – Child Pugh Score

ECOG – Eastern Cooperative Oncology Group

FLR – Future Liver Remnant

HCC – Hepatocellular Cancer

HKLC – Hong Kong Liver Cancr

LRT – Loco-regional Therapy

MDT- Multidisciplinary Team

REC- Research and Ethics Committee

RFA – Radio Frequency Ablation

SPHMMC- Saint Paul Hospital Millennium Medical College

TACE – Trans-arterial Chemoembolization

TARE – Trans-arterial Radioembolization

TASH- Tikur Anbessa Specialized Hospital

ACKNOWLEDGMENT

My appreciation goes to Addis Ababa University, College of Health Science Department of Surgery for giving me the chance to conduct this research project for my subspecialty certificate in HPB surgery. My deepest gratitude goes to my advisors Dr. Shimelis Nigissie and Dr. Henok Teshome for their continuous guidance and feedback during the development of this proposal and their readiness to support until the end of the study.

CHAPTER ONE

1. INTRODUCTION

1.1. Background

Liver cancer represents a significant global health challenge, contributing substantially to cancer-related mortality, morbidity, disability, and economic burden. Hepatocellular carcinoma (HCC) accounts for the majority of liver cancer cases, comprising 75-85%[1, 2], while intrahepatic cholangiocarcinoma constitutes the remaining 20-25%. The cellular origin of HCC can vary, potentially arising from liver stem cells, transit amplifying populations, or mature hepatocytes, all in response to various oncogenic insults. The pathophysiological development of HCC is a complex and multi-step process. Notably, over 90% of HCC cases occur in the context of pre-existing chronic liver disease, with cirrhosis, regardless of its etiology, serving as the most potent risk factor. The early stages of hepatocyte malignant transformation and subsequent HCC development involve a complex interplay of various factors. These factors trigger a series of events, including the activation of proto-oncogenes, loss of sensitivity to tumor suppressor genes, impaired apoptosis, angiogenesis, and suppression of the immune system[3]. These changes ultimately lead to uncontrolled cellular proliferation and the formation of a cancerous mass. A deeper understanding of the molecular mechanisms driving HCC development is crucial for advancing targeted therapies. Nearly half of HCC patients harbor at least one recurring oncogenic mutation, with TP53, CTNNB1, and TERT being among the most frequently observed. Elucidating the intricate cell signaling pathways involved in HCC oncogenesis is essential for identifying potential therapeutic targets and developing novel drugs. Cellular signaling pathways within HCC cells typically converge into two broad categories[3]. The first encompasses Receptor Tyrosine Kinase (RTK) signaling pathways, which involve a complex network of eight key signals, including Vascular Endothelial Growth Factor Receptor (VEGFR), Epidermal Growth Factor Receptor (EGFR), c-Met, Platelet-Derived Growth Factor Receptor (PDGFR), Fibroblast Growth Factor Receptor (FGFR), Insulin-like Growth Factor Receptor (IGFR), KIT, Rearranged during Transfection (RET), and their downstream pathway such as MAPK pathway, Phosphatidylinositol 3-kinase (PI3K) pathway, and the JAK-STAT pathway, which play critical roles in cell proliferation, survival, and angiogenesis[3]. The second category

comprises cell differentiation pathways, including Wnt/β-catenin, Hippo, Hedgehog, and Notch, which are particularly important for maintaining liver tissue homeostasis. These cell signals and mutations are induced by different etiological factors[3]. The leading risk factors for HCC are chronic infections with Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), alcohol consumption, alterations in the gut microbiota, exposure to aflatoxins, and non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD)[2, 4]. HCC often exhibits characteristic imaging features on modalities such as CT and MRI; however, approximately 10% of tumors, particularly those ranging in size from 1 to 2 cm, may lack these hallmarks imaging characteristics, posing a diagnostic challenge. After diagnosis, HCC is typically staged using the Barcelona Clinic Liver Cancer (BCLC) staging system, which integrates tumor size, liver function, and performance status to guide treatment decisions. Current treatment strategies for early-stage HCC primarily include surgical approaches such as liver resection and transplantation, offering the potential for curative outcomes. When surgery is not feasible, local ablation techniques, particularly radiofrequency ablation (RFA), serve as the most common non-surgical intervention for early-stage disease. Transarterial chemoembolization (TACE), which involves delivering chemotherapy directly to the tumor through the hepatic artery, has been a mainstay of treatment and considered the benchmark therapy for intermediate-stage HCC for the past two decades. The advanced HCC will first receive systemic therapies.

1.2. Statement of the problems

Liver cancer represents a significant and growing global health crisis, placing a tremendous burden on healthcare systems and national economies[5, 6]. The most recent GLOBOCAN data indicates the magnitude of the issue, estimating approximately 865,000 new cases and 758,000 deaths attributable to liver cancer in 2022[6]. These figures firmly establish liver cancer as the third leading cause of cancer-related mortality worldwide, trailing only lung and colorectal cancers[6], and the sixth most commonly diagnosed cancer overall. Projections suggest that the incidence of liver cancer will continue to rise, exceeding 1 million cases annually by 2025, further amplifying its global impact. The significant impact of Liver cancer extended contributing significantly to disability-adjusted life years (DALYs). Beyond the direct health consequences, hepatocellular carcinoma (HCC) carries a substantial financial burden, encompassing direct medical costs, lost productivity, and indirect medical expenses. In the United States, annual medical costs associated with HCC have been projected to reach $454.9 million, equating to approximately $32,907 per patient[7]. A breakdown of these costs reveals that healthcare expenditures and lost productivity account for 89.2% and 10.8% of the total economic burden, respectively[7]. Other studies have estimated the cumulative cost of HCC management to range from US$87,556 for patients receiving best supportive care alone to US$208,595 for those undergoing liver-directed treatment in combination with sorafenib[8]. The prevalence and impact of HCC are particularly pronounced in Africa, where significant heterogeneity exists among nations[9]. HCC has been recognized as the fourth most commonly diagnosed cancer in Africa, with estimates suggesting 65,000 new cases, 64,000 deaths, and a prevalence of 57,000 cases in 2018[9]. Of the 25 countries with the highest HCC burden globally, 12 are located within Africa[10]. Underlying the development of HCC is a complex interplay of factors[11], with chronic Hepatitis B Virus (HBV) infection playing a pivotal role. Approximately 55% of HCC cases worldwide are attributed to HBV infection, with this figure rising to 60% in Asia and Africa. Chronic Hepatitis C Virus (HCV) infection, affecting an estimated 170 million people globally, is also a major risk factor, contributing to HCC development in a substantial proportion of patients. Alcohol consumption, a well-established Group 1 carcinogen, contributes to an estimated 17-30% of the global burden of HCC. The mechanisms by which alcohol induces liver cancer are complex and multifaceted.

In Ethiopia, HCC represents a significant and growing concern[12]. The disease is characterized by low survival rates and compounded by a limited and often inadequate healthcare system. The country's low survival and strained system requires effective interventional approaches to save lives.

1.3. Significance of the study

Hepatocellular carcinoma (HCC) represents a significant public health challenge, contributing substantially to mortality, morbidity, disability, and economic burden worldwide. The impact of HCC varies significantly across different geographic regions, influenced by variations in etiological factors, diagnostic practices, and the timeliness of diagnosis. This study provides valuable evidence for healthcare workers by elucidating the etiological patterns, stage at diagnosis, and treatment modalities currently utilized. This information can inform the development and implementation of targeted public health prevention interventions, tailored to the specific context of the study population. A deeper understanding of these factors is crucial for optimizing resource allocation and improving patient outcomes. Furthermore, the findings of this study provide invaluable evidence for policymakers, enabling them to modify and refine existing policies related to HCC prevention, screening, and treatment. This data can support the development of evidence-based guidelines and the implementation of strategies to improve access to care, particularly in resource-limited settings. For researchers, this study serves as a critical baseline for future investigations. It provides a foundation for exploring the underlying etiologies of HCC in the region, identifying potential avenues for prevention, and evaluating the effectiveness of different screening programs and interventions. This research can contribute to the development of innovative strategies for combating HCC in Ethiopia and other low- and middle-income countries (LMICs) facing similar challenges. Finally, the findings of this study can be leveraged by advocacy groups and associations working to raise awareness about HCC, promote early detection, and improve access to care for affected individuals. By disseminating the study's results, these organizations can advocate for policies and programs that prioritize HCC prevention and treatment, ultimately reducing the burden of this devastating disease.

