CLINICAL CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH SORAFENIB AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL: A RETROSPECTIVE STUDY FROM 2008-2016

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A RESEARCH REPORT-

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Declaration

I [Leila Helen do Carmo Bila] declare that this research report is my own original work. It is being submitted for the Degree of Master's in Internal Medicine at the University of Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at any other University.

Signed L. Bila jc. on the 17 day of July 2024 in Johannesburg

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List of Abbreviations

HCC	Hepatocellular carcinoma
HIV	Human Immunodeficiency Virus
DNA	Deoxyribonucleic Acid
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HBx	Hepatitis Bx transcription factor
AFP	Alpha-fetoprotein
CT	Computerised Tomography
MRI	Magnetic Resonance Imaging
BCLC	Barcelona Clinic Liver Cancer
FGFR	Fibroblast growth factor receptor
VEGFR	Vascular Endothelial Growth Factor Receptor
LMIC	Low-middle income country
EAP	Expanded access programme
SSA	Sub-Saharan Africa

Abstract

Background: Hepatocellular carcinoma (HCC) is a notable public health concern worldwide, with HCC incidence rates increasing over the years. In Africa, underreporting of HCC incidence due to limited definitive diagnosis, limited cancer registries and inadequate reporting in existing cancer registries are major challenges. Sorafenib has emerged as a primary systemic therapy for advanced HCC in 2008, improving survival outcomes. However, late diagnosis and limited treatment access in LMICs contribute to a poor prognosis.

Methods: This retrospective study aimed to analyse the clinical characteristics and outcomes of advanced HCC patients who received Sorafenib on an Expanded Access Programme (EAP) at Charlotte Maxeke Johannesburg Academic Hospital in South Africa between 2008-2016.

Results: Forty-five patients were enrolled, with an overall median survival of 32 days. The study identified advanced liver disease at presentation as a key factor associated with early treatment discontinuation and mortality. One patient however, demonstrated a remarkable long-term response to sorafenib, suggesting the potential for tailored treatment strategies. Chronic HBV infection was a predominant risk factor while co-infection with HIV showed an association with rapid disease progression especially in younger patients**.**

Conclusion: The findings underscore the need for improved early detection and targeted management approaches in the Southern African context. Despite the retrospective nature of the study, it provides valuable insights into HCC within the African context, emphasizing the need to address risk factors and optimise treatment outcomes.

Chapter 1: Literature Review

1.1 Introduction

Primary hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third cause of cancer mortality (1-3). According to GLOBOCAN 2020, there were approximately 906,000 new cases reported annually and 830,000 deaths attributed to HCC globally (3). In 2020, the South African National Cancer Registry, reported approximately 211 histologically confirmed HCC new cases (4). The significant mortality associated with HCC poses a substantial public health burden (1, 2). In Sub-Saharan Africa (SSA), HCC emerges as a leading contributor of cancer-related mortality however, there remains a scarcity of documented data regarding its epidemiology, clinical presentation, and management (5).

1.2 Epidemiology

The incidence of HCC is increasing worldwide, exhibiting significant geographic variation associated with the different risk factors (5). There has been a significant increase in both occurrence and death rates of HCC worldwide (1, 3, 5). Significantly, there has been notable decrease in the prevalence of Hepatitis B Virus (HBV) as well as Hepatitis C Virus (HCV) in Eastern Asia countries, while metabolic conditions such as diabetes and obesity have significantly increased in many of these countries (3).

The occurrence and death rate of HCC are greater in males than females with an estimated ratio of 2-3:1 (3). The observed discrepancy can be potentially related to risk factors that are associated with the onset and progression of HCC (3, 5). Globally HCC is the fourth main cause of death for men (3, 5). The age at which HCC develops differs worldwide. Typically in Asia and Southern Europe, the age at which symptoms first appear is during the 5th decade of life, whereas in Africa, the peak incidence occurs earlier in the 2nd to 3rd decades of life. This

difference could be attributed to the high prevalence as well as lack of vaccination against hepatitis B infection in most African countries (3).

The occurrence of HCC varies throughout the different regions of the world with the utmost incidence being in Asia, Europe, and SSA (2, 3, 6). Eastern Asia, in particular, has the highest incidence within Asia with an overall incidence of over 20 cases per 100,000 population, primarily due to chronic hepatitis B and less so hepatitis C infections (2, 3, 7). SSA is another region of concern, with HCC incidence mainly associated with the burden of Human Immunodeficiency Virus (HIV) and HBV co-infection (2, 7). In Africa, HCC is ranked as fourth most prevalent cancer and the third leading cause of cancer-associated mortality with a predicted 70,542 new cases each year and the incidence is higher in males than females (3).

Western countries such as the United States of America, Canada, and Western Europe report lower incidence rates, approximately less than 5 cases per 100,000 population. Limited diagnosis as well as the lack of cancer registries contributes to limited data on the incidence and clinical characteristics of patients with HCC (4). In South Africa, according to the pathology-based National Cancer Registry in 2020 the reported cases of HCC, including both hepatic cancer including both liver and bile duct totaled 211 (3, 8). The female-to-male ratio is 1:1.5 (4). The reduction in reported cases of HCC in SSA can be attributted due to various factors such as lack of cancer registries, delayed clinical presentation, and lack of surveillance programs for individuals at risk of HCC development (3, 4).

1.3 Hepatocellular carcinoma risk factors and pathogenesis

The incidence of HCC has geographical variation, and its development is determined by the prevalence of specific risk factors in different regions (2, 3, 7). Liver cirrhosis is the

predominant risk factor for the onset of HCC (7). Any aetiology that leads to liver cirrhosis can increase the risk for the development of HCC (7). The main risk factors associated with HCC are viral hepatitis such as chronic HBV and HCV, alcohol consumption and aflatoxin ingestion. Type 2 diabetes, excess smoking and metabolic conditions such as excess body weight, hereditary haemochromatosis, and immune-related conditions such as primary biliary cirrhosis and autoimmune hepatitis are also important risk factors (2, 3, 7).

In Africa and Easten Asia, HBV is the primary contributing factor in the onset and development (8). The concurrent infection with HIV increases the prevalence of HCC in individuals with HBV, especially in SSA (8). The proposed mechanism of development of HCC from HBV infection is mainly attributed to the virus's direct impact, by integration of the HBV into hepatocytes genome. The other mechanism of direct effect is hepatitis Bx (HBx) transcription factor associated with the activation of cellular genes responsible for growth control (8). HBx is also responsible for the activation of the RAS-RAF-MAP-K implicated in hepatocarcinogenesis (8). In addition, it interferes with the p53 gene function as a tumour suppressor gene (8). On the other hand, indirect effects of HBV by chronic inflammation, fibrosis, with the addition of oxidative stress, telomere shortening, replicative senescence of hepatocytes also contribute to the development of cancerous changes in cirrhotic nodules and development of HCC (7-9).

Hepatitis C virus (HCV) infection is a prominent risk factor for liver cirrhosis and its prevalence varies globally, with higher rates observed in Europe, North America, and North Africa. Its estimated prevalence in Africa is 2.9% with a total of 26.9 million cases (10), Egypt being the country with the highest HCV prevalence due to use of contaminated needles during a previous national schistosomiasis vaccination campaign (7, 10). Patients with HCV infection

are more likely to develop HCC, the mechanisms are not fully understood, HCV is an RNA-virus with reduced integration capacity into the host genome (10, 11) indirect mechanisms of injury could be responsible for the development of HCC (10, 11).

The development of HCV-induced cancer is promoted by viral-induced factors and immune response of the host (12). The primary impact HCV of viral proteins is to directly influence cell signaling pathways leading to the promotion of HCC, this is achieved through the inhibition of suppressor genes and cell cycle points, as well as the activation of pathways that upregulate growth and division, the specific gene mutations are p53 suppressor gene and retinoblastoma (12). The host immunologic factors cause secondary chronic inflammation mediated by activation of tumor necrosis factor, interferons resulting in immune-mediated hepatocyte death, tissue damage, fibrosis, cirrhosis and lastly HCC development (12). HBV infection has greatest risk in under 5 years of age while HCV occurs in adults. RNA viruses tend to integrate into genomes better than DNA viruses (12).

HIV infection may serve as a contributory risk factor for the development HCC, due to a common mode of transmission, with HBV and HIV and HBV co-infection being common in SSA with an estimated prevalence of 7.8% among people living with HIV (13). HIV infection leads to increased hepatocyte damage through the production of reactive oxygen stress, activation of hepatic stellate cells and promoting liver injury by activation of Kupffer cells in the liver (13).

The consumption of alcohol is a widely recognised risk factor that increases the probability for the development of various cancers including HCC (14). The specific mechanisms by which alcohol alone causes HCC are not well known. However, it has been shown that the

development of alcoholic liver cirrhosis which is directly related to daily alcohol intake, increases when the amount exceeds 80g/day equivalent to 8 standard-sized beers per day or half a liter of hard liquor per day (14). The consumption of alcohol in conjuction with concurrent risk factors such as chronic HBV infection, chronic HCV and the presence of type 2 diabetes and non-alcoholic liver steatohepatitis could result in the development of HCC (7, 14).

Alcohol-induced liver injury is thought to be caused by two mechanisms. Acetaldehyde, a by-product of ethanol metabolism, exhibits carcinogenic properties via binding to DNA and activating CYP2E1, a cytochrome enzyme activated by ethanol use that releases reactive oxygen species resulting in chronic inflammation secondary to chronic oxidative stress leading to cirrhosis and development of HCC (9, 15, 16). The activation of reactive oxygen stress species also produces DNA adducts which may cause alcohol-induced liver injury (9, 15). Indirect effects of alcohol-induced liver injury result in a pro-inflammatory state which activates Kupffer cells which releases chemokines and cytokines resulting in hepatocyte damage and resulting in cirrhosis (15, 16).