CHAPTER TWO

2. Literature review

2.1. Burden of Hepatocellular carcinoma

Liver cancer poses a substantial global health burden, contributing significantly to mortality, morbidity, disability, and economic costs. This burden, however, is not uniformly distributed, exhibiting considerable variation across different geographic regions. A multitude of global epidemiological studies provide compelling evidence regarding the overall impact of liver cancer worldwide. The most recent GLOBOCAN study, a comprehensive global cancer statistics project, estimated approximately 865,000 new cases and 758,000 deaths due to liver cancer in 2022[6]. This data positions liver cancer as the third leading cause of cancer-related death globally, surpassed only by lung and colorectal cancers, and the sixth most frequently diagnosed cancer overall[6]. These figures underscore the continued significance of liver cancer as a major global health challenge, with projections estimating an incidence exceeding 1 million cases by the year 2025. The impact of liver cancer extends beyond mortality, contributing significantly to disability-adjusted life years (DALYs), a metric used to measure the overall burden of disease. Liver cancer accounted for approximately 13 million DALYs globally[13]. A disproportionate share of these DALYs (99.01%) was attributed to years of life lost (YLL), reflecting the premature mortality associated with the disease. Years lived with disability (YLD) accounted for the remaining 0.99% of DALYs. Notably, the highest age-standardized DALYs and mortality rates were observed in countries with a low Socio-Demographic Index (SDI), particularly those located in sub-Saharan Africa[13]. In the African continent, HCC similarly holds the position of the fourth most prevalent cancer affecting both men and women[9]. Recent data from 2018 indicate approximately 65,000 new HCC cases were diagnosed in Africa, resulting in 64,000 deaths[9], underscoring the aggressive nature of the disease and the limited access to effective treatment. Within Ethiopia, liver cancer presents a particularly concerning public health issue. National data from 2019 revealed that liver cancer was responsible for approximately 1,160 new incidence cases, tragically resulting in 1,230 deaths[14]. The disease also contributed significantly to the nation's disease burden, accounting for 370,000 disability-adjusted life years (DALYs)[14].

2.2. Risk factors of HCC

Numerous studies have focused on identifying both modifiable and non-modifiable factors[2, 4] that contribute to the complex pathogenesis of liver cancer, leading to the development of HCC with its unique mutational landscape and cellular signaling pathways. Cirrhosis, regardless of the underlying cause, creates a highly conducive environment for the development and progression of HCC. It is estimated that up to 33% of individuals with cirrhosis will develop HCC during their lifetime, with an annual incidence rate ranging from 1 to 8 percent.

Globally, approximately 400 million people are chronically infected with HBV, and it is estimated that around 100 million of these individuals may eventually develop HCC. The risk of HCC in HBV-infected patients is significantly elevated, estimated to be as much as 100 times higher compared to those without HBV infection[2]. Hepatitis B virus infection accounts for a substantial proportion of HCC cases worldwide, representing approximately 55% of all HCC globally. This figure rises to approximately 60% of HCC cases in Asia and Africa, while representing around 20% of cases in Western countries. As a DNA virus, HBV has the capability to integrate into the host genome, potentially inducing insertional mutagenesis, which can lead to oncogene activation, even in the absence of cirrhosis. However, it is important to note that the majority of patients with HBV-induced HCC do, in fact, have underlying cirrhosis. The lifetime risk of developing HCC among individuals with chronic Hepatitis B Virus (HBV) infection ranges from 10% to 25%.

Chronic Hepatitis C Virus (HCV) infection affects approximately 170 million people worldwide. Cirrhosis resulting from chronic HCV infection is the predominant cause of HCC in several regions, including the United States, Japan, Europe, and Latin America, with an estimated annual incidence rate of 2 to 8%. Patients infected with HCV face a significantly elevated risk of developing HCC, approximately 17 times higher than that of HCV-negative individuals.

A multinational study conducted in Africa, encompassing 2566 patients across 21 tertiary referral centers (including two in Egypt, nine in Nigeria, four in Ghana, and one each in the Ivory Coast, Cameroon, Sudan, Ethiopia, Tanzania, and Uganda), revealed significant regional variations in the etiology of HCC. The study found that Hepatitis C Virus was the leading cause of hepatocellular carcinoma in Egypt (84%), whereas Hepatitis B Virus was the leading cause in the remaining African countries, accounting for 55%[15].

Excessive consumption of alcohol (ie, >45 or 50 g/d) increases the risk of liver cancer, with women showing a higher OR (3.89) than men (1.59). Despite different studies different evidence, Alcohol intake contributes to up to 17 to 30% of the global burden of HCC[16]. The mechanism of alcohol induce liver cancer are complex and multifacet-established group 1 carcinogen that can directly damage DNA and proteins. In addition to the role that acetaldehyde may play, chronic alcohol consumption may (1) increase pro-oxidant states leading to oxidative stress and cellular damage, (2) alter the gut microbiome, resulting in deleterious consequences to the liver, (3) impair immune function, reducing the physiological response to detect and eliminate precancerous cells, and (4) induce chronic inflammation and fibrosis, leading to procarcinogenic environment in the liver

Aflatoxins, a group of mycotoxins produced by fungi of the Aspergillus species[2], have been classified by the International Agency for Research on Cancer (IARC) as Group 1 human carcinogens, signifying that there is sufficient evidence of carcinogenicity in humans[17]. These toxins commonly contaminate various human foodstuffs, with maize, groundnuts, and tree nuts being particularly susceptible. The impact of aflatoxin B1 (AFB1), the most potent and prevalent form of aflatoxin, is projected to expand in the face of climate change. The warmer and more humid conditions, favorable for AFB1 contamination, are becoming increasingly common across the globe, potentially elevating the population attributable fraction (PAF) of AFB1-related HCC cases. Scientific investigations of HCC tumors have identified a specific marker of AFB1 exposure: a characteristic mutation at codon 249 of the TP53 tumor suppressor gene. Studies conducted in China and Taiwan have demonstrated that AFB1 exhibits a particularly strong carcinogenic effect when it co-occurs with chronic HBV infection[16]. The combination of these two factors synergistically increases the risk of HCC development. A meta-analysis conducted in 2012 estimated that AFB1 exposure alone increased the risk of HCC by six-fold, while HBV infection alone increased the risk by eleven-fold. However, when both factors were present, the combined risk surged dramatically to 54-fold[16, 18]. On a global scale, the AFB1 population attributable fraction for HCC is estimated to be 17%, with a range from 8% in populations without HBV infection to 21% in those with existing HBV infection[16]. These statistics highlight the significant role of aflatoxin exposure, particularly in conjunction with HBV, in the global burden of hepatocellular carcinoma. Effective strategies to reduce aflatoxin contamination of food supplies are crucial for preventing HCC, especially in regions with high HBV prevalence.

Metabolic dysfunction-associated steatotic liver disease (MASLD), considered the liver-specific expression of metabolic syndrome[16, 19], is becoming the fastest-growing risk factor for hepatocellular carcinoma (HCC) worldwide. Affecting approximately 30-32% of the global population, formerly known as non-alcoholic fatty liver disease (NAFLD)[20], now MASLD, has an estimated global prevalence of 1.3 billion cases, equivalent to the age-standardized prevalence rate of 15,000 cases per 100,000 people[20].

2.3. Clinical Profile and Prognostic factors

Hepatocellular carcinoma (HCC) is frequently characterized by an asymptomatic early stage, with symptoms typically manifesting only as the tumor progresses[21]. However, patients may become symptomatic earlier in the disease course when HCC develops in the context of pre-existing chronic liver disease. The prognosis for HCC is generally poor, with average survival times ranging from 6 to 20 months. Unlike many other solid tumors, the presence of underlying chronic liver disease or cirrhosis significantly impacts both survival outcomes and treatment options for HCC patients. Generally, prognostic factors in HCC can be categorized into four main domains: tumor-related factors, the severity of the underlying liver disease, the overall health status of the patient, and the efficacy of the chosen treatment strategy. Several independent negative predictive factors have been identified as associated with poorer HCC outcomes. These include elevated α-fetoprotein (AFP) levels (≥ 20 ng/mL), the presence of ascites, a maximal tumor size exceeding 5 cm, the presence of multiple tumor nodules, vascular invasion, extrahepatic metastasis, serum albumin levels below 3.5 g/dL, creatinine levels ≥ 1 mg/dL, bilirubin levels ≥ 1 mg/dL, alkaline phosphatase levels ≥ 200 IU/L, and a poor performance status[22, 23]. Various staging systems have been proposed to aid in predicting prognosis and guiding treatment decisions in HCC, including the Okuda system, the TNM system, the Barcelona Clinic Liver Cancer (BCLC) system, the Cancer of the Liver Italian Program (CLIP) score, the Albumin-Bilirubin (ALBI) grading system, and the Hong Kong Liver Cancer (HKLC) staging system. While a universally accepted staging system remains elusive, the BCLC system is widely considered to provide the most comprehensive prognostic information due to its incorporation of tumor burden, liver function assessment, and patient performance status[22].

2.4. Treatment of HCC

The management of hepatocellular carcinoma (HCC) involves a multifaceted approach, incorporating both curative-intent and palliative interventions, the selection of which is largely dictated by the stage of the disease. Current guidelines for HCC management categorize treatment options as either curative-intended or palliative. Curative treatments aim to eradicate the tumor and include surgical resection, local ablation techniques (radiofrequency ablation), and liver transplantation. Palliative treatments, on the other hand, focus on slowing disease progression, managing symptoms, and improving quality of life. These options include systemic therapies (conventional chemotherapy, molecularly targeted agents, and immunotherapy with checkpoint inhibitors) and transarterial therapies (e.g., bland transarterial embolization TAE, transarterial chemoembolization TACE, transarterial radioembolization TARE, and hepatic arterial infusion chemotherapy HAIC)[24]. However, there are significant geographical disparities in access, affordability, and ultimately, survival rates for HCC patients. The BRIDGE Study, a large international observational study[5], highlighted significant variations in HCC treatment strategies, prognostic factors, and sociodemographic characteristics across different regions of the globe. Similarly, the INSIGHT Study[25], conducted across 33 institutions in nine countries within the Asia-Pacific region, revealed a wide spectrum of clinical management practices for HCC. Factors such as patient demographics, differential healthcare costs, and patient access to various therapies contribute to substantial geographical variations throughout the patient's treatment journey, from initial diagnosis to clinical outcomes[25]. This geographical variability is particularly evident in the proportion of patients receiving curative versus palliative treatments for HCC, and choice of therapy used as first line and subsequent treatment. In high-income countries, approximately 40% of HCC cases are diagnosed at very early, early, or intermediate stages, allowing for the implementation of curative-intent interventions or life-prolonging palliative treatments such as TACE. However, in stark contrast, over 95% of patients with HCC in sub-Saharan Africa present with advanced or terminal disease, severely limiting treatment options and resulting in significantly poorer outcomes[26]. In high-income countries, treatment strategies aim to achieve curative intent in 30-40% of HCC cases, resulting in expected 5-year overall survival rates in the vicinity of 70%. This starkly contrasts with the situation in sub-Saharan Africa (SSA), where less than 1% of patients presenting with hepatocellular carcinoma receive curative treatment[26]. A systematic review encompassing 39 studies across 15 of the 48

SSA countries, analyzing data from a total of 3,989 patients, revealed that curative treatment options (liver resection, transplantation, and ablation) were offered to a mere 6% of the cohort[27]. The vast majority of patients (84%) received only best supportive care (BSC), emphasizing the limited access to active treatment and resulting in poor survival outcomes, with few patients surviving beyond one year. Another multi-center, multi-country, retrospective observational cohort study conducted across several African nations – Cameroon, Egypt, Ethiopia, Ghana, Ivory Coast, Nigeria, Sudan, Tanzania, and Uganda – further corroborated these findings. The study revealed that curative treatment (transplantation, resection, or local ablation) was provided to less than 1% of patients. Notably, transplantation was virtually non-existent outside of Egypt, which possesses a more developed healthcare infrastructure compared to other countries in the region[26]. This data emphasizes the significant barriers to accessing potentially life-saving treatments for HCC in sub-Saharan Africa. Recognizing this critical need, the International Hepato-Pancreato-Biliary Association (IHPBA) launched the Legacy Initiative at the 2024[28]. This initiative aims to create sustainable and positive impacts within host sub-Saharan African nations by addressing the most pressing healthcare challenges in the field of Hepato-Pancreato-Biliary surgery[28]. The Legacy Initiative is specifically focused on hepatocellular carcinoma (HCC) in SSA, a region disproportionately burdened by this disease due to a confluence of factors including a high incidence rate, limited healthcare infrastructure and resources, a lack of effective screening programs, low levels of public awareness, and pervasive financial constraints. The IHPBA Legacy Initiative offers a promising avenue for addressing these challenges and improving outcomes for HCC patients in sub-Saharan Africa[28].

Adherence of field practice to AASLD recommendations studied on 370 HCC patients in different BCLC stages which showed how managements are personalized[29, 30]. A policy review made in Italy 2023 about personalized management of HCC advocated multi-parametric therapeutic hierarchy, which highlighted treatment stage migration from both left-to-right and right-to-left.

Conceptual Framework

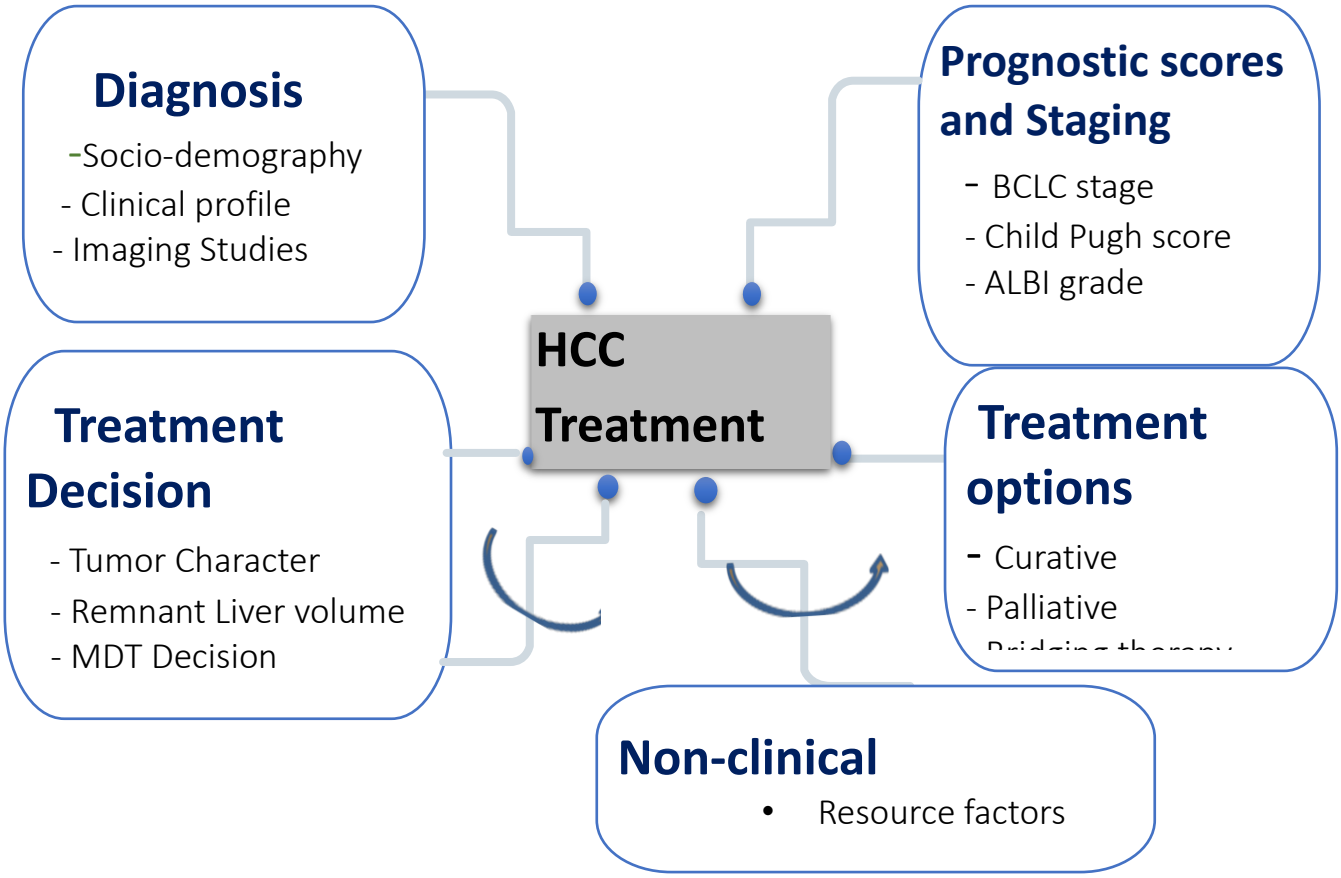


Figure 1: Conceptual Framework for Hepatocellular carcinoma at TASH and SPHMMC, Addis Ababa, Ethiopia 2025

CHAPTER THREE: Objectives

3.1. General Objective

- To assess the clinical profile and hepatocellular cancer treatment patterns in adult patients among tertiary hospitals at Addis Ababa, Ethiopia

3.2. Specific Objectives

- To describe the clinical features of hepatocellular cancer patients
- To assess hepatocellular cancer treatment pattern at tertiary hospitals in Addis Ababa, Ethiopia

CHAPTER FOUR: METHODOLOGY

4.1 Study Area

This study was conducted within the Department of Surgery, internal medicine and oncology at Tikur Anbesa Specialized Hospital (TASH), a prominent healthcare institution established in 1974. TASH serves as the primary teaching hospital for the School of Medicine, School of Pharmacy, School of Public Health, and School of Allied Health Sciences. As the largest referral and teaching hospital in Addis Ababa, Ethiopia, TASH provides comprehensive diagnostic and treatment services to approximately 400,000 patients annually. The hospital plays a crucial role in the community, offering a wide range of specialty and subspecialty medical services. With a dedicated workforce exceeding 1500 clinical and academic staff, TASH maintains a significant capacity for inpatient care, boasting over 800 beds. Notably, Tikur Anbesa Specialized Hospital stands as the leading high-volume center for hepatobiliary and pancreatic surgery in the country.

St. Paul's Hospital Millennium Medical College (SPHMMC) functions as a tertiary-level teaching hospital, employing a comprehensive staff of over 2,800 clinical, academic, administrative, and support personnel. It offers specialized medical services to patients referred from across Ethiopia, while also conducting undergraduate and postgraduate teaching programs and engaging in both basic and applied research. The hospital has a capacity of over 700 inpatient beds and attends to an average of 1,200 emergency and outpatient clients daily. The hospital's facilities include a dedicated Hepato-Pancreato-Biliary (HPB) unit within the General Surgery department, staffed by trained fellows. The Internal Medicine department features a Gastroenterology (GI) unit, also with fellows. The hospital also encompasses endoscopy and interventional radiology units, alongside other essential departments, including Pathology, Emergency Medicine, Anesthesiology, and Intensive Care Units (ICUs), among others. The study conducted from Oct 1, 2024 - May 30, 2025

4.2 Study Design

Hospital based prospective cross-sectional descriptive study design was employed

4.3. Population

4.3.1. Source of population

All adult patients age >18 years with liver mass who visit surgical referral, GI clinic, and **oncology clinic of TASH and SPHMMC**

4.3.2. Study Population

All patients with HCC who visited surgical referral, GI clinic, and oncology clinic of TASH and SPHMMC during the study period

4.4. Study Variables

- **Socio-demographic factors** (age, sex, address)
- **Clinical Factors**
  - Risk factors
  - Tumor Characteristics
  - Liver Function Status
  - Performance Status (ECOG)
  - Comorbidity
  - Tumor stage (BCLC stage)
  - ALBI grade
  - Child Pugh score
- **Treatment pattern is dependent variable**

4.5. Sample Size determination and Sampling Technique

Given the descriptive nature of this analysis, the study did not employ a specific sampling technique or sample size calculation. Instead, a comprehensive approach was adopted, wherein all eligible patients presenting within the defined study period at two high-volume hepatobiliary and pancreatic centers were included in the analysis. This strategy aimed to capture a broad representation of the patient population undergoing treatment for relevant conditions at these

specialized centers, acknowledging that the findings are primarily descriptive and may not be generalizable beyond similar clinical settings.