Metabolic factors such as non-alcoholic liver disease, diabetes mellitus and obesity, have been linked in the development of HCC, there is supportive evidence to suggest their involvement in the pathophysiology of HCC (9, 17). Obesity and diabetes mellitus play a role in the development of HCC (9). From previous studies, the available data suggests that HCC can become a common occurrence among obese and diabetic patients because 90% of the patients have some degree of steatosis and mild inflammation (17). The specific carcinogenetic mechanism for the development of HCC is still unknown. The presence of non-alcoholic steatohepatitis may result in the development of fibrosis which then leads to cirrhosis, this is

due to the presence of chronic low-grade inflammation that predisposes the liver to further damage with the presence of lipid peroxidation and free radical oxidative stress, the proliferation of oval progenitor cells and senescence of hepatocytes thus leading to damage and lastly the development of HCC (9, 17). Overall the development of HCC in metabolic associated fatty liver disease is influenced by multiple factors resulting from chronic inflammation, oxidative stress, insulin resistance, lipotoxicity, and abnormal relationship with visceral adiposity (9).

Aflatoxins are a dietary contaminant produced by the food-borne fungus *Aspergillus flavus* and *Aspergillus parasiticus* which can contaminate a variety of foods such as maize, oilseeds, spices, groundnuts, and tree nuts particularly prevalent in tropical and subtropical regions in the world (18, 19). Aflatoxins present a substantial risk factor for the development of HCC. The global incidence of HCC as a result of aflatoxin exposure is uncertain however it is roughly estimated to be about 4.6-28.2 % of HCC globally (18). The highest incidence of HCC associated with aflatoxin exposure was reported in Sub-Saharan Africa, South-East Asia, and China (18). Aflatoxin exposure with concomitant HCV and HBV con-infection can result in fibrosis which leads to cirrhosis and the result is the development of HCC (18). The mechanism by which aflatoxin causes HCC is not well understood, aflatoxin exposure has been shown to affect the p53 gene once metabolized by the p450 system in the liver, it transforms into a reactive oxygen series causing acute toxicity called aflatoxicosis by binding to proteins, it can also bind to DNA to cause liver lesions that over time can develop into HCC (16, 18).

1.4 Diagnosis

The diagnosis of HCC is unique. It can be made during surveillance, after imaging and when patients become symptomatic or have clinical features thereof, the most common presentation

in LMICs (20-22). The diagnosis of HCC is multifaceted and can be made through various modalities and it does not necessarily need histopathological confirmation (21). HCC is frequently diagnosed without the histopathological confirmation using the criteria established by the American Association of Study of the Liver Disease (AASLD) and European Association of Liver Disease criterion (EASL) (21). Clinical criteria for HCC include different patterns of presentation, patients may exhibit symptoms such as progressive weight loss, or right upper quadrant pain. In a patient with confirmed liver cirrhosis clinical features of worsening liver dysfunction such as jaundice and if a rupture of a liver nodule occurs intra-abdominal bleeding (22, 23).

On the other hand, imaging studies have a crucial role in the diagnosis of HCC (22, 23). Ultrasound plays an important role in diagnosing hepatocellular carcinoma as it can detect small lesions within the liver with relatively high sensitivity and specificity. However liver nodules <1cm, may not always be HCC and there is a necessity of repeating ultrasound within 3 months for surveillance (20,22). For liver nodules larger than 1 cm further imaging needs to be used to investigate the lesion such as spiral computed tomography (CT) and magnetic resonance imaging (MRI) with multiphase enhancement (20, 22, 23).

The hallmark radiological feature of HCC on MRI and CT is called an “arterial enhancement and delayed washout” where HCC lesions exhibit increased brightness relative to the surrounding liver tissue in the arterial phase in a CT or MRI, followed by diminished brightness compared to surrounding liver parenchyma in the venous phase it has a sensitivity of 89% and specificity 96%, in high-risk patients, this confirms the presence of HCC without a histopathological diagnosis (20, 22, 23). Magnetic resonance imaging has become the imaging tool of choice due to its superior contrast resolution enabling the detection of tumours

measuring less than 1cm (23). The tumour lesion is described as a hypodense lesion on T-1 and hyperintense on T-2 weighted images but the appearance may be variable in the presence of foci of haemorrhage, accumulation of copper in areas of fatty change (23).

Serum alpha-fetoprotein (AFP) measurement is widely used in the diagnosis and management of HCC (24). AFP is elevated in more than 70% of patients diagnosed with HCC, with a level of more than 200 ng/mL, however, AFP has low sensitivity and high predictive value (22, 23). Although elevated serum alpha-fetoprotein levels can be present in other liver diseases and cancers especially germ cell tumours, the diagnosis is almost certain with levels >400ng/ml and a suspicious liver lesion on imaging (24).

Liver biopsy, is primarily used for early detection of HCC and for obtaining tissue sample for nodules that are smaller than 2 cm for histological diagnosis (25). The precision of fine-needle biopsy depends on the dimensions of the nodule but this form of diagnostic tool is controversial because of the possibility of local spread once needle biopsy is taken, therefore many clinicians advocate against the need to perform a liver biopsy due to the high risk of local spread of and if one is necessary it needs to be done through ultrasound guidance (22, 23).

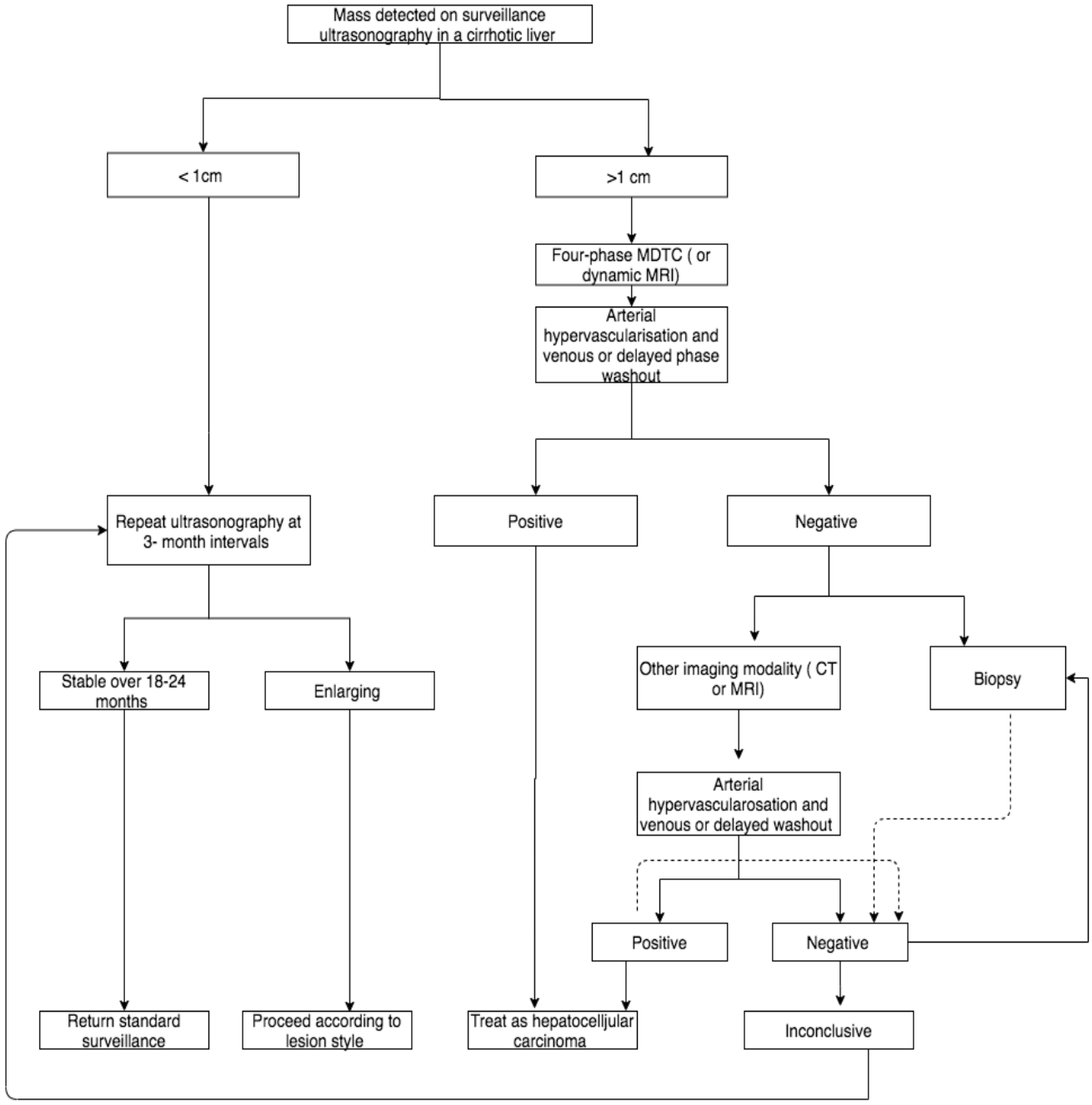


Figure 1: Schematic algorithm for the diagnosis of hepatocellular carcinoma**.** *Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301-14*

1.5 Staging and Prognostic Assessment

Accurate staging and prognostic assessment are crucial for the optimal management of HCC. Various staging classifications have been developed to guide treatment decisions, predict patient outcomes and assess treatment response (21, 25). The two most commonly used systems used for HCC are the TNM staging system and the Barcelona

Clinic Liver Cancer (BCLC) system (21, 27). The TNM staging system focuses on tumour size, nodal status and metastases. The TNM staging system is used for both hepatic resection and transplantation, it provides valuable information to determine the appropriate primary and adjuvant treatment strategies (21, 27), see **Table 1**. On the other hand, the BCLC system is widely validated and predominantly used for non-surgical patients with advanced hepatocellular carcinoma (21, 27) (**Table 2**). It takes into account the tumour stage, liver function, performance status and presence of portal hypertension to categorize patients into different stages, guiding treatment options (27).

Table 1**:** TNM Staging for HCC. *Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. Gastroenterology. 2002;122(6):1609-19*.

Categories	**Definitions**
T	**Primary tumour size, number, and location**
T0	No evidence of primary tumour
T1	Solitary tumour <2 cm without vascular invasion
T2	Solitary tumour <2 cm with vascular invasion or multiple tumours in 1 lobe > 2 cm with or without vascular or solitary tumour > 2cm without vascular invasion
T3	Solitary tumour < 2 cm with vascular invasion or multiple tumours in 1 lobe< 2 cm with vascular invasion or multiple tumours in 1 lobe >2 cm with or without vascular invasion
T4	Multiple tumours in more than 1 lobe or invasion of a major branch of portal or hepatic vein or invasion of adjacent organs other than the gallbladder or perforation of visceral peritoneum
N	**Nodal metastasis**
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastasis
M0	No distant metastasis
M1	Distant metastasis
Stages	**Stage according to the TNM categories**
Stage I	T1N0M0
Stage II	T2N0M0
Stage IIIA	T3N0M0
Stage IIIB	T1N1M0 or T2N1M0 or T3N1M0
Stage IVA	T4, any N, M1
Stage IVB	AnyT, anyN, M1

Table 2: Stages of the Barcelona Clinic Liver Cancer (BCLC) System**.** *Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016;2:16018, Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. Gastroenterology. 2002;122(6):1609-19*

Stage	Performance Status	Tumour stage	Liver Function
Stage A: early HCC			
A1	0	Single < 5cm	No portal HTN and normal bilirubin
A2	0	Single < 5cm	Portal HTN and normal bilirubin
A3	0	Single < 5cm	Portal HTN and elevated bilirubin
A4	0	3 tumours < 3cm	Child-Pugh class A-B
Stage B: Intermediate HCC	0	Large multinodular	Child-Pugh class A-B
Stage C: Advanced HCC	1-2*	Vascular invasion or extrahehaptic spread*	Child-Pugh class A-B
Stage D: End-Stage HCC	3-4**	Any	Child C**

Note: Stage A and B all criteria should be fulfilled
HTN, hypertension
*Stage C: At least 1 criteria should be fulfilled
**Stage D: At least 1 criteria should be fulfilled

In addition to staging, assessing liver function is essential in determining the management and prognosis of HCC (21, 28). The Child-Pugh score is a tool used for measuring the severity of synthetic liver function, it offers a reliable evaluation of liver function and assists in predicting patients outcomes (21, 28).

Table 3: Child-Pugh Classification for the severity of liver function**.** *Jelic S, Sotiropoulos GC, Group EGW. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v59-64.*

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dl	< 2	2-3	>3
Albumin, g/dl	> 3.5	2.8-3.5	< 2.8
Prothrombin time			
Seconds over control	1-3	4-6	>6
INR	<1.8	1.8-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

A total score of 5-6 is considered grade A (well-compensated disease), 7-9 is grade B (significant functional compromise) and 10-15 is grade C (decompensated disease).

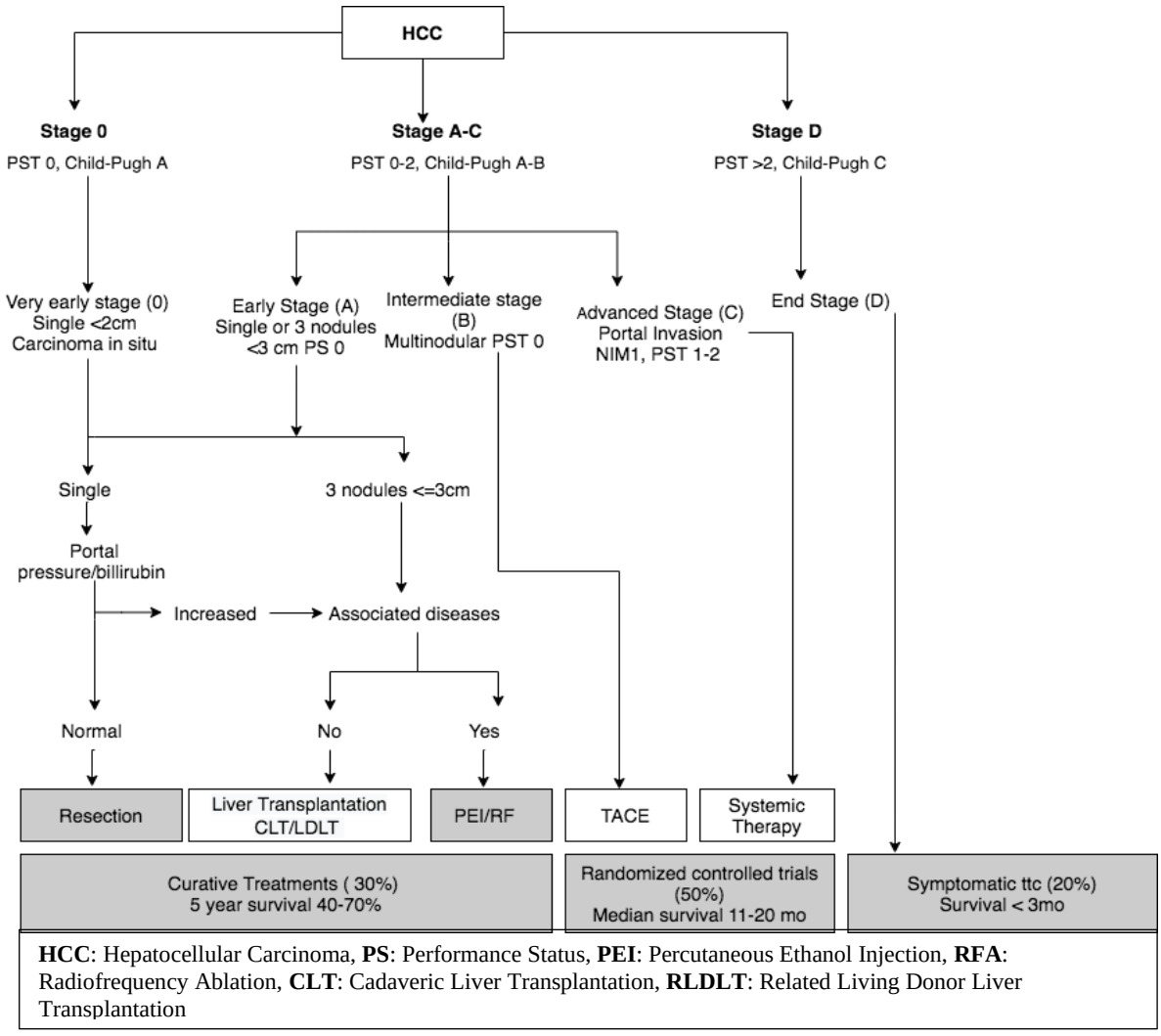
Furthermore, the Eastern Cooperative Oncology Group (ECOG) score is a standardized measure of a patient's performance status which evaluates the impact of disease on the level of daily living abilities and daily functioning (20). The ECOG score is used to assess patient's overall health status and guide treatment decisions (21, 29) (**Table 4**).

Table 4: Eastern Cooperative Oncology Group (ECOG). *Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

1.6 Management

Therapeutic treatment options of HCC depend on the stage of the disease, with treatment options guided by the BCLC. The BCLC evaluates characteristics related to tumour stage, liver functional status, physical status and cancer status (25). **Figure 2** shows a diagram showing the BCLC staging and treatment algorithm used in HCC (21).



HCC: Hepatocellular Carcinoma, **PS**: Performance Status, **PEI**: Percutaneous Ethanol Injection, **RFA**: Radiofrequency Ablation, **CLT**: Cadaveric Liver Transplantation, **RLDLT**: Related Living Donor Liver Transplantation

Figure 2: Algorithm for the treatment of HCC using Barcelona Clinic Liver Cancer Staging**.** *Hartke J, Johnson M, Ghabril M. The diagnosis and treatment of hepatocellular carcinoma. Semin Diagn Pathol. 2017;34(2):153-9.*

For patients with stage 0 early disease, recommendations include radical therapies such as surgical resection, liver transplantation, and percutaneous treatment. Patients diagnosed with stage A-C, the intermediate disease may qualify for chemoembolization and systemic therapy, and lastly patients with stage D qualify for symptomatic treatment (25). Surgical resection is

indicated in patients without cirrhosis and with solitary HCC lesion or unilobar disease without evidence of metastases or vascular invasion, no portal hypertension, and no hepatic dysfunction, typical Child-Pugh A (20, 27).