According to a study done at TASH from July 2016 to July 2017, a total of 70 HCC patients were included. This study used 2/3 of the population size, i.e 47 in 8 months study period.

Sample Size Formula

$$n = N \times \frac{\frac{Z^2 \times p \times (1-p)}{e^2}}{\left[N - 1 + \frac{Z^2 \times p \times (1-p)}{e^2}\right]}$$

N= 47

Z=1.96

P=0.5

e= 0.05

Sample size (n) = 42

- Since the calculated sample size is small, we used census method. **130 eligible patients** found in the study period are included.

N = Population size

n = The minimum sample size

Z = Critical value at 95% confidence interval

p = Estimated sample proportion

e = Margin of error

4.6. Inclusion & Exclusion Criteria

4.6.1. Inclusion Criteria

- All adult patients age above 18years with a clinical diagnosis of HCC who will visit Surgical Referral Clinic, GI/Hepatology Clinic, and Oncology Clinic during the study period at TASH and SPHMMC

4.6.2. Exclusion criteria

- Primary liver masses other than HCC
- Liver secondaries from other primary sites

4.7. Data Collection

The structured questionnaire utilized in the study was crafted based on existing literature and encompassed sections on sociodemographic data, clinical profiles, Surgical intervention, radiological and pathological report, laboratory and surgical outcomes. Prior to the primary data collection, the questionnaire underwent a pretest with 5% of the sample size to ensure the clarity and relevance of the questions. Apart from the questionnaire, electronic medical records were employed to retrieve clinical, surgical, and medical history review. Data collection was done by trained two general practitioner and the principal investigator checked the data consistency and completeness in each day.

4.8. Data processing and Analysis

Following data collection, each questionnaire was reviewed for completeness, referencing the codes assigned during the data collection process. The data were then entered into Epi-Info version 7 before being exported and analyzed using SPSS version 25. Data analysis was performed using SPSS software, version 25. Categorical variables were summarized using frequencies and percentages, and comparisons between groups were conducted using the chi-square test. The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed data were described using means and standard deviations, while skewed data were characterized using medians and interquartile ranges.

4.9. Data Quality Assurance

The principal investigator provided supportive supervision to the data collector to make sure that it is performed according to the protocol. Each day the collected data checked for accuracy and completeness. The participant's names not collected and the data identified after the questionnaire is completed. The collected data stored in a secure location and only the lead investigator had access to this location.

4.10. Ethical Considerations

Ethical clearance to conduct this study was obtained from the Department of Surgery Research and Publications Committee of the School of Medicine, College of Health Sciences, Addis Ababa University. Confidentiality has been fully maintained during Data collection and further analysis and dissemination of results

4.11. Term Definitions

- **Hepatocellular Cancer (HCC) -** is a primary liver malignancy described by typical Liver protocol triphasic CT scan/MRI features with or without histopathology
- **Liver cirrhosis –** is an advanced stage liver fibrosis with a combination either the following imaging features:
    - Micro or macronodular liver surface
    - Coarse and heterogeneous echotexture
    - Irregular or blunt liver borders
    - Atrophy of the right lobe and hypertrophy of the caudate or left lateral lobes
    - Widening of the interlobar fissures
    - Features of portal hypertension (splenomegaly, ascites , portosystemic collaterals)
    - Liver Fibro scan > 12kpa
- **Vascular invasion on cross-sectional imaging**
    - **Intrahepatic vascular invasion –** invasion of lobar, sectoral or segmental vessels

- **Extrahepatic vascular invasion –** invasion or tumor thrombus of main portal vein, IVC, or hepatic veins

❖ **HCC stage –** according to BCLC staging
- 0-Very early stage
- A- Early stage
- B- Intermediate stage
- C- Advanced stage
- D- Terminal stage

❖ **Treatment Pattern** – first and/or planned subsequent therapy among multimodal HCC treatments.
- **Curative treatment –** Resection, LT, Ablations
- **Palliative treatment –** TACE, TARE, Systemic therapy and BSC
- **Bridging therapy** - is defined as the use of LRT- such as TACE, yttrium-90 (Y90), ablative therapy, or a combination of different types of LRT to induce tumor death and inhibit tumor progression beyond the Milan criteria**.**
- **Best supportive care –** nutrition, analgesics, psychosocial support

CHAPTER FIVE: RESULTS

5. Results

An analysis of 130 patients diagnosed with hepatocellular carcinoma (HCC) at two high-volume hepatobiliary centers revealed a mean age at diagnosis of 54.5 ± 16.5 years. The study population exhibited a male predominance (82/130, 63.1%). As shown in Table 1, the majority of participants had a normal BMI (93/130, 71.5%), while grade 1 obesity was observed in 33/130 (25.4%) of the participants (Table 1).

Table 1: Sociodemographic characteristics of patients diagnosed Hepatocellular carcinoma at TASH and Sait Paul, Addis Ababa, Ethiopia 2025

Variables	Response	Frequency	Percentage
Age(years)	Mean ± SD	54.5±16.5	
Sex	Male	82	63.1
	Female	48	36.9
Address	Urban	79	60.8
	Rural	51	39.2
BMI	< 18.5	2	1.5
	18.5 – 24.9	93	71.5
	25 – 29.9	33	25.4
	> 30	2	1.5

5.1 Clinical Profile

The predominant presenting complaint among the study participants was abdominal pain, reported by 112 out of 130 individuals (86.2%), with a mean duration of 14.9 ± 11.3 weeks. Significant weight loss was also a common symptom, observed in 80 participants (61.5%). Upper gastrointestinal (UGI) bleeding, however, was a less frequent presentation, occurring in only 5 patients (3.8%). Nearly half of the participants (62/130, 47.7%) had a history of hepatitis infection. Among those with hepatitis, the majority were infected with Hepatitis B Virus (HBV) (45/62, 72.6%), while a smaller proportion had Hepatitis C Virus (HCV) (14/62, 22.6%). Co-infection with both HBV and HCV was present in 3 participants (3/62, 4.8%). Chronic alcohol use was reported in 18 participants (13.8%). Significantly high proportion (48/130, 37%) of patients in our cohort have unidentified risk factor for their HCC development. The majority of participants had a relatively good Eastern Cooperative Oncology Group (ECOG) performance status: 20 participants (15.4%) had an ECOG score of 0, and 75 participants (57.7%) had an

ECOG score of 1. A substantial proportion of patients (81.5%) exhibited alpha-fetoprotein (AFP) levels above the 75th percentile. A detailed breakdown of the clinical presentations is provided in Table 2.

Table 2: Clinical profile of patients diagnosed Hepatocellular carcinoma at TASH and Sait Paul, Addis Ababa, Ethiopia 2025

Variables	Response	Frequency	Percentage
Abdominal pain	Yes	112	86.2
	No	18	13.8
Mean duration of abdominal pain (weeks)	Mean+SD	14.9±11.3	
Significant weight loss	Yes	80	61.5
	No	50	38.5
History of UGI bleeding	Yes	5	3.8
	No	125	96.2
History of chronic alcohol intake (M-80gm/d & F-50gm/d)	Yes	18	13.8
	No	112	86.2
Hepatitis virus infection	Yes	62	47.7
	No	68	52.3
Type of hepatitis infection	HBV	45	72.5
	HCV	14	10.8
	HBV & HCV	3	2.3
Budd Chiari Syndrome with CLD	Budd Chiari	2	1.5
Jaundice	Yes	18	13.8
	No	112	86.2
Palpable mass	Yes	42	32.3
	No	88	67.7
Clinical Ascites	None	99	76.2
	Mild	20	15.4
	Moderate to Large	11	8.5
Hepatic Encephalopathy and grade	None	123	94.6
	Grade 1-2	6	4.6
	Grade 3-4	1	.8
AFP	Below 75 percentiles (1000)	106	81.5
	above 75percentile	24	18.5