Liver transplantation is considered the most effective curative treatment for HCC, efficiently targetting both the tumour and the underlying liver cirrhosis. It is reserved for patients presenting with cirrhosis and limited disease burden (20, 26, 27). The criterion to choose liver transplantation as the best treatment choice depends on patients' assessment of predicted immediate and long-term survival (27). Poor prognostic factors include clinically significant portal hypertension and other patient comorbidities. The Milan criteria which include a single HCC nodule 5 cm, or less, or l to 3 nodules 3cm or less, without evidence of macrovascular invasion on imaging, are commonly selected for liver transplantation (23, 27) (**Table 5**). Additionallly, an elevated AFP level has been demonstrated to enhance the predictive value of the Milan criteria, in general patients with AFP levels > 200ng/mL have significantly worse outcomes (27). The choice of liver transplantation depends mainly on the availability of liver donors, which can be limited (20, 23, 27).

Table 5: Milan criteria for liver transplantation in adult patients with HCC. *Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. Gastroenterology. 2002;122(6):1609-19, Pons F, Varela M, Llovet JM. Staging systems in hepatocellular carcinoma. HPB (Oxford). 2005;7(1):35-41.*

Single tumour diameter less than 5cm;
Not more than three foci of tumour, each one not exceeding 3 cm;
No angioinvasion
No extrahepatic involvement

Loco-regional therapies typically represent the preferred treatment for patients with less advanced disease such as BCLC Stage A disease and can provide curative therapy for small

early HCC for tumours (<2cm) or in early-stage tumours (>4cm or between 2-3cm), the presence of complications such as tumour nodularity or development of liver dysfunction excludes them for liver transplantation (20, 23). Ablation techniques including thermal, chemical or electrical methods can directly cause injury to the tumour (20). Transarterial therapy and trans-arterial embolization (TACE) and local radiofrequency ablation are the two types of therapies that are administered percutaneously (30). Local radiofrequency ablation is the most commonly used method it is preferred in tumour sizes <2cm and in early-stage tumours single tumour 2-3cm can be an alternative to surgery (20). It uses an ultrasound-guided probe to reach the liver through the skin and target the tumour, which is then heated to a steadily increasing temperature for approximately 15 minutes. This method has a response rate of 70-90% with high precision and is associated with improved overall survival (OS) (20, 30).

Transarterial therapy and trans-arterial embolization (TACE) can be considered in patients with BCLC B and the intermediate-stage disease (20, 23, 30). It combines two types of treatment, clinically a catheter is inserted via the femoral artery and guided to the tumour via angiography. This catheter is used to deliver a cytotoxic agent such as doxorubicin with an emulsion of Lipiodol utilized to increase the tumour's exposure to the drug followed by embolisation (23, 26, 30). Both techniques are effective in solitary HCC nodules measuring less than 2 cm and the main determinant of outcome is portal hypertension (23).

The best patients qualifying for TACE are asymptomatic patients with a solitary or limited multifocal HCC in the absence of vascular invasion or extrahepatic spread, additionally these patients should exhibit well-preserved liver function Child-Pugh class A or B 7 points without ascites (23). Some contra-indications for TACE are tumour burden size >10cm and liver impairment (23). Newer options such as radioembolization with an intra-arterial administration

of microspheres containing Yttrium-90, a short-half-life pure beta-emitter with restricted tissue-penetrating capacity facilitates tumour destruction (23, 31).

Systemic therapy is reserved for patients with advanced HCC represented by BCLC C, with no markedly advanced liver with child Pugh A and B reporting better outcomes (23, 27, 30). Studies with chemotherapy such as doxorubucin and nolatrexed did not improve the overall survival for patients with advanced HCC. According to Gish et al. 2004, both medications have activity against HCC, with doxorubicin showing superior therapeutic activity, a more favourable safety profile and median overall survival of 32.3 weeks (32).

Modern treatment options including angiogenesis inhibitors can be divided into first and second-line treatments (20, 27). Sorafenib a multi-kinase inhibitor, has emerged as a first-line treatment for advanced HCC, the SHARP trial published in 2008 demonstrated its superiority over placebo, resulting in an improved overall median survival of 10.7 months compared to placebo with median survival of 7.9 months (20, 27).

Sorafenib exerts its effects by inhibiting tyrosine kinase receptors such as the RAF serine/threonine kinases, vascular endothelial growth factor receptor 1, 2, 3 (VEGF-1,2,3), platelet-derived growth receptor (PDGFR) and KIT (33). The exact mechanism of action is unknown, it has been shown to reduce tumour cell proliferation, angiogenesis, and induce apoptosis through various pathways such as by blocking VEGFR-1, PDGFR and the RAS/RAF/MEK/ERK pathway in endothelial cells, pericytes and tumour cells (33) and also induces major changes in stromal cells (23, 27, 30).

In HCC, sorafenib causes damages to cells lines such as PLC/PRF-5 and Hep G2 by inhibiting proliferation and inducing apoptosis(33). In the pivotal SHARP trial, sorafenib demonstrated an overall survival of 10.7 months in patients with Child-Pugh score A and B (23, 27, 30, 34). In another phase III trial in 2009, Cheng et al. in the Asian Pacific region, showed similar efficacy and safety with sorafenib in HCC, suggesting its applicability across different prognostic factors (35). Sorafenib was the first-approved drug for the treatment of advanced unresectable HCC, offering improved overall survival (32). However, in Africa, further studies are needed to evaluate the effects of sorafenib especially in Sub-Saharan African patients.

The phase III open-label trial conducted by Kudo M et.al., 2018 showed that lenvatinib is more effective than Sorafenib treating HCC. Lenvatinib showed the median survival of 13.6 months whereas sorafenib achieved 12.6 months (36). The trial excluded patients demonstrating extra-hepatic invasion including main portal vein invasion, clear bile duct invasion and > 50% tumour to total liver volume (20, 31). Lenvatinib is an orally administered drug that acts as multikinase inhibitor specifically targets VEGFR1-3 and fibroblast growth factor receptor (FGFR)1-4 (20, 31, 36).

For targeted second-line treatment in patients' who progressed on sorafenib three main agents may be used: regorafenib, cabozantinib, and ramucirumab (30, 31). In addition, immune checkpoint inhibitors such as single-agent nivolumab and pembrolizumab, or nivolumab and ipilimumab have been investigated after phase II/III clinical trials as treatments following sorafenib (20). Regorafenib, a multi-kinase inhibitor similar to sorafenib, targets VEGFR 1-3 and other kinases. It is reserved for patients who have progressed on sorafenib and is most effective in those with preserved liver function (20, 31).

In clinical trials, regorafenib showed a median survival of 10.6 months when compared to placebo 7.8 months (20). Cabozantinib another multi-kinase inhibitor with activity against VEGFR 2, MET, AXL and RET inhibitors used in the treatment of thyroid and renal cancer, in a global phase III trial showed a better response (10.2 months vs 8.0 months) to placebo (20, 31). Ramucirumab, anti GFR-2 human immunoglobulin G1 monoclonal antibody, is the only biomarker-guided therapy for HCC, it inhibits ligand activation of VEGFR2 (20, 31). All have shown significant effects in the treatment of HCC (31). The REACH- 2 Trial showed an overall survival of 8.5 months when compared to placebo of 7.3 months, this treatment was reserved for patients with baseline alpha-fetoprotein measurement of >400ng/dl (20).

Immunotherapy including nivolumab and pembrolizumab has emerged as a newer treatment option for HCC (20, 30). Mechanism of action of immunotherapy is believed to be in upregulating the immune system via immune checkpoint inhibitors. This class of drugs has been shown to be better tolerated and demonstrated better overall survival when used as first-line treatment in patients with newly diagnosed advanced HCC. Immunotherapy can additionally serve as second-line treatment in patients with HCC who have experience progression while on sorafenib.

In the IMBrave150 2022 by Cheng et al. demonstrated that atezolizumab plus bevacizumab extended overall survival by 5.8 months than sorafenib alone in newly diagnosed patients, this findings may suggest a change in the primary treatment for advanced HCC (20, 30, 37).

The study aimed to characterise the clinical features and treatment outcomes of patients treated with sorafenib at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 2008-2016. Specifically, the study sought to identify key risk and aetiological factors associated with hepatocellular carcinoma (HCC) and analyse overall survival outcomes.

Through comprehensive analysis, the study aimed to provide insights into HCC occurrence, progression and treatment response. Additionally, it aimed to quantify factors contributing to HCC development. By evaluating survival data, the study aimed to understand the impact of sorafenib treatment on patient outcomes.

Chapter 2: Methodology

2.1 Study Design

This was retrospective study using patient records from a compassionate Sorafenib Expanded Access Program (EAP) sponsored by Bayer Pharmaceutical in the treatment of advanced HCC in the Medical Oncology Department at Charlotte Maxeke Johannesburg Academic Hospital from 2008-2016

2.2 Study population and setting

We identified 45 patients diagnosed with advanced HCC at CMJAH from 2008-2016. The hardcopy files of these patients were reviewed for initiation of treatment. The Inclusion criteria included: patients older than 18 years old; patients with hepatocellular carcinoma diagnosis based on radiological and/or histological features, or AFP levels >200ng/ml and all patients treated on the Sorafenib Compassionate Program for HCC Child Pugh A-B at Medical Oncology Department at Charlotte Maxeke Johannesburg Academic Hospital. The Exclusion Criteria included: patients diagnosed with HCC Child Pugh C and BCLC Stage D (**Table 6**).

Table 6: Inclusion and Exclusion Criteria for patients with HCC treated with Sorafenib on the EAP

Inclusion criteria	-Patients aged 18 years or older. -Hepatocellular carcinoma diagnosis based on radiological and/or histological features, or AFP levels. -All patients treated on the Sorafenib Compassionate Program for HCC Child Pugh A-B at Medical Oncology Department at Charlotte Maxeke Johannesburg Academic Hospital.
Exclusion criteria	-Patients younger than 18 -Patients diagnosed with HCC Child Pugh C and BCLC Stage D.

The study population characterised by demographic and clinical characteristics including age, gender, and country of origin, and age was subcategorized into older than 50 years and younger than 50 years. The clinical characteristics included comorbidities (including HIV status, hypertension, and diabetes), HIV viral load, CD4 count and treatment status for patients who were HIV positive, Eastern Cooperative Oncology Group (ECOG) performance status, Child-Pugh Score to determine hepatic functional reserve, previous treatment, and clinical outcomes. The data for risk factors included HBV and HCV infection, aflatoxin exposure, ethanol use, and smoking status, a composite variable for substance use was created using ethanol, and smoking status.

The diagnosis of HCC was based on various criteria such alpha-fetoprotein measurement, imaging studies such as ultrasound, computerized tomography, or magnetic resonance, a combination of clinical, and alpha-fetoprotein measurement and imaging results, and lastly histopathological confirmation. HCC was considered unresectable according to the BCLC, it incorporates tumour invasion involving the portal or hepatic veins and extrahepatic veins, multi-nodule disease and bi-lobar liver disease (20).

2.3 Statistical analysis

Categorical data was stratified by gender and age group, and frequencies and percentages were given. The Fisher's Exact test and Chi-Square test were used to compare categorical variables. Descriptive statistics such as median, inter-quartile range (IQR), mean, and standard deviation were presented for continuous variables. Wilcoxon rank sum test was used to compare medians for continuous data whereas student t-test was used to compare means stratified by gender and age-group. Kaplan-Meier curve, was used to represent overall treatment status, including time to treatment discontinuation and those who stopped treatment due to death, stratified by gender and age. This curve describes the survival estimates among the participants, both overall and stratified by treatment status. The log-rank test was used to compare survival between patients that received treatment and those that did not. A p-value <0.05 denoted statistical significance. All statistical analysis was conducted in SAS Enterprise guide 7.1 using procedures FREQ, MEANS, NPARIWAY, TTEST and LIFETEST.

2.4 Ethical considerations

Anonymity and confidentiality were maintained throughout the study, the study participants were identified by unique identification numbers. Ethics clearance for this study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Certificate no: M201034 – **Appendix 3**).

Chapter 3: Results

A total of 45 patients were enrolled in the study and their demographic characteristics categorised by gender and age group are represented in **Tables 7** and **8**. The study population was predominantly male accounting for 73.3% (33/45) of the participants. In terms of age distribution, most patients were ≥50 constituting 55.6% (25 /45) of the study population.

The majority of patients were from the black ethnic group at 88.9%, (40/45) and of South African origin at 53.3%, (24 /45).

Table 7: Demographic characteristics by gender with advanced hepatocellular carcinoma treated with sorafenib Charlotte Maxeke Johannesburg Academic Hospital from 2008-2016.

Variable	Overall	Female	Male	P-Value
Age (in years)				
<50 (%)	20/45 (44.4)	5/12 (41.6)	15/33 (45.4)	0.9999
≥50 (%)	25/45 (55.5)	7/12 (58.3)	18/33 (54.6)	
n, Median (IQR)	45, 52.0 (41.0-64)	12, 51.5 (37.5-60)	33, 54.0 (42.0-65)	0.3551
n, Mean (SD)	45, 51.2 (15.1)	12, 47.4 (16.8)	33, 52.5 (14.5)	0.3225
n, Min, Max	45, (18-73)	12, (18-68)	33, (23-73)	
Ethnicity				
Black (%)	40/45 (88.9)	9/12 (75.0)	31/33 (93.9)	0.1091
Other (%)	5/45 (11.1)	3/12 (25.0)	2/33 (6.06)	
Country of origin				
South Africa (%)	24/45 (53.3)	8/12 (66.7)	16/33 (48.5)	0.3293
Other/Unknown (%)	21/45 (46.7)	4/12 (33.3)	17/33 (51.5)	
Comorbidities				
None (%)	26/45 (57.7)	9/12 (75.0)	17/33 (51.5)	0.1911
HIV (%)	9/45 (20.0)	2/12 (16.6)	7/33 (21.2)	0.9999
Hypertension (%)	8/45 (17.7)	1/12 (8.3)	7/33 (21.2)	0.4186
Diabetes Mellitus (%)	1/45 (2.2)	0/12 (0.0)	1/33 (3.0)	-
If HIV+: CD4 Count (U/L)				
≤250 (%)	1/8 (12.5)	0/2 (0.00)	1/6 (16.7)	-
>250 (%)	7/8 (87.5)	2/2 (100.0)	5/6 (83.3)	
If HIV+: Viral Load				
Suppressed <1,000 cp/ml (%)	7/7 (100.0)	2/2 (100.0)	5/5 (100.0)	-
If HIV+: Treatment status				
On treatment (%)	7/7 (100.0)	2/2 (100.0)	5/5 (100.0)	-

Table 8: Demographic characteristics of patients with advanced hepatocellular carcinoma treated with sorafenib from 2008-2016 at Charlotte Maxeke Johannesburg Academic Hospital by age-group.

Variable	Overall	<50	50+	P-Value
Gender				
Female (%)	12/45 (26.7)	5/20 (25.0)	7/25 (28.0)	0.9999
Male (%)	33/45 (73.3)	15/20 (75.0)	18/25 (72.0)	
Ethnicity				
Black (%)	40/45 (88.9)	18/20 (90.0)	22/25 (88.0)	0.9999
Other (%)	5/45 (11.1)	2/20 (10.00)	3/25 (12.0)	
Country of origin				
South Africa (%)	24/45 (53.3)	7/20 (35.0)	17/25 (68.0)	0.0379
Other/Unknown (%)	21/45 (46.7)	13/20 (65.0)	8/25 (32.0)	
Comorbidities				
None (%)	26/45 (57.8)	11/20 (55.0)	15/25 (60.0)	0.7697
HIV (%)	9/45 (20.0)	7/20 (35.0)	2/25 (8.0)	0.0567
Hypertension (%)	8/45 (17.8)	1/20 (5.0)	7/25 (28.0)	0.0592
Diabetes Mellitus (%)	1/45 (2.2)	0/20 (0.0)	1/25 (4.0)	-
If HIV+: CD4 Count (U/L)				
<=250 (%)	1/8 (12.5)	1/6 (16.7)	0/2 (0.0)	-
>250 (%)	7/8 (87.5)	5/6 (83.3)	2/2 (100.0)	
If HIV+: Viral Load				
Suppressed <1,000 cp/ml (%)	7/7 (100.0)	5/5 (100.0)	2/2 (100.0)	-
If HIV+: Treatment status				
On treatment (%)	7/7 (100.0)	5/5 (100.0)	2/2 (100.0)	-

Among the enrolled patients 20% (9/45) were HIV positive, the younger group had a higher proportion of HIV positive individuals compared to the older age-group (35% vs 8% p=0.057). (**Table 7**) Among those who were HIV infected 87.5% (7/8) had a CD4 >250, and were virologically suppressed while on anti-retroviral treatment, although not statistically significant males had a higher proportion of HIV positive compared to females (21.2% vs 16.7%,

p=0.999). Regarding comorbidities, 17% (8/45) of the participants had hypertension. The prevalence of hypertension was higher in participants older than 50 years compared to the younger group (28% vs 5% p=0.592) and males had a higher proportion compared to females (21.2% vs 8.3%). Additionally, 2.2% (1/45) of the study participants had diabetes mellitus type 2 (**Table 8**).

Figure 3, provides an assessment of risk factors among participants stratified by gender and age. Hepatitis B infection was present in nearly half of the patients (48.9%, (22/45)) with males showing a higher proportion of hepatitis B infection when compared to females (54.6% vs 33.3%). Hepatitis B infection was more common in patients younger than 50 years (70.0% vs 32.0%). Hepatitis C infection was observed in 15.6% (7/45) of participants with males having a higher proportion compared to females (18.2% vs 8.3%). Hepatitis B infection was more common in patients younger than 50 years compared to hepatitis C infection observed in patients older than 50 years 15.6% (7/45). Alcohol abuse was noted in 17.8% (8/45). Among these participants alcohol consumption ranged between 0-750ml per day. Smokers constituted 14.6% (7/45) and the mean number of cigarettes smoked per day was 14 ± (7.1). Although not statistically significant males smoked more (18.2% vs 8.3%) compared to females. Hepatitis B infection was identified as the common risk factor for the development of HCC among study participants as shown in **Figure 3**, among these 36.4% (8/22) were HIV positive and 9% (2/22) had concomitant Hepatitis C infection.