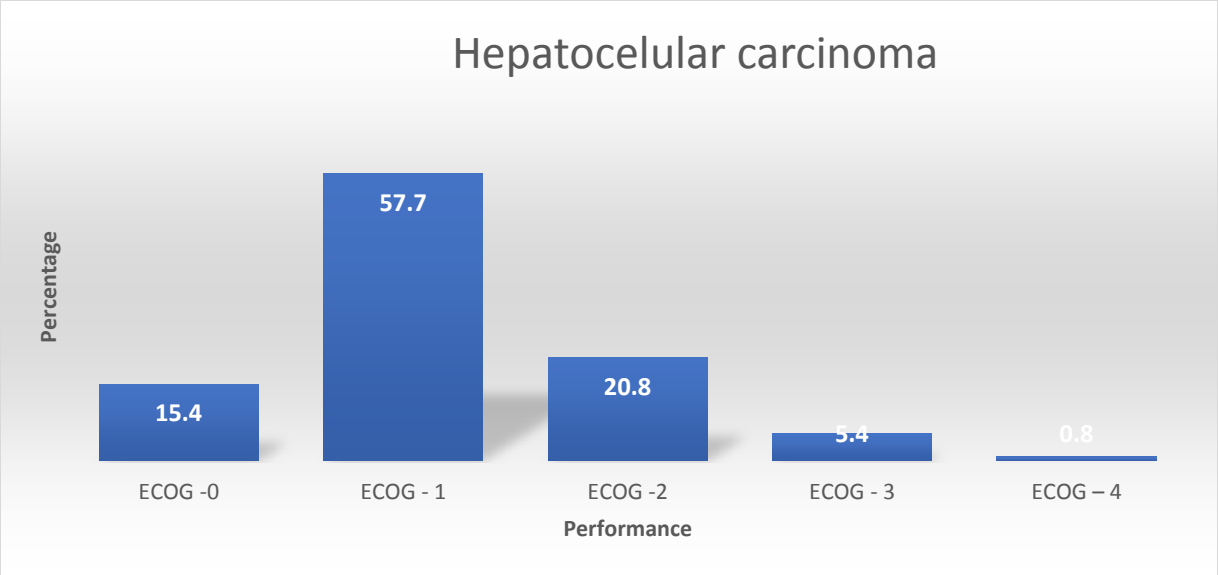


Figure 2:Performance status of patients with hepatocellular carcinoma at TASH and SPHMMC Addis Ababa, Ethiopia 2025

5.2 Diagnosis and prognostic profiles in the study cohort

In nearly all cases, triphasic abdominal computed tomography (CT) scans served as the primary diagnostic modality, utilized in 128 out of 130 participants (98.5%). Image analysis revealed vascular invasion in more than half of the cases (74/130, 56.9%) out of which 59.5% were intrahepatic invasions and 40.5% involved extra-hepatic invasion, while distance metastasis was present in 30 participants (23.1%). The most common site of distant metastasis was lung (63.4%, 19/30). Furthermore, imaging features of advanced HCC, extra-hepatic vascular invasion and/or extra-hepatic distance metastasis were found in 36.9%, of our patients. Signs of portal hypertension were observed in 34/130 participants (26.2%), while 58/130 participants (44.6%) exhibited evidence of cirrhosis. The majority of HCC cases presented as either multinodular/multifocal (58/130, 44.6%) or single/solitary (57/130, 44.5%) lesions with mean size 10.0± 4.6cm. Adequate future liver remnant (FLR) was observed in 58/130 participants (44.6%). In terms of tumor location, the right lobe of the liver was the most frequently affected (54/130, 41.5%) and bilobar involvement (55/130, 42.3%).

Table 3: Diagnosis and prognostic factors for Hepatocellular carcinoma at TASH and Sait Paul, Addis Ababa, Ethiopia 2025

Variables	Response	Frequency	Percentage
Diagnosis	Triphasic abdominal CT scan	128	98.5
	MRI	1	.8
	Both CT scan and MRI	1	.8
Vascular invasion	Yes	74	56.9
	Intrahepatic invasion	44	59.5
	Extrahepatic invasion	30	40.5
	No	56	43.1
Imaging features of cirrhosis	Yes	58	44.6
	No	72	55.4
Portal hypertension	Yes	34	26.2
	No	96	73.8
Extra-hepatic(distant) metastasis	Yes	30	23.1
	No	100	76.9
Metastasis (n=30)	Lung	19	63.4
	Extra-regional Lymph nodes	4	13.3
	Lung + other site	3	10
	Other site	4	13.3
Number of liver lesion	Single/Solitary	57	43.8
	less than or equal 3 nodules	8	6.2
	Multinodular/Multifocal	58	44.6
	Diffuse/Infiltrative type	7	5.4
Size of tumor (cm)	Mean ± SD	10.0± 4.6	
Ascites on Imaging	Absent	86	66.2
	Mild	26	20.0
	Moderate to large	18	13.8
FLR Adequate	Yes	58	44.6
	No	72	55.4

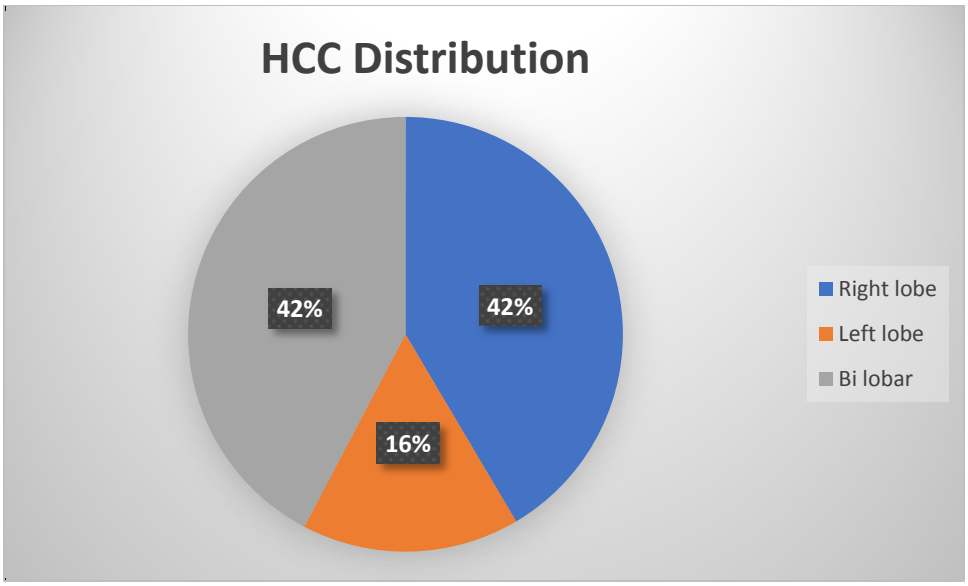


Figure 3:Location of Hepatocellular carcinoma at TASH and SPHMMC Addis Ababa, Ethiopia 2025

5.3 Stages and management of hepatocellular cancer

Based on the Albumin-Bilirubin (ALBI) grade, the majority of patients presented with either ALBI grade 1 (30/130, 23.1%) or ALBI grade 2 (84/130, 64.6%). Child-Pugh score was computed for 58/130 patients who had features of cirrhosis on imaging; Child-Pugh score A, indicative of well-compensated cirrhosis, was observed in 37.9% (22/58), whereas Child-Pugh score B was evident in 50% (29/58) of participants. Significantly, a large proportion of patients presented with advanced-stage disease according to the Barcelona Clinic Liver Cancer (BCLC) staging system: BCLC stage C was observed in 83 participants (63.8%) and BCLC stage D was present in 22 participants (16.9%). In terms of treatment modalities, systemic therapy was the most frequently administered (46/130, 35.4%), followed by transarterial chemoembolization (TACE) (36/130, 27.7%). Liver resection, a potentially curative option, was performed in only 23 participants (17.7%), highlighting the challenges in offering surgical management to this patient population. Among those who underwent liver resection, left hepatectomy (8/23, 34.8%) and right hepatectomy (5/23, 21.7%) were the most common types of resections performed.

Table 4: Stages and management Hepatocellular carcinoma at TASH and Sait Paul, Addis Ababa, Ethiopia 2025

Variables	Response	Frequency	Percentage
ALBI grade	Grade 1	30	23.1
	Grade 2	84	64.6
	Grade 3	16	12.3
Child Pugh score **(n=58, cirrhosis evidence)**	Child A	22	37.9
	Child B	29	50
	Child C	7	12.1
First line (initial) therapy given	Liver resection	23	17.7
	TACE	36	27.7
	Ablation therapy (RFA)	4	3.1
	Systemic therapy	46	35.4
	Best supportive care	21	16.2
Liver resection (n=23)	Right hepatectomy	5	21.7
	Left hepatectomy	8	34.8
	Right anterior Sectionectomy	1	4.3
	Left lateral sectionectomy	3	13.0
	Right posterior sectionectomy	1	4.3
	Non anatomic resection	4	17.4
	Bisegmentectomy	1	4.3
Resection margin (n=23)	Positive	2	
	Negative, but less than 10mm	8	
	Negative, greater than 10mm	13	

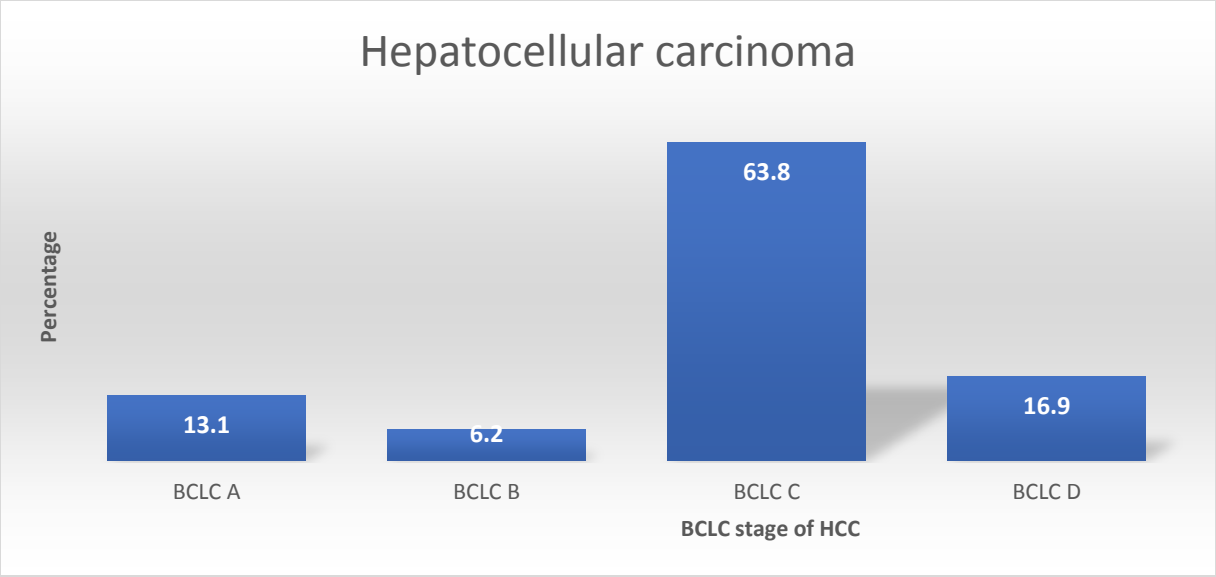


Figure 4:BCLC stage of Hepatocellular carcinoma at TASH and SPHMMC Addis Ababa, Ethiopia 2025

In this study, patients with hepatocellular carcinoma (HCC) were categorized according to the Barcelona Clinic Liver Cancer (BCLC) staging system. A significant proportion of the patient cohort presented with disease amenable to liver resection, specifically 82.4% of those classified as BCLC stage A, 37.5% of BCLC stage B, and 7.2% of BCLC stage C. Transarterial chemoembolization (TACE), a locoregional therapy, was performed on a subset of patients within each BCLC stage: 17.6% of BCLC A patients, 37.5% of BCLC B patients, and 34.9% of BCLC C patients (Table 5). Regarding the ALBI grade, patients with grade 1 were managed with liver resection (43.3%), TACE (23.3%), or systemic therapy (23.3%) (Table 6).

Table 5:BCLC stage versus Management for HCC at TASH and SPHMMC Addis Ababa, Ethiopia 2025

BCLC stage	Liver resection	TACE	Ablation therapy	Systemic therapy	Best supportive care	Total
BCLC A	14 (82.4%)	3(17.6%)	None	None	None	17(100%)
BCLC B	3(37.5%)	3(37.5%)	1(12.5%)	None	1(12.5%)	8(100%)
BCLC C	6(7.2%)	29(34.9%)	3(3.6%)	42(50.6%)	3(3.6%)	83(100%)
BCLC D	None	1(4.5%)	None	4(18.2%)	17(77.3%)	22(100%)
Total	23(17.7%)	36(27.7%)	4(3.1%)	46(35.4%)	21(16.2)	130(100%)

Table 6:ALBI grade versus Management for HCC at TASH and SPHMMC Addis Ababa, Ethiopia 2025

ALBI grade	Liver resection	TACE	Ablation therapy	Systemic therapy	Best supportive care	Total
Grade 1	13(43.3%)	7(23.3%)	0(0%)	7(23.3%)	3(10%)	30(100%)
Grade 2	10(11.9%	263(31%)	2(2.4%)	36(42.9%)	10(11.9%)	84(100%)
Grade 3	0(0%)	3(18.8%)	2(12.5%)	3(18.8%)	8(50%)	16(100%)
Total	23(17.7%)	36(27.7%)	4(3.1%)	46(35.4%)	21(16.2%)	122(100%)

5.4 Trans-arterial chemoembolization procedure and systemic treatment

The vast majority of patients undergoing transarterial chemoembolization (TACE) received a regimen consisting of doxorubicin and Lipiodol, representing 97.2% of all TACE procedures and 94.5% of selective/segmental TACE performed. For systemic therapy, the study population received either sorafenib or lenvatinib. Sorafenib was administered to 60% of the patients requiring systemic treatment, while lenvatinib was utilized in 36% of these cases. This suggests a preference for doxorubicin-based TACE as the primary locoregional treatment strategy, and a utilization of sorafenib and lenvatinib as the most common first-line systemic therapies.

Table 7: TACE and systemic management for HCC at TASH and SPHMMC Addis Ababa, Ethiopia 2025

	Drugs	Frequency	Percentage
Type of TACE	Nonselective /Lobar	2	5.5
	Selective/segmental	34	94.5
Drugs/Chemical used for TACE N=36	Doxorubicin and Lipiodol	35	97.2
	Doxorubicin with Lipiodol and Gelfoam	1	2.7
Systemic chemotherapy (n=50)	Sorafenib	30	60
	Levantinib	18	36
	Doxorubicin	2	4

CHAPTER SIX: DISCUSSION AND RECOMMENDATIONS

6.1. **Discussion**

This study offers a detailed and comprehensive analysis of the demographic characteristics, diagnostic pathways, treatment strategies, and existing gaps in the management of Hepatocellular Carcinoma (HCC) within the context of two national high-volume hepatobiliary and pancreatic centers in Ethiopia. Our investigation revealed a significant male predominance in the study population, with HCC primarily occurring in individuals around 50 years of age. This sociodemographic profile aligns consistently with findings from previous global, regional, and local studies, suggesting a relatively stable pattern across different populations. For instance, a multinational study conducted across several African nations reported that the mean age at HCC diagnosis in Egypt was 58 years, whereas the corresponding figure for the remaining African countries was notably lower at 46 years[15]. Similarly, previous studies conducted within Ethiopia have reported a male predominance in HCC cases (approximately 67%) and a mean age of around 52.0 years[12], findings that are consistent with the results obtained in our current study. These observed similarities may be attributed to the distribution of known HCC risk factors, which often vary across different sexes and geographic locations.

A multitude of risk factors, both modifiable and non-modifiable, contribute to the complex pathophysiology of Hepatocellular Carcinoma (HCC). These factors can either directly exert oncogenic effects on liver cells or promote the development of cirrhosis, which then serves as a fertile ground for HCC development. In our study, we observed that chronic hepatitis infections were associated with 47.7% of HCC cases, with HBV accounting for 34.6%, HCV for 10.8%, and co-infection of HBV and HCV for 2.3%. Furthermore, chronic alcohol consumption was implicated in 13.8% of the HCC cases, whereas for a significantly proportion (37%) risk factor has not identified which might imply the under-screening of HCC patients for possible risk factors especially for the increasingly prevalent MAFLD related HCC, and environmental toxins (aflatoxins). Our findings otherwise are generally consistent with global, African, and previous Ethiopian studies, although the precise proportions of each etiological factor may vary depending on the specific population and geographic location. On a global scale, chronic HBV and HCV infections are recognized as the most significant etiological factors for HCC, accounting for 50-80% of all HCC cases[19]. Chronic HBV infection is particularly prevalent as a cause of HCC in

Eastern Asian countries and the majority of African countries, with the notable exception of Northern Africa[19], where HCV prevalence is highest. A multi-national study encompassing 2566 patients across 21 tertiary referral centers in various African countries (including Egypt, Nigeria, Ghana, Ivory Coast, Cameroon, Sudan, Ethiopia, Tanzania, and Uganda) revealed that HBV was the leading cause of HCC in the majority of African countries (55%)[15]. However, in Egypt, HCV was identified as the predominant etiological factor, accounting for 84% of HCC cases[15]. This difference may be attributed to the high prevalence of HCV in Egypt compared to other African nations. It is worth noting that HCV infection is primarily associated with the development of cirrhosis, which subsequently increases the risk of HCC. On the other hand, HBV can exert both direct oncogenic effects on liver cells and contribute to the development of cirrhosis, thereby providing a "fertile ground" for HCC development. Nearly half of the patients in our study presented with advanced disease characteristics, including large tumor size, vascular invasion, and a multinodular or multifocal presentation, often against a backdrop of cirrhosis. Despite this advanced presentation, almost half of the patients also had adequate future liver remnant (FLR). Alarmingly, only 13% of the patients were diagnosed at BCLC stage A, leading to a situation where less than 18% ultimately received curative liver resection. This highlights a significant challenge in HCC management: the lack of early detection and screening, particularly in low- and middle-income countries (LMICs), results in a disproportionate number of patients being diagnosed at advanced stages, limiting treatment options and contributing to poor survival rates in Sub-Saharan Africa (SSA).

In our study, curative liver resection was performed in approximately 18% of cases, a figure that is significantly higher compared to a multi-center study in Ethiopia where resection was conducted in less than 8% of cases[12]. Additionally, Transarterial Chemoembolization (TACE) was performed in approximately 28% of our patients, a substantially higher rate than the 2.8%[12] reported in the aforementioned multi-center study. Radiofrequency ablation (RFA) was utilized in 3% of cases, a step forward considering that previous studies in Ethiopia reported zero RFA utilization[12]. The remaining majority patients primarily received systemic therapy and best supportive care. Hepatic resection is considered the gold standard curative treatment for early-stage HCC, particularly for those without cirrhosis who are classified as BCLC stage 0 or A. Better treatment adherence to BCLC staging was found in BCLC A 82.5% and BCLC-D 77.3% whereas notable disparity observed in BCLC B(37.5%) and BCLC C(50.6%) stages, the

observed difference may be due limited access to alternative treatment options, and/or a trend toward personalized management to overcome some of the drawbacks of BCLC staging by navigating other staging system.