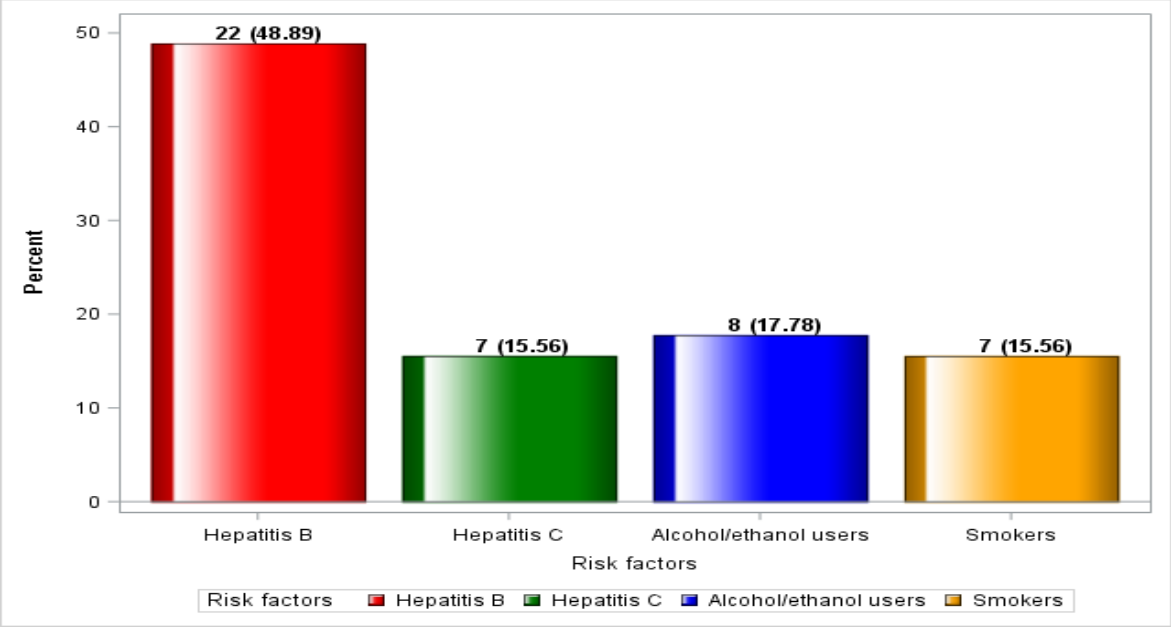


Figure 3: Distribution of risk factors for hepatocellular carcinoma among participants with advanced hepatocellular carcinoma treated with sorafenib at Charlotte Maxeke Johannesburg Hospital from 2008-2016.

Table 9: Clinical information of patients with advanced hepatocellular carcinoma treated with sorafenib from 2008-2016 at Charlotte Maxeke Johannesburg Academic Hospital by gender.

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Variable	Overall	Female	Male	P-Value
ECOG Performance Status				
0 (%)	6/45 (13.3)	2/12 (16.7)	4/33 (12.1)	0.6916
1 (%)	36/45 (80.0)	10/12 (83.3)	26/33 (78.8)	0.7360
2 (%)	3/45 (6.7)	0/12 (0.00)	3/33 (9.1)	-
Child Pugh at Presentation				
A (%)	31/45 (68.9)	9/12 (75.0)	22/33 (66.7)	0.7254
B (%)	14/45 (31.1)	3/12 (25.0)	11/33 (33.3)	
Barcelona Clinic Liver Cancer Classification				
A (%)	5/45 (11.1)	1/12 (8.3)	4/33 (12.1)	0.7207
B (%)	33/45 (73.3)	11/12 (91.7)	22/33 (66.7)	0.0935
C (%)	6/45 (13.3)	0/12 (0.00)	6/33 (18.2)	-
D (%)	1/45 (2.2)	0/12 (0.00)	1/33 (3.0)	-
Histology				
No (%)	19/45 (42.2)	6/12 (50.0)	13/33 (39.4)	0.7340
Yes (%)	26/45 (57.7)	6/12 (50.0)	20/33 (60.6)	

Variable	Overall	Female	Male	P-Value
Clinical				
No (%)	43/45 (95.6)	12/12 (100.0)	31/33 (93.9)	-
Yes (%)	2/45 (4.4)	0/12 (0.00)	2/33 (6.1)	
Alpha-fetoprotein measurement				
No (%)	8/45 (17.8)	2/12 (16.7)	6/33 (18.2)	0.9999
Yes (%)	37/45 (82.2)	10/12 (83.3)	27/33 (81.8)	
Imaging of choice				
Abdominal ultrasound (%)	12/44 (27.3)	4/11 (36.4)	8/33 (24.2)	0.4344
Computer Tomography (%)	31/44 (70.5)	7/11 (63.6)	24/33 (72.7)	0.5671
Magnetic Resonance (%)	1/44 (2.3)	0/11 (0.00)	1/33 (3.0)	-
Treatment duration (in days)				
n, Median (IQR)	43, 28.0 (0.00-162)	12, 19.0 (7.00-143)	31, 28.0 (0.00-189)	0.8261
n, Mean (SD)	43, 152 (291)	12, 122 (236)	31, 164 (312)	0.6823
n, Min, Max	43, (0-1377)	12, (0-835)	31, (0-1377)	
Reason for stopping treatment				
Advanced disease does not qualify for treatment (%)	2/45 (4.4)	0/12 (0.0)	2/33 (6.1)	-
Death (%)	15/45 (33.3)	6/12 (50.0)	9/33 (27.3)	0.1527
Medication side-effects (%)	3/45 (6.7)	1/12 (8.3)	2/33 (6.1)	0.7869
Patient lost to follow up (%)	5/45 (11.1)	0/12 (0.0)	5/33 (15.2)	-
Progression of disease (%)	20/45 (44.4)	5/12 (41.7)	15/33 (45.5)	0.8211
Outcome				
Died (%)	42/45 (93.3)	12/12 (100.0)	30/33 (90.9)	0.5535
Lost to follow up (%)	3/45 (6.7)	0/12 (0.00)	3/33 (9.1)	

Table 10: Clinical information of patients with advanced hepatocellular carcinoma treated with sorafenib from 2008-2016 at Charlotte Maxeke Johannesburg Academic Hospital by age-group.

Variable	Overall	<50	50+	P-Value
ECOG Performance Status				
0 (%)	6/45 (13.3)	4/20 (20.0)	2/25 (8.0)	0.2393
1 (%)	36/45 (80.0)	15/20 (75.0)	21/25 (84.0)	0.4533
2 (%)	3/45 (6.7)	1/20 (5.0)	2/25 (8.0)	0.6885
Child Pugh at Presentation				
A (%)	31/45 (68.9)	12/20 (60.0)	19/25 (76.0)	0.3357
B (%)	14/45 (31.1)	8/20 (40.0)	6/25 (24.0)	
Barcelona Clinic Liver Cancer Classification				

Variable	Overall	<50	50+	P-Value
A (%)	5/45 (11.1)	3/20 (15.0)	2/25 (8.0)	0.4578
B (%)	33/45 (73.3)	16/20 (80.0)	17/25 (68.0)	0.3657
C (%)	6/45 (13.3)	1/20 (5.0)	5/25 (20.0)	0.1413
D (%)	1/45 (2.2)	0/20 (0.0)	1/25 (4.0)	-
Histology				
No (%)	19/45 (42.2)	9/20 (45.0)	10/25 (40.0)	0.7697
Yes (%)	26/45 (57.8)	11/20 (55.0)	15/25 (60.0)	
Clinical				
No (%)	43/45 (95.6)	20/20 (100.0)	23/25 (92.0)	-
Yes (%)	2/45 (4.4)	0/20 (0.0)	2/25 (8.0)	
Alpha-fetoprotein measurement				
No (%)	8/45 (17.8)	3/20 (15.0)	5/25 (20.0)	0.7157
Yes (%)	37/45 (82.2)	17/20 (85.0)	20/25 (80.0)	
Imaging of choice				
Abdominal ultrasound (%)	12/44 (27.3)	5/19 (26.3)	7/25 (28.0)	0.9011
Computer Tomography (%)	31/44 (70.5)	14/19 (73.7)	17/25 (68.0)	0.6823
Magnetic Resonance (%)	1/44 (2.3)	0/19 (0.0)	1/25 (4.0)	-
Treatment duration (in days)				
n, Median (IQR)	43, 28.0 (0.00-162)	19, 28.0 (14.0-123)	24, 23.5 (0.00-176)	0.3921
n, Mean (SD)	43, 152 (291)	19, 189 (361)	24, 123 (225)	0.4917
n, Min, Max	43, (0-1377)	19, (0-1377)	24, (0-1030)	
Reason for stopping treatment				
Advanced disease does not qualify for treatment (%)	2/45 (4.4)	0/20 (0.00)	2/25 (8.0)	-
Death (%)	15/45 (33.3)	7/20 (35.0)	8/25 (32.0)	0.8320
Medication side-effects (%)	3/45 (6.7)	0/20 (0.0)	3/25 (12.0)	-
Patient lost to follow up (%)	5/45 (11.1)	3/20 (15.0)	2/25 (8.0)	0.4578
Progression of disease (%)	20/45 (44.4)	10/20 (50.0)	10/25 (40.0)	0.5023
Outcome				
Died (%)	42/45 (93.3)	19/20 (95.0)	23/25 (92.0)	0.9999
Lost to follow up (%)	3/45 (6.7)	1/20 (5.0)	2/25 (8.0)	

Clinical characteristics by age and gender are described in **Tables 9** and **10**. The majority of patients exhibited ECOG performance status of 1 (80.0% (36/45)) Child-Pugh presentation A (68.9% (31/45)) and a BCLC B (73.3% 33/45). Patients aged above 50 years of age showed a higher proportion of ECOG 1 performance status (84.0% vs 75.0% p=0.4533) and a Child-Pugh Classification A at presentation (76.0% vs 60,0% p=0.3357) compared to those younger

than 50 years of age. On the other hand, patients younger than 50, had a higher proportion of BCLC B (80.0% vs 68.0% p=0.3657) and stopping treatment due to progression of disease (50.0% vs 40.0%; p=0.5023). The most common mode of diagnosis was through alpha-fetoprotein measurement (82.2% (37/45)) followed by histology (57.8% (26/45)) and lastly clinical (4.4% (2/45)). Computer tomography (70.5% (31/45)) was the diagnostic imaging of choice.

3.1 Treatment Outcomes

The treatment outcomes of the 45 enrolled patients are illustrated in **Figures 4** and **5** respectively. **Figure 4** displays the time to treatment discontinuation by gender, revealing that females had higher probability of discontinuation due to death than males although not statistically significant. Conversely, **Figure 5** shows no significant difference in the probability of treatment discontinuation due to death by age group.