The INSIGHT study, a multi-site longitudinal cohort study conducted in several Asia-Pacific countries, reported a liver resection rate of 34%, primarily for patients with BCLC stage A and B HCC[25]. Ablative therapy (RFA) was performed in 8% of patients, while locoregional therapy (TACE) was utilized in 23.5% of cases[25]. The BRIDGE Study reported varying resection rates across different regions: 18% in North America, 16% in Europe, and 33% in Asia[5]. TACE utilization was also variable, with rates of 33% in North America, 29% in Europe, and 35% in Asia[5]. Italian study on adherence of field practice to different BCLC stages[29, 30] showed, adherence was 81% in the BCLC A stage and dropped to 53% in the BCLC C stage patients: similar variation in treatment adherence and choice of initial modality noted in a larger INSIGHT Study[25] and BRIDGE Study[5]. In stark contrast, a multi-national study conducted in Africa involving 2566 patients across 21 tertiary referral centers observed resection rates of less than 1%, RFA rates of 0%, and TACE rates of 1% in most African countries[15]. Egypt, however, showed slightly better progress, with resection performed in 2% of cases, transplantation in 1%, RFA in 32%, and TACE in 36%[15]. Another systematic review from 15 sun-Saharan African countries showed curative treatment was 6% and 84% received best supportive care only. These significant differences in treatment modalities likely stem from variations in infrastructure and human capacity, healthcare policies, and prioritization of resources across different geographic regions.

In conclusion, despite observed improvements in the surgical management of Hepatocellular Carcinoma (HCC), reflected in increased rates of curative resection and local ablative therapies and TACE, these interventions are often limited to patients with relatively good performance status and younger age profiles. The advanced stage at presentation, characterized by high rates of vascular invasion and large tumor size, contributes significantly to the challenges in achieving optimal outcomes and places Ethiopia behind high- and middle-income countries in HCC management. This disparity is further compounded by limitations in human resources, infrastructure, and advanced treatment options, most notably the absence of a liver

transplantation center within the nation. The lack of transplantation options limits the curative potential for patients with end-stage liver disease and unresectable HCC.

Strength of the study

The study was conducted as a prospective design and included a wide spectrum of clinical variables which enabled to generate better quality data. The study was conducted in the two biggest tertiary teaching referral hospitals of the country and the findings are more comprehensive and informative for further studies on the area.

Limitations of the study

Inadequate screening of HCC patients for risk factors and limited availability of treatment options may affect selection of therapy.

6.2. **Recommendation**

Several recommendations are crucial for various stakeholders to achieve this goal. For health workers, the implementation of enhanced public health awareness programs is essential, with a focus on educating the public about HCC risk factors, particularly those linked to chronic liver disease, and the importance of early detection and prevention. Furthermore, health workers should advocate for routine screening programs, especially for high-risk individuals, and establish streamlined referral pathways for HCC patient to ensure prompt access to specialized care at hepatobiliary centers, incorporating strategies like telemedicine for remote consultations.

Policy makers are urged to prioritize human resource capacity building through investments in training and education programs for healthcare professionals specializing in hepatobiliary surgery, oncology, interventional radiology, and nursing, potentially through collaborations with international institutions. Infrastructure expansion and modernization, including diagnostic imaging, interventional radiology facilities and surgical theaters with liver transplantation, should be prioritized, alongside the equitable distribution of resources across both urban and rural areas. Moreover, policymakers must ensure strategic resource allocation to support both curative and palliative care services for HCC patients, including essential medications and psychosocial support, and integrate HCC prevention and control strategies within the national cancer control plan, setting measurable targets for early detection, treatment, and survival.

Global surgery advocates should play a vital role by highlighting the stark inequities in HCC care in Ethiopia and promoting increased global attention to the disparities in access to diagnostic and treatment services. They should foster collaborative partnerships between Ethiopian healthcare institutions and international organizations, facilitating knowledge transfer, technology sharing, and resource mobilization, while also championing sustainable solutions that empower Ethiopian healthcare professionals to deliver high-quality HCC care.

Finally, researchers are encouraged to generate local evidence by conducting prospective studies to evaluate treatment outcomes, including survival rates and quality of life. They should also investigate the feasibility and effectiveness of different HCC screening strategies tailored to the Ethiopian population, identify the major etiological factors contributing to HCC development, and conduct health services research to understand healthcare-seeking behaviors and barriers to accessing care, ultimately informing improved patient outcomes.

Reference

1. Thomas London W, Petrick JL, McGlynn KA. Liver cancer. In: Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, eds. Cancer Epidemiology and Prevention. 4th ed. Oxford University Press; 2018:635-660.
2. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis. 2015 May;19(2):223-38. doi: 10.1016/j.cld.2015.01.001. Epub 2015 Feb 26. PMID: 25921660; PMCID: PMC4712629.
3. Zheng J, Wang S, Xia L, Sun Z, Chan KM, Bernards R, Qin W, Chen J, Xia Q, Jin H. Hepatocellular carcinoma: signaling pathways and therapeutic advances. Signal Transduct Target Ther. 2025 Feb 7;10(1):35. doi: 10.1038/s41392-024-02075-w. PMID: 39915447; PMCID: PMC11802921.
4. Herbst DA, Reddy KR. Risk factors for hepatocellular carcinoma. Clin Liver Dis (Hoboken). 2013 Jan 23;1(6):180-182. doi: 10.1002/cld.111. PMID: 31186882; PMCID: PMC6499296.
5. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int. 2015 Sep;35(9):2155-66. doi: 10.1111/liv.12818. Epub 2015 Mar 25. PMID: 25752327; PMCID: PMC4691343.
6. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 May-Jun;74(3):229-263. doi: 10.3322/caac.21834. Epub 2024 Apr 4. PMID: 38572751.
7. Lang K, Danchenko N, Gondek K, Shah S, Thompson D. The burden of illness associated with hepatocellular carcinoma in the United States. J Hepatol. 2009 Jan;50(1):89-99. doi: 10.1016/j.jhep.2008.07.029. Epub 2008 Oct 1. PMID: 18977551.
8. Singavi AK, Szabo A, Thomas JP. et al. Costs of care with liver directed therapy (LDT) and sorafenib (S) in patients (pts) with hepatocellular carcinoma (HCC). J. Clin. Oncol. 36(4), 383 (2018).
9. Ndom P. Cancer prevention in Africa: liver cancer. Ecancermedicalscience. 2019 Jul 25;13:950. doi: 10.3332/ecancer.2019.950. PMID: 31552123; PMCID: PMC6722110.
10. Okeke E, Davwar PM, Roberts L, Sartorius K, Spearman W, Malu A, Duguru M. Epidemiology of Liver Cancer in Africa: Current and Future Trends. Semin Liver Dis. 2020 May;40(2):111-123. doi: 10.1055/s-0039-3399566. Epub 2019 Nov 14. PMID: 31726474.
11. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019 Oct;16(10):589-604. doi: 10.1038/s41575-019-0186-y. Epub 2019 Aug 22. PMID: 31439937; PMCID: PMC6813818.
12. Abza, G.B.; Ahmed, J.H.; Yesufe, A.A.; Seife, E.; Erkie, M.; Spriet, I.; Chelkeba, L.; Annaert, P. Clinicopathological Features and Survival of Patients with Hepatocellular Carcinoma in Ethiopia: A Multicenter Study. Cancers 2023, 15, 193. https://doi.org/10.3390/cancers15010193.
13. Jiang Z, Zeng G, Dai H, Bian Y, Wang L, Cao W, Yang J. Global, regional and national burden of liver cancer 1990-2021: a systematic analysis of the global burden of disease study 2021. BMC Public Health. 2025 Mar 8;25(1):931. doi: 10.1186/s12889-025-22026-6. PMID: 40057711; PMCID: PMC11890516.

14. Awedew AF, Asefa Z, Belay WB. National Burden and Trend of Cancer in Ethiopia, 2010-2019: a systemic analysis for Global burden of disease study. Sci Rep. 2022 Jul 26;12(1):12736. doi: 10.1038/s41598-022-17128-9. PMID: 35882895; PMCID: PMC9325704.
15. Yang JD, Mohamed EA, Aziz AO et al. Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium. Lancet Gastroenterol Hepatol. 2017 Feb;2(2):103-111. doi: 10.1016/S2468-1253(16)30161-3. Epub 2016 Dec 3. Erratum in: Lancet Gastroenterol Hepatol. 2022 Aug;7(8):704. doi: 10.1016/S2468-1253(22)00208-4. PMID: 28403980.
16. Rayapati D, McGlynn KA, Groopman JD, Kim AK. Environmental exposures and the risk of hepatocellular carcinoma. Hepatol Commun. 2025 Jan 16;9(2):e0627. doi: 10.1097/HC9.0000000000000627. PMID: 39813595; PMCID: PMC11737496.
17. IARC monographs. Some naturally occurring substances: Food items and constitutents, heterocyclic aromatic amines and mycotoxins. IARC Monogr Eval Carcinog Risk Hum. 1993;56.
18. Liu Y, Chang CC, Marsh GM, Wu F. Population attributable risk of aflatoxin-related liver cancer: Systematic review and metaanalysis. Meta-Analysis Research Support, N.I.H., Extramural Review. Eur J Cancer. 2012;48:2125–36.
19. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019 Oct;16(10):589-604. doi: 10.1038/s41575-019-0186-y. Epub 2019 Aug 22. PMID: 31439937; PMCID: PMC6813818.
20. Huang M, Chen H, Wang H, Zhang Y, Li L, Lan Y, Ma L. Global burden and risk factors of MASLD: trends from 1990 to 2021 and predictions to 2030. Intern Emerg Med. 2025 Jun;20(4):1013-1024. doi: 10.1007/s11739-025-03895-6. Epub 2025 Feb 28. PMID: 40019669; PMCID: PMC12130103.
21. L, Zusmanovitch L, Charach G Hepatocellular Carcinoma. Part 2: Clinical Presentation and Diagnosis. Emj Hepatol. 2017;5[1]:81-88.
22. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018 Jan;67(1):358-380. doi: 10.1002/hep.29086. PMID: 28130846.
23. Selçuk H. Prognostic Factors and Staging Systems in Hepatocellular Carcinoma. Exp Clin Transplant. 2017 Mar;15(Suppl 2):45-49. doi: 10.6002/ect.TOND16.L11. PMID: 28301998.
24. Kudo M, Ueshima K, Yokosuka O, et al. Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial.

Lancet Gastroenterol Hepatol 2018; 3: 424–32.
25. Sim YK, Chong MC, Gandhi M, Pokharkar YM, Zhu Y, Shi L, Lequn L, Chen CH, Kudo M, Lee JH, Strasser SI, Chanwat R, Chow PKH; Asia-Pacific Hepatocellular Carcinoma Trials Group. Real-World Data on the Diagnosis, Treatment, and Management of Hepatocellular Carcinoma in the Asia-Pacific: The INSIGHT Study. Liver Cancer. 2023 Oct 9;13(3):298-313. doi: 10.1159/000534513. PMID: 38756144; PMCID: PMC11095624.
26. Jonas E, Bernon M, Robertson B, Kassianides C, Keli E, Asare KO, Alatise IO, Okello M, Blondel NO, Mulehane KO, Abubeker ZA, Nogoud AA, Nashidengo PR, Chihaka O, Tzeuton C, Dusheiko G, Sonderup M, Spearman CW; Gastroenterology and Hepatology Association of sub-Saharan Africa (GHASSA). Treatment of hepatocellular carcinoma in sub-Saharan Africa:

challenges and solutions. Lancet Gastroenterol Hepatol. 2022 Nov;7(11):1049-1060. doi: 10.1016/S2468-1253(22)00042-5. Epub 2022 Jul 8. PMID: 35810767.
27. Sobnach S, Kotze U, Spearman CW, Sonderup M, Nashidengo PR, Ede C, Keli E, Chihaka O, Zerbini LF, Li YJ, Gandhi K, Krige J, Jonas E. The management and outcomes of hepatocellular carcinoma in sub-Saharan Africa: a systematic review. HPB (Oxford). 2024 Jan;26(1):21-33. doi: 10.1016/j.hpb.2023.09.015. Epub 2023 Sep 22. PMID: 37805364.
28. Jonas E, Smith M, Kassianides C, Luyirika E, Wendy Spearman C. IHPBA White Paper - The improvement of management pathways and access to care in sub-Saharan Africa for patients with hepatocellular carcinoma. HPB (Oxford). 2025 May;27(5):585-590. doi: 10.1016/j.hpb.2025.02.007. Epub 2025 Feb 18. PMID: 40037975.
29 Vitale A, Cabibbo G, Iavarone M, Vigano L, Pinato DJ, Ponziani FR, et al. Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept. The Lancet Oncology 2023; 24(7):e312-e22. Epub 2023 July 7.
30. Sangiovanni A, Triolo M, Iavarone M, Forzenigo LV, Nicolini A, Rossi G, et al. Multimodality treatment of hepatocellular carcinoma: How field practice complies wi th international recommendations. Liver international: official journal of the International Association for the Study of the Liver 2018; 38(9):1624-34. Epub 2018 May 24.

APPENDEX

ANNEX I: Approval Sheet

I the undersigned agree to accept responsibility for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the research and publications office of Addis Ababa University.

Principal Investigator:

Dr. Tebarek Jemal (MD, General Surgeon, HPB surgery fellow)
Email: tebarekjemal696@yahoo.com, Phone number: +251 913238476

Signature _____Date _____

Advisor:

Dr. Shimelis Nigussie (MD, Assistant professor of General Surgery, Consultant HPB surgeon)
Email: drshimelisnig@gmail.com, Phone number: +251 911763623

Signature _____ Date_____

Co-Advisor:

Dr. Henok Teshome (MD, Assistant professor of General Surgery, Consultant HPB surgeon)
Email: henokteshome2@gmail.com, Phone number: +251 911020038

Signature _____ Date_____

Annex II: Questionnaire

Research questionnaire on clinical profile and Treatment Pattern of HCC patients at TASH and SPHMMC, Addis Ababa Ethiopia, 2024/25.

Part 1. Socio demographic data

S. No	**Socio-demographic profile**		Remark
1	Age in complete years	_____	
2	Sex	1. Male 2. Female	
3	Address	1. Urban 2. Rural	
4	BMI in kg/m^2 (if possible)	1. <18.5 2. 18.5 to 24.9 3. 25 to 29.9 4. >30	

Part 2.Clinical profile of the patient

S. No	**Symptom, sign and treatment**		Remark
1	Abdominal pain	1. Yes 2. No	
1.1	If yes, duration in weeks	----------	
2	Weight loss	1. Yes 2. No	
2.1	If yes, how much?	1. ----- Kg over---- month 2. -------% weight loss/ --- months	
3	Anorexia	1. Yes 2. No	
4	History of upper GI Bleeding	1. Yes 2. No	
5	History of alcohol abuse?	1. Yes 2. No 3. Unknown	
7	Jaundice	1. Yes 2. No	
8	Palpable mass	1. Yes 2. No	

8.1	If yes, location	1. RUQ 2. Epigastric 3. Others	
9	Clinical Ascites	1. Yes 2. No	
9.1	If yes	1. Mild 2. Moderate 3. Uncontrolled	
10	Encephalopathy present	1. Yes 2. No	
10.1	If yes, grade?	….	
11	Performance status of patient (ECOG)	1. 0 2. 1 3. 2 4. 3 5. 4	
12	Comorbid illness	1. DM 2. Hypertension 3. Dyslipidemia 4. Others_____	

Part 3.Radiologic Findings of HCC

1	Imaging modalities	1. Triphasic CT scan 2. MRI 3. Both CT and MRI	
2	Number of tumor	1. Single 2. ≤3 nodules 3. Multinodular /Multifocal 4. Diffuse/infiltrative	
3	Involved lobe	1. Right 2. Left 3. Bilobar	
3	The largest tumor size in cm		
4	Vascular Invasion present	1. Yes 2. No	
5	If yes, specify (intrahepatic versus extra-hepatic vascular invasion)	1. Sectoral branches 2. PV invasion/thrombosis 3. Hepatic Vein invasion 4. IVC invasion 5. Combination of major vessels 6. Others specify	
6	Extrahepatic(distant) metastasis present	1. Yes 2. No	
6.1	Site of metastasis	1. Lung 2. Extra-regional LNs 3. Peritoneum 4. Others	

7	Imaging Features of Cirrhosis	1. Yes 2. No	
8	Imaging evidence of portal HTN	1. Yes 2. No	
9	Ascites	1. Present 2. Absent	
10	Fibroscan(kpa)	1. Less than 7 2. 7 to 14 3. Greater than 14 4. Not done	
11	Is the estimated FLR adequate	1. Yes 2. No	
12	Pre-op PVE indicated	1. Yes 2. No	
12.1	If no, why?	1. Can't afford 2. No available 3. Will not change management 4. Others	

Part 4.Laboratory and pathology results

S. No	Pre-operative Laboratory and pathology findings		Remark
1	Serum Albumin (g/dl)		
2	Total Bilirubin (mg/dl)	----------/----------	
3	INR		
4	Platelet count (x10^3)		
5	Hgb in mg/dl		
6	AST		

7	ALT		
8	ALP		
9	AFP (ng/ml)	……	
10	Hepatitis Virus status	1. Positive 2. Negative 3. Unknown	
11	If positive, type?	1. HBV 2. HCV 3. Both HBV and HCV 4. Others	
12	If positive, on treatment	1. Yes 2. No 3. Unknown	
10	Histopathologic Diagnosis of HCC	1. Yes 2. No	
10.1	If yes, type of specimen	1. CNB 2. FNAC 3. Open biopsy	
11	Child Pugh Score	1. A 2. B 3. C	
12	ALBI grade	1 , 2, 3	
Part 5. HCC stage and Treatment			
1	**BCLC stage of HCC**	1. 0 2. A 3. B 4. C	

		5. D	
2	**First (Initial) Therapy Given**	1. Resection 2. TACE 3. RFA 4. Chemotherapy 5. Best Supportive Care **6.** Transplantation **7.** Refused treatment	
3	**Subsequent Therapy Panned**	1. Resection 2. Chemotherapy 3. TACE 4. RFA 5. Others specify	