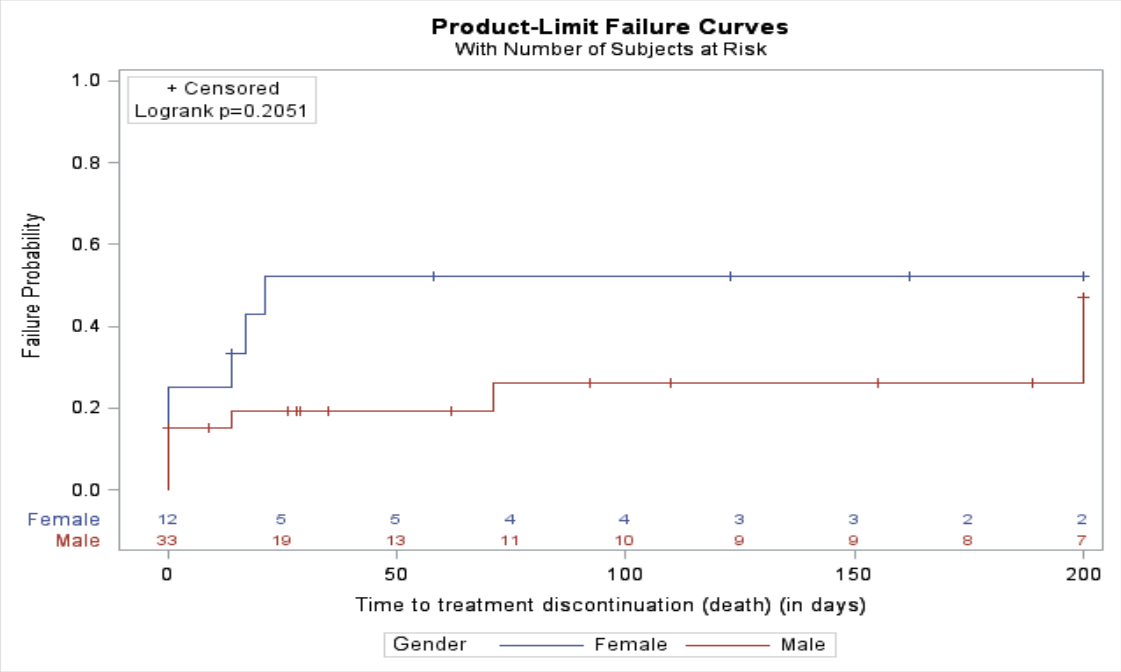

Figure 4: Time to treatment discontinuation (death) of patients with advanced hepatocellular carcinoma treated with sorafenib from 2008-2016 at Charlotte Maxeke Johannesburg Academic Hospital by gender.

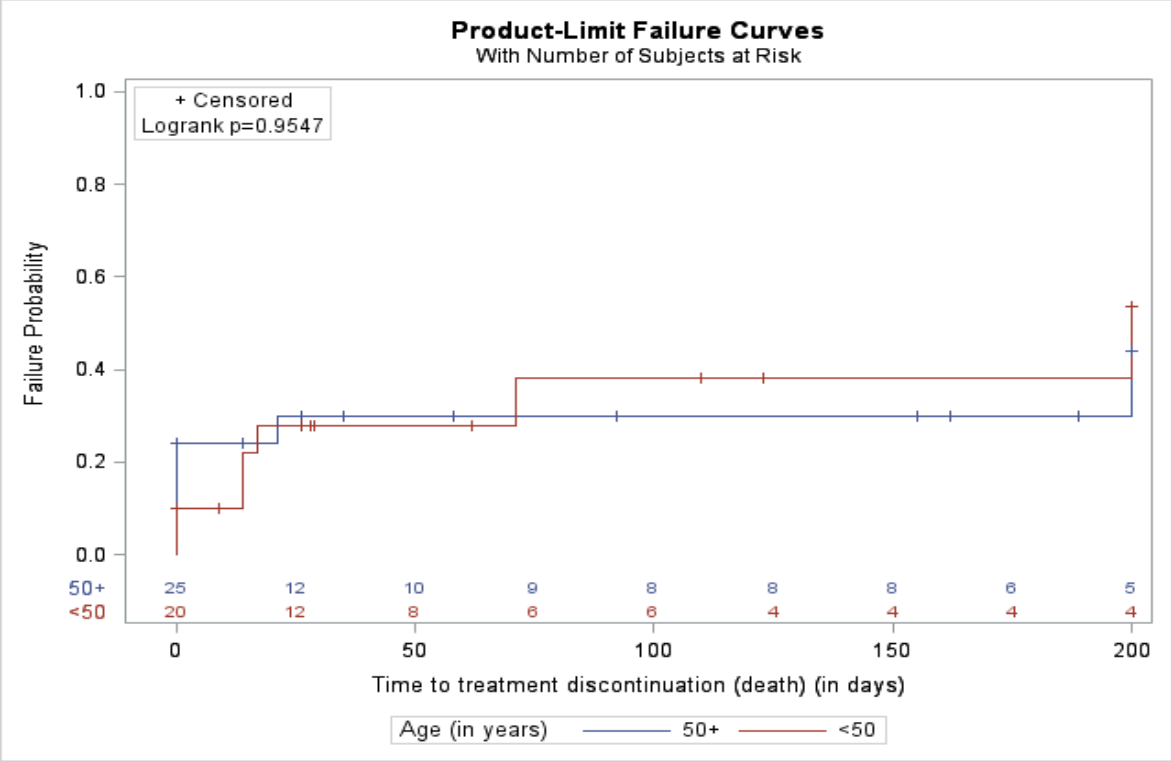

Figure 5: Time to treatment discontinuation to (death of patients with advanced hepatocellular carcinoma treated with sorafenib from 2008-2016 at Charlotte Maxeke Johannesburg Academic Hospital by age.

Most of the deaths occurred within the first 30 days of treatment and the longest surviving patient remained on treatment for up to 45 months. The mean time to death was 14.8 (SD 2.8) days for females and 153.1 (SD 16.7) days for males. By age group, the mean time to death was 133.4 (SD 23.9) days for patients younger than 50 and 141.5 (SD 201.) days for those age 50 and above. Adverse events in the form of treatment intolerance with nausea and vomiting, and the development of hand-foot syndrome were observed in 3 out of 45 patients, resulting in

treatment discontinuation for 1 patient. For detailed clinical information of patients with advanced hepatocellular carcinoma treated with sorafenib from 2008-2016 at Charlotte Maxeke Johannesburg Academic Hospital by gender and age-group (see **Appendices 1** and **2**).

Chapter 4: Discussion

HCC stands as the sixth most common cancer worldwide, and its incidence is increasing. Unfortunately, in Sub-Saharan Africa (SSA), due to underdiagnosis and a lack of population-based comprehensive cancer registries, the true incidence of HCC is likely underreported (1-3). Sorafenib has emerged as the primary systemic chemotherapy for patients diagnosed HCC, offering improved survival outcomes. However, in most developing countries, late diagnosis and limited access to treatments contribute to HCC becoming a significant public health burden (4).

Comparison between SHARP Trial with a median OS 10.7 months, and the Asian Pacific Trial with median OS was 6.5 months, showed poorer outcomes in the Asian Pacific Trial although both studies reported improved overall median survival with sorafenib as treatment (35). In our study the median overall survival was found to be 32 days, lower than the SHARP Trial and Asian Pacific Trial, this discrepancy can be attributed to late clinical presentation, and the advanced liver disease status of enrolled patients, as most of them presented with Child-Pugh A (68.89%) and BCLC B (73.3%) unlike the Asian-Pacific region study (38). The advanced disease stage likely led to rapid disease progression, early treatment discontinuation and higher mortality.

The mean time to disease progression was 14.8 days (SD 2.8) for females and 153.6 days for males (SD 16.7) suggesting a survival advantage for males who received treatment. However,

the small sample size limits the ability to draw meaningful conclusions. On average, males survived an additional 90 days. Remarkably, one patient demonstrated long-term tumour response and received treatment for 45 months before experiencing clinical deterioration and progression. This finding suggests that certain patients can derive substantial benefits from sorafenib therapy. Further research into clinicopathological features is needed to identify which patients could benefit the most from this treatment in the future.

The median age at which HCC presented in our study was 45 years, showing a difference from both SHARP Trial (65 years of age) and Asian Pacific (51 years of age). Notably, the youngest patient enrolled in our study was 18 years of age. This age difference is consistent with a cohort study on HCC in Malawi of 24 patients, where the median age of presentation was 42 years. The earlier age of onset of HCC in SSA coupled with advanced clinical presentation (39) can be attributed to dominant risk factor HBV infection, which is prevalent in many SSA countries usually acquired at ages less than 5 years. However, it is worth mentioning that in most of these countries, hepatitis B vaccination has been introduced.

Different risk factors contribute to the development of HCC worldwide. Our study demonstrated chronic HBV infection as the main risk factor, accounting for 48.8% of cases, followed by ethanol use at 17.9%. This finding contrasts with the SHARP Trial, where HCV was the primary factor, and the Asian Pacific Trial, where HBV dominated. HBV infection's aggressive impact on the hepatocytes, inflammation and fibrosis leading to cirrhosis likely plays a role in association with HCC development (40).

Our study identified a possible relationship between chronic HBV and HIV co-infection as additional risk factors that may contribute to the rapid progression of HCC in younger patients.

Previous studies have reported on the implication of HIV co-infection in the progression of HCC and several mechanisms have been proposed to explain this association. Firstly, hepatotoxic damage resulting from anti-retroviral treatment may play a role in accelerating HCC progression in HIV-positive individuals (41). Secondly, HIV infection itself can lead to increased inflammation and fibrosis in the liver. Chronic inflammation is a well-known risk factor for the development and progression of HCC and the HIV-related inflammation may accelerate the process in co-infected individuals (42).

Moreover, patients who are virologically unsuppressed with HIV may experience more severe liver damage and inflammation, further promoting HCC progression (41). Poorly controlled HIV infection can lead to higher viral replication rates, potentially worsening liver health and HCC outcomes (41). Given the potential impact of HIV co-infection on HCC progression and treatment response, further studies are warranted, especially in endemic areas with a high prevalence of both infections. Assessing the specific impact of HIV on the clinical presentation and progression of HCC in the context of sorafenib treatment is crucial to optimizing therapeutic strategies (41).

4.1 Study limitations

It is important to recognize that it was a retrospective study based on patients' medical records, which introduces the possibility of missing data. Due to the nature of the data collection, information regarding medication compliance and adverse effect might have been under-reported as it relied on clinician-dependent documentation. Despite these limitations, the study sample size although small, provided valuable insights notably highlighting the high prevalence of HBV infection as the primary risk factor of HCC in the Southern African setting, the synergic relationship between HBV and HIV co-infection and accelerated development of

HCC, the younger age of presentation and advanced clinical presentation which can all contributed to the HCC prognosis.

4.2 Conclusion

Although not statistically significant this study provides a good descriptive picture of HCC within our setting, it shows the necessity for larger prospective studies, for more robust conclusions on clinical characteristics, evaluation of available treatments, and the response to those treatments in the African continent. Given, the higher incidence of hepatitis B infection in the African continent, there is an urgent need for comprehensive follow-up programs to enable early detection and potentially offer early curative treatment for HCC. As primary prevention measures, an emphasis on immunization of children against hepatitis B infection can significantly reduce the incidence of HCC. Additionally, the establishment and utilisation of cancer registries in Africa are crucial for accurate reporting and monitoring of the prevalence of HCC in the continent. Larger prospective studies are necessary to provide a better conclusion on the use of sorafenib in HCC in the African continent.

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Appendices

Appendix 1: Clinical information of patients with advanced hepatocellular carcinoma treated with sorafenib from 2008-2016 at Charlotte Maxeke Johannesburg Academic Hospital by gender.

Variable	Overall	Female	Male	P-Value
ECOG Performance Status				
0 (%)	6/45 (13.33)	2/12 (16.67)	4/33 (12.12)	0.6916
1 (%)	36/45 (80.00)	10/12 (83.33)	26/33 (78.79)	0.7360
2 (%)	3/45 (6.67)	0/12 (0.00)	3/33 (9.09)	-
Child Pugh at Presentation				
A (%)	31/45 (68.89)	9/12 (75.00)	22/33 (66.67)	0.7254
B (%)	14/45 (31.11)	3/12 (25.00)	11/33 (33.33)	
Barcelona Clinic Liver Cancer Classification				
A (%)	5/45 (11.11)	1/12 (8.33)	4/33 (12.12)	0.7207
B (%)	33/45 (73.33)	11/12 (91.67)	22/33 (66.67)	0.0935
C (%)	6/45 (13.33)	0/12 (0.00)	6/33 (18.18)	-
D (%)	1/45 (2.22)	0/12 (0.00)	1/33 (3.03)	-
Histology				
No (%)	19/45 (42.22)	6/12 (50.00)	13/33 (39.39)	0.7340
Yes (%)	26/45 (57.78)	6/12 (50.00)	20/33 (60.61)	
Clinical				
No (%)	43/45 (95.56)	12/12 (100.0)	31/33 (93.94)	-
Yes (%)	2/45 (4.44)	0/12 (0.00)	2/33 (6.06)	
Alpha-fetoprotein measurement				
No (%)	8/45 (17.78)	2/12 (16.67)	6/33 (18.18)	0.9999
Yes (%)	37/45 (82.22)	10/12 (83.33)	27/33 (81.82)	
Imaging of choice				
Abdominal ultrasound (%)	12/44 (27.27)	4/11 (36.36)	8/33 (24.24)	0.4344
Computer Tomography (%)	31/44 (70.45)	7/11 (63.64)	24/33 (72.73)	0.5671
Magnetic Resonance (%)	1/44 (2.27)	0/11 (0.00)	1/33 (3.03)	-
Treatment duration (in days)				
n, Median (IQR)	43, 28.0 (0.00-162)	12, 19.0 (7.00-143)	31, 28.0 (0.00-189)	0.8261
n, Mean (SD)	43, 152 (291)	12, 122 (236)	31, 164 (312)	0.6823
n, Min, Max	43, (0-1377)	12, (0-835)	31, (0-1377)	
Reason for stopping treatment				
Advanced disease does not qualify for treatment (%)	2/45 (4.44)	0/12 (0.00)	2/33 (6.06)	-
Death (%)	15/45 (33.33)	6/12 (50.00)	9/33 (27.27)	0.1527
Medication side-effects (%)	3/45 (6.67)	1/12 (8.33)	2/33 (6.06)	0.7869

Variable	Overall	Female	Male	P-Value
Patient lost to follow up (%)	5/45 (11.11)	0/12 (0.00)	5/33 (15.15)	-
Progression of disease (%)	20/45 (44.44)	5/12 (41.67)	15/33 (45.45)	0.8211
Outcome				
Died (%)	42/45 (93.33)	12/12 (100.0)	30/33 (90.91)	0.5535
Lost to follow up (%)	3/45 (6.67)	0/12 (0.00)	3/33 (9.09)	

Appendix 2: Clinical information of patients with advanced hepatocellular carcinoma treated with sorafenib from 2008-2016 at Charlotte Maxeke Johannesburg Academic Hospital by age-group.

Variable	Overall	<50	50+	P-Value
ECOG Performance Status				
0 (%)	6/45 (13.33)	4/20 (20.00)	2/25 (8.00)	0.2393
1 (%)	36/45 (80.00)	15/20 (75.00)	21/25 (84.00)	0.4533
2 (%)	3/45 (6.67)	1/20 (5.00)	2/25 (8.00)	0.6885
Child Pugh at Presentation				
A (%)	31/45 (68.89)	12/20 (60.00)	19/25 (76.00)	0.3357
B (%)	14/45 (31.11)	8/20 (40.00)	6/25 (24.00)	
Barcelona Clinic Liver Cancer Classification				
A (%)	5/45 (11.11)	3/20 (15.00)	2/25 (8.00)	0.4578
B (%)	33/45 (73.33)	16/20 (80.00)	17/25 (68.00)	0.3657
C (%)	6/45 (13.33)	1/20 (5.00)	5/25 (20.00)	0.1413
D (%)	1/45 (2.22)	0/20 (0.00)	1/25 (4.00)	-
Histology				
No (%)	19/45 (42.22)	9/20 (45.00)	10/25 (40.00)	0.7697
Yes (%)	26/45 (57.78)	11/20 (55.00)	15/25 (60.00)	
Clinical				
No (%)	43/45 (95.56)	20/20 (100.0)	23/25 (92.00)	-
Yes (%)	2/45 (4.44)	0/20 (0.00)	2/25 (8.00)	
Alpha-fetoprotein measurement				
No (%)	8/45 (17.78)	3/20 (15.00)	5/25 (20.00)	0.7157
Yes (%)	37/45 (82.22)	17/20 (85.00)	20/25 (80.00)	
Imaging of choice				
Abdominal ultrasound (%)	12/44 (27.27)	5/19 (26.32)	7/25 (28.00)	0.9011
Computer Tomography (%)	31/44 (70.45)	14/19 (73.68)	17/25 (68.00)	0.6823
Magnetic Resonance (%)	1/44 (2.27)	0/19 (0.00)	1/25 (4.00)	-

Variable	Overall	<50	50+	P-Value
Treatment duration (in days)				
n, Median (IQR)	43, 28.0 (0.00-162)	19, 28.0 (14.0-123)	24, 23.5 (0.00-176)	0.3921
n, Mean (SD)	43, 152 (291)	19, 189 (361)	24, 123 (225)	0.4917
n, Min, Max	43, (0-1377)	19, (0-1377)	24, (0-1030)	
Reason for stopping treatment				
Advanced disease does not qualify for treatment (%)	2/45 (4.44)	0/20 (0.00)	2/25 (8.00)	-
Death (%)	15/45 (33.33)	7/20 (35.00)	8/25 (32.00)	0.8320
Medication side-effects (%)	3/45 (6.67)	0/20 (0.00)	3/25 (12.00)	-
Patient lost to follow up (%)	5/45 (11.11)	3/20 (15.00)	2/25 (8.00)	0.4578
Progression of disease (%)	20/45 (44.44)	10/20 (50.00)	10/25 (40.00)	0.5023
Outcome				
Died (%)	42/45 (93.33)	19/20 (95.00)	23/25 (92.00)	0.9999
Lost to follow up (%)	3/45 (6.67)	1/20 (5.00)	2/25 (8.00)	

Appendix 3: Ethics Clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Leila Bila

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M201034

NAME: (Principal Investigator)	Dr Leila Bila
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Clinical characteristics and outcomes of patients with hepatocellular carcinoma treated with sorafenib at Charlotte Maxeke Johannesburg Academic Hospital: a retrospective study from 2008-2016
DATE CONSIDERED:	30/10/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Dineo Tshabalala and Prof Paul Ruff
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/12/2020

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore be due in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signa[redacted]

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES