Diplomarbeit

Hepatocellular Carcinoma

Changes in the epidemiology of Hepatocellular Carcinoma at *Klinikum Klagenfurt* 2012-2023

eingereicht von

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Graz, am 13.09.2023 Heleen Emmer eh.

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Zusammenfassung

Hintergrund: Das hepatozelluläre Karzinom (HCC) ist eine der führenden krebsbezogenen Todesursachen weltweit. Zudem stellt es nach wie vor eine große Belastung für das Gesundheitssystem dar. Die Inzidenz des HCC nimmt trotz vermehrter präventiver Maßnahmen global weiterhin zu.

Ziel: Ziel dieser Studie war es epidemiologische Veränderungen in der Ätiologie und den Endergebnissen von HCC-Patient*innen am Klinikum Klagenfurt am Wörthersee zu beobachten und zu analysieren.

Methoden: Es handelt sich um eine monozentrische Kohorten-Beobachtungsstudie. Die Daten wurden retrospektiv aus der elektronischen Patientendatenbank des Klinikum Klagenfurt erhoben. Es wurden zwei Zeiträume (2012-2017 und 2018-2023) gegenübergestellt, um einen Vergleich zwischen diesen beiden Intervallen zu ermöglichen.

Ergebnisse: Im zweiten Zeitraum wurden mehr Patient*innen im Klinikum diagnostiziert und behandelt, was der allgemein steigenden Inzidenz entspricht. Die Inzidenzrate von HCC blieb bei Männern und Frauen im Laufe der Zeit ähnlich, wobei Männer ein fünfmal höheres Risiko hatten, an HCC zu erkranken. Das mediane Diagnosealter betrug 72,5 Jahre. Die Patient*innen waren im zweiten Zeitraum durchschnittlich 2 Jahre jünger als im ersten. Alkohol blieb die Hauptursache für HCC, und es wurde keine statistisch signifikante Veränderung im Laufe der Zeit beobachtet, wobei ein Anstieg von NASH-Erkrankungen zu beobachten war. Die Überlebenszeit für HCC-Patient*innen blieb trotz Änderungen der Behandlungsstrategien und der Verfügbarkeit neuer systemischer Behandlungen ähnlich. Fast die Hälfte der Patient*innenpopulation hatte zum Zeitpunkt der Diagnosen kein erhöhtes alpha-Fetoprotein (AFP). Insgesamt wurde jedoch in den letzten Jahren ein Anstieg der HCC-Patient*innen ohne Leberzirrhose identifiziert. NASH war die häufigste zugrunde liegende Ätiologie bei HCC-Patient*innen ohne Leberzirrhose.

Beurteilung: Das hepatozelluläre Karzinom ist nach wie vor ein wichtiges Gesundheitsproblem unserer Gesellschaft. Die Zahl der Patient*innen mit HCC und ohne Leberzirrhose nimmt stetig zu. Bei Patient*innen ohne Leberzirrhose ist der NASH aufgrund von Life-Style Erkrankungen eine wichtige ätiologische Rolle zuzuschreiben. Es sollten weiterhin große Anstrengungen unternommen werden, um HCC zu verhindern und gefährdete Bevölkerungsgruppen zu screenen.

Abstract

Background: Hepatocellular carcinoma is one of the leading causes of cancer-related deaths and remains a major burden on health-care systems worldwide. The incidence of HCC continues to rise globally, despite preventative efforts being made.

Aims: This study aimed to investigate epidemiological changes observed in the aetiology and outcomes of HCC patients at *Klinikum* Klagenfurt *am Wörthersee* between 2012 and 2023.

Methods: This was a single-centre cohort observational study. Data was collected retrospectively from the hospitals' electronic patient database. Two time-periods (2012-2017 and 2018-2023) were created to enable comparison between the two intervals.

Results: More patients were diagnosed with HCC during the second time-period, proving that the incidence of HCC is rising. The incidence rate of HCC remained similar in males and females over time, with males having a 5 times higher risk to develop HCC. The median age of diagnosis was 72.5 years. Patients were on average 2 years younger in the second time-period compared to the first. Alcohol remained the leading underlying cause of HCC and no statistically significant change was seen over time, although a rise in the number of NASH cases was observed. The survival time for HCC patients remained similar, despite changes in management strategies and the availability of new systemic treatments. Nearly half of the patient population did not have a raised AFP at the time of diagnosis. Overall, an increasing number of HCC patients without liver cirrhosis were identified during recent years. NASH was the most common underlying aetiology in HCC patients without liver cirrhosis.

Conclusions: Hepatocellular carcinoma continues to be an important health concern in our society. The number of patients with HCC and no liver cirrhosis is steadily increasing. In patients without liver cirrhosis, NASH due to underlying life-style diseases, played an important aetiological role. Continued efforts should be made to prevent HCC and to screen at-risk population groups.

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1. List of Acronyms

AFP	alpha-fetoprotein
AFLD	Alcoholic Fatty Liver Disease
AJCC	American Joint Committee on Cancer
ALBI	Albumin-Bilirubin Score
BCLC	Barcelona Clinic Liver Cancer system
BMI	Body Mass Index
CCC	Cholangiocarcinoma
CI	Confidence Interval
CLIP	Cancer of the Liver Italian Program
DAA	Direct-acting antiviral
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
EU	European Union
GLOBOCAN	Global Cancer Observatory
HBeAg	Hepatitis B e-antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDI	Human Development Index
HDV	Hepatitis delta virus
HBsAg	Hepatitis B surface antigen
INR	International Normalized Ratio
LI-RADS	Liver Imaging Reporting and Data System
MELD score	Model for end-stage liver disease score
MVI	Microvascular invasion
MWA	Microwave ablation
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
OS	Overall survival
PS	Performance status
RFA	Radiofrequency ablation
RNA	Ribonucleic acid

SD	Standard deviation
TACE	Trans-arterial chemoembolization
TERT	telomerase reverse transcriptase
TNM	Tumour (size) Node (lymph node spread) Metastasis
UCSF	University of California, San Francisco
US	Ultrasonography
WHO	World Health Organization

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4. Introduction

4.1. Background and Epidemiology

Hepatocellular carcinoma (HCC) is a type of primary liver malignancy. The majority of (80-90%) primary liver malignancies are attributed to HCC. HCC mainly develops in patients with underlying liver disease such as liver cirrhosis. [1]

HCC is one of the leading causes of cancer-related deaths in adults, globally. According to the World Health Organization's (WHO), Global Cancer Observatory (GLOBOCAN) a total of 905 677 new cases of liver cancer were recorded in 2020. This accounts for 4.7% of all new cancer cases in 2020. 830 180 deaths due to liver cancer were documented in 2020, which attributes to 8.3% of all cancer related deaths. [2]

Liver cancer is currently the sixth most common cancer worldwide. In 46 countries, liver cancer was one of the three most common causes of cancer-related deaths. It is estimated that the burden of liver cancer will increase over the course of the next 20 years. [3]

In Central and Eastern Europe, a total number of 24 782 new cases were recorded, as well as 23 002 deaths due to primary liver cancer. In Western Europe, a total of 26 128 new cases occurred in 2020, with 23 657 subsequent deaths. [2] The highest incidence of liver cancer was documented in Eastern-Asia (keeping in mind that 21.5% of the world population resides in Eastern-Asia). It is estimated that approximately 54% of all new cases and deaths from primary liver cancer took place in Eastern-Asia. [3]

A clear discrepancy between males and females is apparent, where males have a higher incidence and mortality compared to females with primary liver cancer. This imparity was visible across all geographical regions listed in the GLOBOCAN 2020 database. The highest rates of liver cancer cases and deaths were found in countries with a high Human Development Index (HDI). [3]

It is predicted that the number of new cases of primary liver cancer will rise drastically between 2020 and 2040. 1.4 million new diagnoses are anticipated to occur in 2040. [3]

In Austria specifically, a total number of 1.114 new liver cancer cases were documented in the 2020 GLOBOCAN database, with 993 deaths reported. Liver cancer ranked as the 14th most commonly diagnosed cancer and obtained the 6th place for highest number of deaths caused by cancer in Austria. [4] In a study published by

Hucke et al. about the Epidemiology of Hepatobiliary Carcinomas in Austria between the years 2010 and 2018 a total of 7146 individuals were diagnosed with HCC of which 75% were male and 25% were female. Patients were on average diagnosed at the age of 70 years with 8% of patients having distant metastases at the time of presentation. The 1-year survival rate was 46% for men and 43% for women and an 8% 5-year survival rate for both sexes. [5]

4.2. Etiology and Risk Factors

Hepatocellular carcinoma (HCC) is responsible for an estimated 90% of primary liver malignancies. [6] HCC is rarely found in patients with no background of underlying liver disease. Liver cirrhosis, regardless of the cause, significantly increases the risk of developing HCC. The prevalence of various risk factors differs between countries, regions, sex, age, and degree of liver damage. Globally seen, Hepatitis B Virus (HBV) is still the leading cause of HCC. [1] HBV infection is especially prevalent in South-East Asian countries, as well as in sub-Saharan Africa. [3] In the West however, Non-alcoholic steatohepatitis (NASH), which is associated with metabolic disease, is rapidly becoming one of the major role-players in the aetiology of HCC. [6]

4.2.1. Liver Cirrhosis

Chronic liver damage leads to liver cirrhosis. HCC is the principal cause of death in patients with liver cirrhosis, with an incidence of 1-6% annually. [6] Cirrhosis develops when hepatocytes suffer damage and become necrotic, this promotes an inflammatory response, and the subsequent repair process leads to fibrosis (a surplus of connective tissue). Cirrhosis destroys the architecture of the liver tissue and inevitably leads to impaired liver function. [7]

The causes of liver cirrhosis can be grouped into the following categories: [7]

- Inflammatory: Chronic viral hepatitis B/D, C and other less common causes of inflammation which include autoimmune hepatitis, parasitic infections, primary biliary cholangitis and primary sclerosing cholangitis.
- Hepatotoxicity: Chronic excessive alcohol consumption, certain medications, or the ingestion of Aflatoxins (produced by *Aspergills* fungus species).

- Metabolic Diseases: e.g., non-alcoholic steatohepatitis, haemochromatosis, α1-antitrypsin deficiency
- Vascular abnormalities: e.g., Budd-Chiari syndrome

In Germany and Austria, Alcoholic Fatty Liver Disease (AFLD) accounts for the most cases of liver cirrhosis. [7]

4.2.2. Hepatitis B and D virus infection

HBV is responsible for the majority of HCC cases in Asia and Africa. [8] According to the WHO factsheet on Hepatitis B, it was estimated that there were 296 million people living with chronic HBV infection in 2019. Approximately 1.5 million new cases occur each year. [9]

HBV is a type of DNA virus that has the ability to integrate itself into the host genome and generate mutations that lead to oncogenic activation. [10] The HBV virus is not a cytopathic virus and causes tissue damage through a cell-mediated immune response. [11] HCC may evolve from chronic HBV infection without the presence of cirrhosis. [12]

Risk factors of developing HCC in patients with chronic HBV infection aside from liver cirrhosis include:

- A high HBV DNA viral load (≥10 000 copies/mL) [13]
- Positive HBeAg [11]
- HBsAg levels >1000 IU/mL [11]
- Coinfection with hepatitis C and D [14, 15]

Universal vaccination programs have the potential to significantly decrease the incidence rate of HCC. The WHO aims to have 90% of the world's population vaccinated by 2030, with the ultimate goal of eradicating HBV. HBV vaccination has also proven to be exceptionally cost-effective in the long-run by reducing the incidence of HCC and HCC-related deaths. [16] Although great strides have been made with global vaccination programs; it has unfortunately become apparent that this goal is unlikely be reached within the proposed time frame.

Hepatitis delta virus (HDV) is a small RNA virus that needs the HBsAg in order to replicate. [17] HDV is found in nearly 5% of individuals world-wide who are infected with chronic HBV. [18] HBV/HDV co-infection causes more severe hepatic disease and

leads to an increased risk of developing cirrhosis. It has also been proven that HBV and HDV co-infection is associated with a higher risk of HCC, opposed to HBV infection only. [17]

4.2.3. Hepatitis C virus infection

In North America, other Western countries and Japan, chronic infection with **Hepatitis C Virus (HCV)** remains one of the most common underlying liver diseases in patients with HCC. As opposed to HBV, HCV is a RNA virus that does not incorporate itself into the host genome; therefore HCC almost exclusively develops in patients with chronic hepatic damage or cirrhosis. [6] Patients infected with HCV, have a 15 to 20 times higher risk to develop HCC compared to HCV-negative individuals. Over the course of a 30-year period, the rate of HCC development varies between 1-3% in HCV infected patients. Other co-existing risk factors could increase the risk of HCC development, such as alcohol and tobacco use, co-infection with HBV or HIV, diabetes mellitus, obesity, steatosis, age and sex. [20] In recent years, the use of direct-acting antiviral (DAA) therapy has shown very promising results in reducing the risk of HCC development. In patients with a sustained virological response (undetectable HCV RNA, 6 months after completing treatment), the risk of HCC development reduces by 50-80%. [21]

4.2.4. Lifestyle Factors

Alcohol – Chronic alcohol use disorder is a well-known risk factor for liver cirrhosis. Liver cirrhosis in its turn is an established predisposing factor for HCC. The estimated risk to develop HCC in patients with decompensated cirrhosis due to alcohol use is around 1% per year. It is however still possible for HCC to occur in patients with chronic alcohol use disorder without liver cirrhosis, meaning that a direct toxic effect might be possible. Drinking activates an inflammatory tumour marker, namely NF-kB which acts as a signalling pathway in promoting oncogenesis. [22] HCV and alcohol have a synergistic effect that nearly doubles the risk for HCC development. [23] In Austria, alcohol remains the number one cause of liver cirrhosis. Beer drinking especially, has become ingrained in the Austrian culture. It is estimated that the average Austrian consumes around 24.7g of pure alcohol on a daily basis and 11.4 litres of pure alcohol per year from the age of 15. Alcohol is easily accessible and affordable for most of the

population in Austria. 15% of Austrians consume alcohol to an extend that may be harmful to short- and long-term health. Austria is amongst the top 15 countries in the European Union (EU) for consuming the highest amount of alcohol per year. The EU have created initiatives to help combat this problem. According to the textbook of alcohol in Austria, the number of hospital admission for alcohol dependency have steadily declined over the past 10 years. [24]

Tobacco – It has been proven that smoking is associated with the development of liver cancer, along with many other cancers. [25]

4.2.5. Metabolic Factors

Nonalcoholic fatty liver disease (NAFLD) – This disease process starts with a nonalcoholic fatty liver (NAFL) which may worsen and develop into nonalcoholic steatohepatitis (NASH). The difference between these two entities is the presence of hepatic inflammation associated with NASH. Patients with NAFLD are often found to also suffer from other components of the metabolic syndrome, such as obesity, diabetes, hypertension, and hypercholesterolemia. NASH is rapidly becoming one of the most common causes of HCC in Western countries. HCC mostly develops on a background of liver cirrhosis induced by NASH, but can also originate without the presence of cirrhosis. [26]

4.2.6. Environmental Risk Factors

Aflatoxin B1 – Aflatoxin is a type of mycotoxin with carcinogenic potential, that has been associated with HCC. It is mainly produced by *Aspergillus flavus* and *Aspergillus parasiticus*. These mold species thrive in warm, moist conditions. They are ingested by contaminated foods such as wheat, rice, corn, peanuts etc. Aflatoxin contamination is especially a problem in Asia and Africa. [27]

4.2.7. Age and Sex

Age – Individuals older than 70 years of age have a higher risk to develop HCC. The incidence of HCC is found to be lower amongst younger adults. HCC is rarely seen in patients below the age of 40. [28] This is also proven to be true within the Austrian population. According to data collected from the Austrian National Cancer Registry in a recent study by Hucke et al., the average age at time of diagnosis was 70 years. [5]

Sex – The incidence of HCC is higher amongst males than females. Internationally the male to female ratio is around 2-3:1. [6] Oestrogen has a protective and anti-cancer effect on the liver. [29] In Austria only one quarter of patients diagnosed with HCC between 2010 and 2018 were female. The age adjusted incidence rate was 5 times higher for males compared to females. [5]

4.3. Pathology

4.3.1. Molecular Pathology

The molecular pathophysiology of HCC is a complex process with multiple steps involved. The development of HCC on the background of cirrhosis follows a number of events that starts with low-grade dysplastic nodules, which have the potential to transform into high-grade dysplastic nodules and eventually lead to early-stage HCC. [30]

Next generation sequencing technology has made great strides in uncovering cancer driver genes. Abnormal telomerase reverse transcriptase activation (TERT), through promoter mutations, accounts for the most frequently encountered genetic alteration seen in HCC. [31] HBV commonly inserts into the TERT promoter and thereby activates telomerase and other oncogenes. Mutations within TP53 frequently occurs when HBV infection in combination with Aflatoxin B1 ingestion takes place. In patients without HBV infection, who develop HCC, the Wnt-β-catenin signaling pathways are often activated through CTNNB1 mutations. [30]

In HCC secondary to NASH, oxidative stress, abnormal inflammatory responses and systemic endocrine changes all play a role in liver-specific changes, in which NASH promotes HCC. [6]

HCC is associated with chronic inflammation in 90% of cases. Here, the altered immune microenvironment plays an important role in enabling the development and progression of HCC. [30]

4.3.2. Anatomical Pathology

Hepatocellular carcinoma is a type of primary liver cancer that originates from hepatocytes. Hepatocytes account for the majority of cells that are found in the liver parenchyma and subsequently contribute the most to the total liver mass. According

to the WHO several forms of HCC exist, namely: fibrolamellar, scirrhous, clear cell, steatohepatitic, macro-trabecular, chromophone, neutrophil-rich and lymphocyte-rich. [33] Otherwise, the tumour can also be described by grade of differentiation, its morphology or by cell type (clear cell, small cell, spindle or giant cell).

The macroscopic/ gross pathology of HCC may vary, from of a well-circumscribed solitary nodule to multinodular disease diffusely spread throughout the liver. In Austria, the Edmonson and Steiner Classification System is widely used to grade the degree of tumour differentiation. This system grades tumours histologically from grade 1 tumours containing cells with abundant cytoplasm and minimal atypia to grade 4 cells showcasing marked nuclear pleomorphism. Major vascular invasions typically include the portal vein, hepatic vein or the inferior vena cava.

4.4. Clinical presentation and symptomatology

Since HCC mainly occurs in patients with underlying chronic liver disease, the presenting symptoms are frequently caused by the underlying liver cirrhosis, rather than the tumour itself.

Patients with compensated liver cirrhosis may either be asymptomatic or present with non-specific symptoms such as loss of weight, general malaise and anorexia. The clinical manifestation of patients with cirrhosis and hepatic decompensation may include jaundice, ascites, pruritis, upper gastrointestinal bleeding and eventually confusion due to hepatic encephalopathy. The physical signs of patients with chronic advanced liver disease may include skin findings such as jaundice, spider nevi, palmer erythema, clubbing, leukonychia, Muehrcke and Terry nails, rosacea and scratch marks due to pruritis. Upon inspection, gynecomastia, striae due to ascites or caput medusae may be found. In alcohol-related liver disease, Dupuytren’s contractures could be observed on the palmer aspect of the hands. [34] Other symptoms may include muscle cramps and diarrhoea. On clinical examination, a decrease in blood pressure, hepato-splenomegaly or hypogonadism might be noticed. On palpation a cirrhotic liver may be enlarged or decreased in size. A palpable liver with longstanding cirrhosis has a firm, nodular consistency. [35]

Symptomatic patients with advanced stages of HCC may present with mild upper abdominal pain, loss of weight or possibly even a palpable mass in the upper abdomen. Some patients may also present with features of a paraneoplastic syndrome such as

hypoglycaemia, erythrocytosis, hypercalcemia, diarrhoea or cutaneous manifestations like dermatomyositis. Less commonly, patients may present with signs and symptoms of intraperitoneal bleeding secondary to tumour rupture. Patients could also present at a late stage with lung, lymph node or bone metastases. [36]

4.5. Diagnosis

HCC is unfortunately often only diagnosed at a late stage of the disease; firstly, due to the lack of symptoms in the early stages and secondly due to insufficient screening and surveillance programs in high-risk patients in some parts of the world. [37]

4.5.1. Screening

Patients at high-risk for HCC, such as those with chronic liver cirrhosis or chronic HBV infection, should ideally be screened. Surveillance typically involves regular ultrasonography (US). Serum alpha-fetoprotein (AFP) monitoring may be used in conjunction with US and other imaging modalities to screen for HCC. [38] AFP is a glycoprotein used as a tumour marker for certain cancers. It is physiologically produced during gestation by the foetal liver and yolk sack; thereafter levels should decrease and be very low in adults. In patients with chronic liver disease, an AFP level of more than 10-20 ng/mL has a sensitivity of around 60% and specificity of approximately 70-80% for detecting HCC. Due to the low sensitivity and specificity, AFP cannot be used as the sole surveillance test for HCC. Ultrasonography is generally the preferred initial imaging modality, as it is cost-effective and readily available. Further imaging (contrasted CT, MRI with or without contrast or ultrasound with contrast) is warranted if a lesion is more than 1 cm in diameter, or if a lesion is less than 1 cm in diameter, but accompanied by a raised AFP level (>20 ng/mL). [39, 40] Bi-annual surveillance ultrasounds should be done in patients at risk for HCC.

4.5.2. Imaging

Multi-phase imaging such as quadruple-phase CT or contrast-enhanced MRI are the best imaging modalities for the diagnosis of lesions that are suspicious of HCC. On CT and MRI, HCC lesions may appear brighter compared to the surrounding liver tissue during the arterial phase (arterial hypervascularisation) and less bright during venous and delayed phases (venous wash-out). This phenomenon occurs due to the difference in

blood supply of the tumour, compared to the rest of the liver parenchyma. [42] The arterial enhancement and delayed wash-out patterns are considered to be the hallmark of HCC, with a sensitivity of 89% and specificity of 96%. The diagnosis of HCC can thus successfully be made without the need for histological confirmation through a biopsy. [43]

Liver lesions categorised according to LI-RADS in patients at risk for HCC			
Category	***Assessment***	***Diagnostic considerations***	***Action***
LR-1	Definitely benign	Haemangiomas with characteristic features/ cysts	Routine surveillance imaging
LR-2	Probably benign	Haemangiomas without characteristic features/ wedge-shaped arterioportal shunts	Routine surveillance imaging ± contrasted CT/ MRI
LR-3	Intermediate probability of malignancy	Dysplastic nodules, benign lesions without characteristic features/ rounded arterioportal shunts	- Repeat contrasted CT/ MRI or ultrasound in 3-6 months - Serial imaging 3-6 monthly while lesion remains LR-3 for ≥2 years or until conclusive diagnosis - If LR-3 for ≥ 2 years return to routine surveillance imaging
LR-4	Probably HCC	HCC with some characteristic features	Individualised management which may include further imaging, biopsy or treatment without conclusive diagnosis
LR-5	Definitely HCC	HCC with characteristic features	- HCC treatment - Biopsy not needed
LR-M	Probably/definitely malignant, not specific for HCC	Mostly malignant lesions (HCC without characteristic features or other malignancies)	Multidisciplinary consultation for individualised treatment plan
LR-NC	Not categorizable	Imaging insufficient	Repeat imaging with same or other modality in ≤3 months
LR-TIV	Tumour in vein	Soft tissue enhancement indicating tumour invasion of vein (either HCC or other malignancy)	Multidisciplinary consultation for individualised treatment plan including follow-up imaging or biopsy

Table 1 *Liver imaging reporting and Data System categorization, modified after [41]*

The Liver Imaging Reporting and Data System (LI-RADS) as described in *Table 1* was developed in order to help clinicians and radiologists categorize liver lesions in patients at risk for developing HCC in a standardized method. The higher the score, the higher the likelihood of HCC.

4.5.3. Liver biopsy / Histopathology

Around 10% of tumours lack the typical features of HCC on imaging. If HCC is clinically suspected, but the lesion appears atypical, a liver biopsy should be performed. In smaller lesions less than 2 cm in diameter, the diagnostic yield of an image-guided percutaneous liver biopsy can be quite low (around 70%). Some patients therefore may require multiple biopsies before a diagnosis can be made. One advantage of diagnosing HCC through a biopsy is that the tumour can be molecularly characterized. [44] HCC is one of the very few tumours that can be diagnosed solely based on radiological features. Not having a biopsy may however be of disadvantage when having to decide on the most appropriate course of treatment. Another problem of not having a biopsy arises in cases where mixed HCC and bile duct cancer occur within the same patient. Such cases can only be diagnosed histologically and requires a different therapeutic approach. Rarely, dangerous complications, such as tumour spread along the needle track, hemoperitoneum, pneumothorax etc. may take place during a liver biopsy.

4.6. Staging

4.6.1. Staging the severity of liver cirrhosis

In patients with cirrhosis, there are two commonly used models to predict prognosis/ severity.

4.6.1.1. Child-Pugh-Classification

This grading scale uses serum albumin, bilirubin, prothrombin time/ INR, the presence/ severity of ascites and encephalopathy to predict the survival rate of patients with cirrhosis and the likelihood of developing complications. A score of 5-6 points is considered Child-Pugh Class A with a 1-year survival rate of approximately 100%, Class B with 7-9 points and an 80% survival rate and lastly Class C with 10-15 points

and a 45% one-year survival rate. Child-Pugh Class C is associated with severe decompensated cirrhosis and patients have a higher change of variceal bleeding. [45] One limitation of the Child-Pugh score includes the fact that ascites and hepatic-encephalopathy are subjective variables, dependant on clinician experience. (See *Table 2* for Child-Pugh Classification.)

Parameter	**Points**		
	1	**2**	**3**
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
INR	<1.7	1.7-2.3	>2.3
Ascites	Absent	Mild	Moderate
Hepatic encephalopathy	None	Minimal (Grade 1-2)	Advanced (Grade 3-4)

Table 2 *Child-Pugh classification determining the severity of cirrhosis, created by the author*

4.6.1.2. MELD score

The model for end-stage liver disease (MELD) score is used to predict what the three-month survival rate for patients with liver cirrhosis will be. The score can range from 6-40 and is based on bilirubin, creatinine and more recently added sodium levels, INR, and the cause of cirrhosis. It is mainly used in the setting of patients awaiting liver transplantation. [46, 47] A high MELD score correlates with a poor liver function. [48] The MELD score was only later expanded to include serum sodium levels. Serum sodium levels were proven to be an important predictor of survival, as patients with hyponatremia have a higher mortality rate. [49]

4.6.2. HCC staging

A few staging systems have been introduced in an attempt to predict the outcome of patients with HCC. The four systems that are mainly used in clinical practice include the TNM system (tumour, node and metastasis), Okuda, Barcelona Clinic Liver Cancer system (BCLC) and the Cancer of the Liver Italian Program (CLIP) score. There is no

universal agreement on which system is the best to predict the survival of patients diagnosed with HCC. The Okuda, BCLC and CLIP systems might be more useful in patients with advance stages of HCC with poor liver function, undergoing nonsurgical treatment. [50, 51]

4.6.2.1. TNM-staging

The latest update and revision of the TNM system for HCC was done in 2017 by the American Joint Committee on Cancer (AJCC). T1 was divided into T1a solitary tumours less than 2 cm in diameter and T1b solitary tumours more than 2 cm without vascular invasion. T2 comprises of solitary tumours more than 2 cm, with vascular invasion or multiple tumours, but all less than 5 cm in diameter. T3 now includes multiple tumours of which at least one is more than 5 cm. T4 may be a single or multiple lesions of which one invades the portal/ hepatic vein or invades nearby organs. [52]

Primary tumour (T)			
TX		Primary tumour cannot be assessed	
T0		No evidence of primary tumour	
T1		Solitary tumour, no vascular invasion	
T2		Solitary tumour, vascular invasion present or multiple tumours all ≤ 5 cm	
T3a		Multiple tumours > 5 cm	
T3b		Single or multiple tumours any size involving major branch of portal or hepatic vein	
T4		Direct invasion of adjacent organs other than gallbladder/ perforation of visceral peritoneum	
Regional lymph nodes (N)			
NX		Regional lymph nodes cannot be assessed	
N0		No regional lymph node metastases present	
N1		Regional lymph node metastases present	
Distant metastases (M)			
M0		None	
M1		Present	
Anatomic stage			
Stage I	T1	N0	M0
Stage II	T2	N0	M0

Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Table 3 *TNM Staging of HCC, modified after [41]*

4.6.2.2. Okuda system

The Okuda system was developed in Japan to aid in the staging of HCC. It is a clinical scoring system that takes into account the degree of liver cirrhosis. It is divided into three stages and the criteria consists out of tumour size, the presence of clinically detectable ascites, albumin and bilirubin levels. The survival rate without treatment for patients with stage I disease is approximately 8.3 months, 2 months for stage II and 0.7 months for stage III. [53]

4.6.2.3. Cancer of the Liver Italian Program (CLIP) score

The CLIP score does not only look at the tumour morphology, but also incorporates the severity of liver cirrhosis. Alpha-fetoprotein (AFP) levels and the presence or absence of portal vein thrombosis also play a role in determining the score. The CLIP score is not use as often in clinical practice anymore, but may still be useful in patients undergoing non-surgical treatment such as trans-arterial chemoembolization (TACE). [54]

4.6.2.4. The Barcelona Clinic Liver Cancer (BCLC) staging

The BCLC, is the most frequently used staging system used in clinical practice today. The European Association for the Study of the Liver (EASL) recommends the BCLC system for the prediction of prognosis and the allocation of treatment. [55] The 2018 BCLC system for prognosis and treatment of HCC, has recently been updated to allow for major advances, in all aspects of HCC management to be included. In the new 2022 version of the BCLC model, liver function is determined more thoroughly and not just through the conventional Child-Pugh classification (see *Figure 1* for updated 2022 BCLC model). The albumin-bilirubin score and AFP concentration are examples of the additions made to better determine compensated liver function. The BCLC system

uses the Eastern Cooperative Oncology Group (ECOG) scale to determine performance status (PS). It ranges from a PS of 0, where a patient is fully active to a PS of 4 where a patient is bed/wheelchair-bound and completely dependent on others for activities of daily living. The PS assessment should entail cancer-related symptoms, not baseline symptoms that were already present before the time of HCC diagnosis. [56]

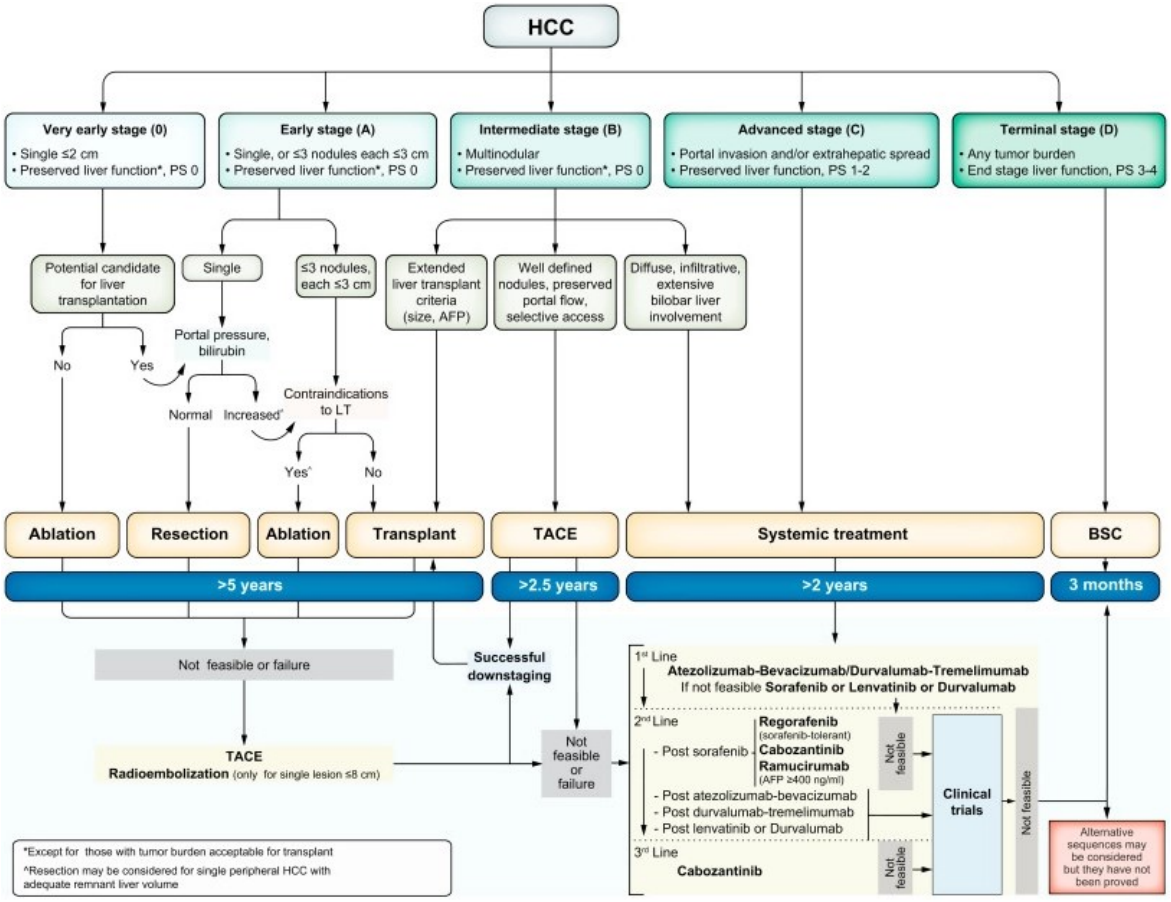

Figure 1 *The 2022 updated BCLC staging and treatment strategy, modified after [56]*

The BCLC stages will briefly be discussed individually below:

4.6.2.4.1. Very early stage (BCLC 0)

Very early stage (BCLC 0) HCC is described as a single tumour less than 2 cm in diameter, where no vascular invasion has taken place and no evidence of tumour spread beyond the liver can be found. The liver function is preserved in such a patient. These patients are fully active and show no symptoms due to the cancer itself. [56] The treatment option of choice is ablation. Ablation by means of radiofrequency or microwaves are considered the superior techniques in current clinical practice. Resection (partial hepatectomy) is another treatment option for BCLC 0 patients and

have similar outcomes. These patients should be evaluated for the possibility of a liver transplant. A liver transplant is beneficial, as HCC is known for its high recurrence rate. [57] If a patient however, is not fit for surgery or if a liver transplant is not attainable; then the patient should still undergo an ablation. [58].

4.6.2.4.2. Early stage (BCLC A)

Early stage (BCLC A) HCC is described as a single tumour, regardless of its size, or multifocal with a maximum of 3 nodules, none of which is more than 3 cm in diameter. Furthermore, no macrovascular invasion or tumour spread outside of the liver may be present and the patient should have a PS score of 0. In the case of a solitary nodule, the degree of portal hypertension should be assessed. [56] If no clinically significant portal hypertension is present, the patient should be considered for a resection. If there is a high risk of tumour recurrence, a possible liver transplantation should be taken into consideration. If a patient has raised portal hypertension, with no contraindications to liver transplantation, a transplant should be done. [59] Since the risk of recurrence is high for patients with a multifocal BCLC A tumour (3 or less nodules, each of which are equal to or less than 3 cm in diameter), the best course of action, if no contraindications are present, is to perform a liver transplant. If a liver transplant is not possible, radio-frequency ablation (RFA) should be considered. [60]

4.6.2.4.3. Intermediate stage (BCLC B)

Intermediate stage (BCLC B) HCC is defined as a multifocal/multinodular tumour, surpassing the BCLC A criteria. As in the above-mentioned stages, patients with stage BCLC B should also have preserved liver function, a PS of 0, with no invasion of major vessels and no extrahepatic spreading. In the new 2022 BCLC model, intermediate stage patients are divided into three groups. Group one includes patients with well-defined HCC tumour nodules. Patients in this subgroup are considered candidates for liver transplant if they meet the extended liver transplant criteria. Tumour size and AFP levels are also taken into account when deciding whether a liver transplant is feasible or not. [56] The second group, comprises of patients who are not eligible for liver transplant. Patients in this subgroup have well circumscribed tumour nodules, preserved portal blood flow and the availability of selective access to tumour arteries. These patients are good candidates for trans-arterial chemoembolization (TACE). If

TACE is not suitable or if it fails as a treatment option, systemic therapy should be offered in terms of a treatment stage migration. [61] Patients in the third BCLC B subgroup have diffused, infiltrative disease with substantial liver involvement. These patients will unfortunately not profit form TACE and systemic therapy is the preferred treatment option. [62]

4.6.2.4.4. Advanced stage (BCLC C)

Advanced stage (BCLC C) disease is defined as patients with HCC, where vascular invasion has occurred or where extrahepatic tumour spread has taken place. These patients are still fit to a certain extent and able to take care of themselves (PS less or equal to 2). Patients with preserved liver function should be considered for systemic therapy. [63] The current first line systemic therapy is the combination of Atezolizumab and Bevacizumab (in patients with preserved liver function, where there is no history of variceal haemorrhage). It has shown an improved progression-free survival rate compared to Sorafenib. [64, 65]

4.6.2.4.5. End stage (BCLC D)

Patients with end-stage (BCLC D) HCC are terminally ill. These patients present with a PS of 3-4, meaning that they need help to take care of themselves for basic activities of daily living. This category also includes all patients with impaired liver function, where liver transplantation is not an option. These patients have a poor short-term survival rate and should be offered supportive care by means of a multidisciplinary palliative care team. [56]

4.6.2.5. The ALBI (albumin-bilirubin) score:

The ALBI score was developed in Japan to objectively determine liver function in patients with HCC. Albumin and bilirubin were found to be the only two non-tumour related factors that played a role in survival. The ALBI score is divided into three grades of which grade 1 has the best prognosis and grade 3 the worst. The ALBI score is able to detect small chances in liver function. The biggest advantage of ALBI compared to the conventional Child-Pugh score, is that it is calculated by only making use of objective laboratory values and not subjective variables such as ascites and

encephalopathy. The ALBI score can also be used to determine liver function in the setting of chronic liver disease without malignancy. [66]

4.7. Management

The treatment of HCC faces a unique challenge, as the majority of patients have underlying liver cirrhosis, which is often accompanied by a poorer overall health status. Large strides have been made to improve HCC treatment over the past 10 years. The BCLC system as discussed above provides the most widely used model for staging HCC and guiding the course of treatment accordingly. In general, patients with early-stage disease are good candidates for resection, liver transplantation and ablation. Intermediate stage patients are potential candidates for TACE and patients with advanced disease will most likely receive systemic therapy. [6] There are however some controversies, especially in the Asia-Pacific region on which lesions in the intermediate group qualifies as 'resectable' and which not. The different treatment options will be discussed in more detail below:

4.7.1. Surgical interventions

Surgical interventions in essence consist out of liver resection and liver transplantation. Surgical therapy plays an important role as possible curative form of treatment.

4.7.1.1. Liver resection

Before a partial hepatectomy, it should be confirmed that the disease did not spread beyond the liver and that the size and location of the tumour in relation to the patient's liver function allows for resection without increasing the morbidity and mortality. Patients with localized cancer (single tumour), preserved liver function (Child-Pugh class A in patients with cirrhosis), no evidence of clinically significant portal hypertension and a ECOG score of 0 are the optimal candidates for resection. Some studies do however suggest that a partial hepatectomy for patients with multinodular lesions may be superior to conventional TACE. [67] Different surgical techniques may be use depending on where the tumour is located and how severe the cirrhosis is. Surgical techniques can grossly be divided into open and laparoscopic surgery. Open techniques include anatomical resection, non-anatomical resection, the anterior or no touch technique or the central hepatic resection technique. Minimally invasive

laparoscopic surgery has a number of advantages that include a quicker recovery time, a shorter hospital stay, less blood loss and fewer adhesions which is beneficial for future transplant surgery. [68] Unfortunately, HCC recurrence remains a significant problem after liver resection (as high as 70% after 5 years). [69]

4.7.1.2. Liver transplantation

The major advantage of a liver transplant does not only lie in its ability to potentially cure HCC, but it also replaces some of the underlying cirrhotic liver and therefore decreases the chances of developing new cancerous lesions. Patients with early-stage disease, who fulfil the Milan criteria are considered optimal candidates for liver transplantation. The Milan criteria is defined as a single lesion less than 5 cm in diameter or two to three nodules all of which are less than 3 cm, with no major vascular invasion. [70] When the Milan criteria is used to select candidates for liver transplant, a 5-year survival rate of 70%-75% and 10-year survival rate of 50% can be achieved. The biggest obstacle of liver transplantation is the shortage of suitable organs, which in effect causes a prolonged waiting period. In some cases, the cancer unfortunately progresses during this waiting time and patients may end up not fitting the Milan criteria any longer. Some studies have explored the use of ablation and TACE as either a bridging therapy or a way to downscale patients to fit the Milan criteria. Tabrizian P. et al. conducted a large, multicentre study that revealed promising results when patients were downscaled in order to fit the Milan criteria before undergoing a liver transplant. [71] Many clinicians however argued that the Milan criteria is too strict in its requirements for the size of cancerous lesions. The Milan criteria is also considered to be restrictive by some as it does not take tumour biology into account. Subsequently, a variety of extended criteria were developed for liver transplantation in HCC patients. Examples include the Up-to-seven criteria, the UCSF (University of California, San Francisco) criteria, Pittsburgh criteria and the Toronto criteria. The Up-to-seven criteria is calculated as the sum of the largest lesion in centimetres plus the number of lesions. If the sum is 7 or less, with no vascular invasion, then the overall survival should be similar to that of the Milan criteria. The UCSF criteria is defined as a single lesion ≤6.5cm or a maximum of 3 lesion of which the largest lesion is ≤4.5cm and a total tumour diameter of ≤8cm. [72]

4.7.1.2.1. Liver transplantation statistics specific to Austria

Organ donation in Austria works with an opt-out policy. This means that consent is presumed for an organ to be removed unless the donor specifically objected during his/her lifetime. Arshad A. et al. published a study that compared organ donation and transplantation rates in countries with opt-out policies vs. countries with opt-in systems. They looked at 35 countries in total, 17 of whom had an opt-out system in place. No major difference was found in the total deceased donor rates, but living donors were markedly less in the countries with an opt-out policy. [73] In Austria, a total number of 157 liver transplants from deceased donors were performed in 2022 and 2 transplants from living donors. This roughly translates to 17.7 transplants per million people. [32] In 2021, liver transplants were the second most frequently performed transplants in Austria after kidney transplants. [74]

4.7.2. Other interventions

Other interventions include ablation techniques such as radiofrequency ablation (RFA) and microwave ablation (MWA), percutaneous ethanol injection, cryoablation, irreversible electroporation, trans-arterial techniques such as bland hepatic artery embolization, chemoembolization, radioembolization and external beam radiotherapy. The most important interventions will be discussed below.

4.7.2.1. Ablation

The two most used techniques for local ablation, in clinical practice today are RFA and MWA. RFA has been used most frequently in clinical practice, but MWA is becoming increasingly popular. Ablation techniques are used in patients who do not fulfil the criteria for resection and transplantation, but still have early-stage HCC. Ablation causes direct damage to the tumour by inducing a thermal, chemical or electrical injury. [6]

RFA offers good an outcome for patients presenting with an HCC lesion of ≤2 cm and has the same survival rate compared to patients undergoing resection (refer to *Table 4* for general survival outcomes). RFA may therefore be used as the first line treatment in such patients and has proven to be superior to percutaneous ethanol injections. [75] RFA can be used for larger single tumours between 3 and 4 cm or for tumours with 2-3 lesions less than 3 cm each, but it is less successful in these patients. RFA is

performed by advancing a needle electrode into the tumour. This can be done via ultrasound guidance, a laparoscopy or via open surgery. [58]

MWA has the potential to induce necrosis to larger areas, as several needles can be used at the same time. MWA may be the better option for tumours more than 2cm, but less than 4cm in diameter. MWA causes necrosis by means of heat and friction through electromagnetic microwaves. One other advantage of MWA is that the duration of the procedure is shorter and can therefore be done under local anaesthesia. [76]

HCC stage	Treatment	Overall Survival Outcome
Resection		
Early	HCC ≤ 5 cm, no portal hypertension	50-70%
	HCC > 5 cm or portal hypertension	35-55%
Early/ intermediate	Optimal candidates	65%
	Suboptimal candidates	35%
Liver transplantation		
Early	Milan	70-80%
Early or intermediate	down staged	60-70%
Ablation		
Early	RFA	70%
	MWA	65%

Table 4 *Summary of survival outcomes for surgical and interventional therapy, modified after [6]*

4.7.2.2. Trans-arterial techniques

Trans-arterial chemoembolization (TACE) is mainly used in patients with intermediate stage HCC (BCLC B). TACE is a good option for patients with larger, unresectable tumours or multiple HCC lesions that are not responsive to ablation. Patients should ideally have a well-preserved liver function, since those with bilirubin levels above 2 mg or fluid retention that requires diuretic therapy, are generally associated with a poorer outcome and an increased risk of complications. [77] Doxorubicin, Epirubicin and Cisplatin are the three chemotherapeutic agents most widely used for TACE. There are two methods of conducting TACE therapy. The standard method is performed by injecting a chemotherapeutic agent into the hepatic artery. Lipiodol is an oily substance that serves as a contrast agent and is commonly used in conjunction with conventional TACE. Lipiodol followed by the administration of a gel-foam was

thought to enhance drug delivery and cause embolization. [78] This method has however led to higher rates of chemotherapy induced toxicity. In recent years, drug-eluting bead TACE (DEB-TACE) has become a favorable alternative to conventional TACE. DEB-TACE is associated with less treatment related side-effects, possibly due to the slower rate of chemotherapy release and decreased systemic availability. [79, 80]

Another example of a trans-arterial therapy is known as trans-arterial radioembolization (TARE). TARE is performed by delivering microspheres intra-arterially (through percutaneous access), with a radioactive agent such as yttrium-90. Some studies suggest that TARE might have similar outcomes compared to TACE in patients with intermediate stage HCC. [81]

4.7.3. Systemic therapies

Systematic therapy for HCC plays an important role in the treatment of advanced-stage HCC (BCLC C), where resection, liver transplantation and other direct-liver therapies are not an option. For about 10 years, Sorafenib was the mainstay of systemic treatment for advanced HCC, after being registered in 2007. It was the only medical treatment that showcased improved survival over placebo (10.7 vs. 7.9 months). [82] It was especially effective in patients with HCV-associated HCC. [83]

4.7.3.1. First line

The current recommended first-line therapy is the combination of Atezolizumab and Bevacizumab. The IMbrave150 trail compared Sorafenib to the Atezolizumab/ Bevacizumab combination and proved a better overall survival rate with the latter treatment strategy. [84] The overall survival for the Atezolizumab/ Bevacizumab combination was 67.2% compared to the 54.6% for Sorafenib alone. A prolonged progression free survival of 6.8 months was demonstrated for the Atezolizumab/ Bevacizumab combination compared to 4.3 months for Sorafenib. [82]

Sorafenib is a type of tyrosine kinase inhibitor (TKI), whereas Atezolizumab is a type of immune checkpoint inhibitor (ICI), that functions as an anti-PDL1 antibody. ICI's have demonstrated a favourable side-effect profile compared to TKI's. [85]

For patients who are not suitable candidates for Bevacizumab (an anti-VEGF antibody); Durvalumab (anti-PD-L1 antibody) together with Tremelimumab (anti-CTLA-

4 antibody) may be used in combination with Atezolizumab as an alternative first-line regime. Bevacizumab is associated with an increased risk of haemorrhage and gastro-intestinal perforation. Patients should therefore undergo a gastroscopy prior to treatment, to ensure that oesophageal varices are appropriately managed. Bevacizumab is also associated with adverse cardiovascular events and caution should be taken in patients already suffering from hypertension, heart failure or coronary artery disease. [86]

Tremelimumab is administered as a once off dose, followed by the administration of Durvalumab every 4 weeks. This combination also displayed a survival advantage above Sorafenib alone (16.4 vs. 13.8 months); as well as a much higher overall response rate (20.1 vs. 5.1%). [82]

If it is not possible to administer the above-mentioned drug combination for any given reason, Sorafenib, Lenvatinib (also a TKI) or Durvalumab may be used as monotherapy. [87]

4.7.3.2. Second / third line

If HCC progresses despite Sorafenib administration; Regorafenib, Cabozantinib or Ramucirumab may be used as a second-line regime. Cabozantinib (a multi-kinase inhibitor) is recommended as a third line therapy in the latest BCLC guidelines. [56]

The COSMIC-312 trail proved that Atezolizumab in combination with Cabozantinib had a longer progression free survival time of 6.8 months compared to 4.2 months in patients who received Sorafenib alone. [82]

The KEYNOTE-394 trail compared Pembrolizumab (also an ICI/ PDL-1 inhibitor) plus best supportive care (after Sorafenib administration), as a second-line treatment to BSC and placebo. Pembrolizumab together with BSC showed a 21% mortality risk reduction. [82]

4.7.3.3. Systemic therapy in cases other than BCLC C

In BCLC B patients, that are not candidates for TACE, systemic therapy should be offered. After the initial successful treatment with resection, ablation or TACE, the cancer may return at a different area within the liver. In some cases, TACE may be repeated, but if the tumour has spread into the portal vein or if extra-hepatic spread has taken place, systemic therapy should be considered. [62]

4.7.4. Palliative care

Patients who are diagnosed with BCLC D HCC are considered terminally ill, with end stage liver failure and a poor performance score. These patients are expected to survive between 3 and 6 months. Best supportive care should be offered to such patients. Palliative care consists out of a multidisciplinary team that offers a holistic approach to patients with terminal or serious illness. Good palliative care has the potential to decreased pain and discomfort, improve quality of life and support psychological needs. [88]

4.8. Prognosis and Prevention

4.8.1. Prognosis

The prognosis of HCC is related to the stage of the tumour at the time of diagnosis, as well as the extent of liver impairment. A high survival rate is attainable in patients who are diagnosed at an early stage of disease and treated with a partial hepatectomy, liver transplant or ablation. Generally speaking, for patients with early stage disease, a 5-year survival rate above 50% is attainable, for intermediate to advanced stage HCC, the survival rate is around 20-50% at 3 years and those presenting with terminal HCC, will mostly die within 6 months of diagnosis. [89]

Factors other than the tumour itself may also play a role in overall survival. Patients in high-incidence regions, tend to have a shorter survival rate, as they present at a later stage of disease with extrahepatic metastasis already being present. Tumour histology may also play a role in the prognosis, as patients with well-differentiated clear cell tumours have better outcomes. Encapsulated tumours are inclined to grow slower, with less invasion of surrounding structures. [69] An unfavourable prognosis is also associated with a very high AFP level at the time of diagnosis. [90] Lastly, Diabetes Mellitus is also linked to a lower overall survival rate. [91]

4.8.2. Prevention

The single most important primary prevention factor is vaccination against HBV, especially in endemic areas such as Asia and sub-Saharan Africa, where the highest number of HCC cases originate from.

Vertical transmission from mother-to-child may be prevented if active HBV infection is treated intra-partum, by means of antiviral-drugs such as Tenofovir. [92]

HCV prevention lies in preventing horizontal spread. This can be done by educating people on the danger of sharing needles with intravenous drug abuse. Blood banks should also ensure the safety of blood and blood products used for transfusion. [92]

Secondary prevention of HCC entails treating HBV infection with anti-viral drugs to hinder replication, as well as DAA therapy for patients with chronic HCV infection. [92]

Surveillance programs for high-risk patients is also crucial in ensuring an early diagnosis. Patients diagnosed at an early stage of disease, through regular screening programs, have a much lower mortality rate. [93]

Living a healthy lifestyle may reduce the chances of developing HCC, especially given the fact that underlying NAFLD/NASH is increasingly adding to the burden of HCC. [94] This includes smoking cessation, avoiding alcohol, eating a healthy diet, maintaining a normal weigh through regular physical activity and managing diabetes appropriately. [92] Some observational studies suggest that drinking coffee has a protective effect against liver cancer. [95]

5. Study Objectives

This study aims to investigate the changes observed in the epidemiology and aetiology of Hepatocellular Carcinoma (HCC) at *Klinikum* Klagenfurt, Austria.

It has been suggested that alcoholic related liver cirrhosis as the primary cause of HCC has declined in population over the past few years. It is also suspected that an increasing number of HCC cases are occurring, without underlying liver cirrhosis being present. The period between 2012-2017 will be compared to 2018-2023.

The main objectives include:

1. To observe changes in the epidemiology of HCC.
2. To investigate the aetiology of HCC within our study population.
3. To investigate the changes in survival between the two time intervals in light of the availability of new medical treatments.

6. Methods

6.1. Study design, data collection and patient selection:

This was a single-centre cohort study. Data was obtained retrospectively from the electronic hospital system at *Klinikum Klagenfurt am Wörthersee*. The hospital's clinical information system is known as *Orbis* and the laboratory results were obtained from the electronic system named, *Lauris*. The study was granted approval by the Ethical Committee of Carinthia. Patient data was kept confidential by allocating numbers to patient names.

A total of 285 patients were diagnosed with HCC, either histologically by means of a liver biopsy or through multi-phase imaging techniques, from January 2012 to February 2023 and captured in our data collection.

Inclusion criteria:

- All patients over the age of 18 years diagnosed with HCC.
- Patients diagnosed between 2012 and 2023.
- Patients with confirmed HCC, either histologically or via imaging (quadruple-phase CT or contrast enhanced MRI).

Exclusion criteria:

- Missing patient data vital to our study aim (e.g., the presence/absence of cirrhosis not known)
- Patients with mixed HCC and biliary tract tumours.

Statistical analysis:

The *IBM SPSS 25* statistical software was used to analyse the captured data from the selected patient population. Nominal data was given as absolute numbers (n) and percentages (%) and numerical data was presented as the median with the standard deviation range included. Pearson´s Chi-square test was applied to analyse categorical data and to determine how likely it was for differences between data sets to occur due to chance. A *p*-value of <0.050 was seen as statistically significant. The Kaplan-Meier method was used to estimate and analyse survival probability. First the survival of all HCC patients was evaluated, then the statistical analysis was repeated, after removing all patients who underwent an OLT from the calculations. (Patients who underwent a liver transplant could falsely influence the survival rate.)

7. Results

A total of 276 patients met the requirements of the inclusion criteria and were taken into account for further statistical analysis. (Refer to *Table 5* for complete descriptive analysis comparing the two time periods.)

The period of investigation was divided into two time-categories to allow for comparison between the two intervals. The first time-period included all patients diagnosed with HCC from January 2012 until the end of 2017. The second time-period comprised of patients diagnosed between the beginning of 2018 and February 2023. The first group consisted out of 128 patients (46.4% of the total patient population) and the second group out of 148 patients (53.6%). In 2018 a marked change in the medical management of HCC started to take place and therefore 2018 was used as the time cut-off for comparison. Ramucirumab and TACE was offered as an alternative to Sorafenib. Other Immunotherapies were also starting to be included in treatment plans for advanced stage HCC.

In this specific patient population, it was proven once more that HCC occurs more commonly in males compared to females. A total of 232 patients were male (84.1%) and 40 were female (14.5% of total patient population). The incidence rate was therefore 5.8 times higher in males than in females. No significant change in incidence was observed among males compared to females between the two time-period categories ($p = 0.878$). The median age of diagnosis for all patients was 72.5 years with a SD of 8.6 years. In the first time-period before 2018, the median age of diagnosis was 73 years (SD 8.6) and 71 years (SD 8.6) in the second time-period ($p = 0.042$).

Out of the 276 patients, 207 (75%) had liver cirrhosis present at the time of HCC diagnosis and 69 (25%) had no cirrhosis. During 2012-2017, 22 patients (17.2% of total patients within time category) had HCC without underlying liver cirrhosis. This number increased to 47 (31.8%) during the second period of 2018-2023. This is a marked difference with a p-value of 0.005.

The aetiology of HCC was known for a total of 250 out of the 276 patients. Alcoholic liver disease was the most common underlying aetiology with a total of 139 patients (55.6%). 55 patients (22%) had viral hepatitis and 43 patients (17.2%) had underlying NASH. A total of 13 patients (5.2%) were classified as “other”, which included for

example Hemochromatosis, Budd-Chiari syndrome and Primary Biliary Cholangitis. Before 2018, 58.5% of patients had underlying alcoholic liver disease, compared to 52% in the second time-period. 23.7% of patients had viral hepatitis in the first time-period and 20.5% in the second. NASH as underlying aetiology for HCC increased from 12.7% (15 patients) in the first time-period to 21.2% (28 patients) in the second. There was however no statistically significant change observed in the aetiology of HCC between the two time-categories (p = 0.353).

Around 40.8% of the total population group had oesophageal varices close to the time of diagnosis. A slight increase in oesophageal varices was observed in the second time-period (2018 – 2023). The percentage increased from 36.6% within the first category to 44.5% in the second. This increase however was seen as statistically insignificant with a p-value of 0.18.

The AFP values were documented for 272 patients within this study population. A total of 206 patients (75.7%) had an AFP level of less than 200 and only 66 patients (24.3%) had an elevated AFP level of above 200. In the first time-interval before 2018, 72% of patients had an AFP level of less than 200 and 28% of patients had a level above 200. In the second group from 2018 onwards, 78.9% of patients had an AFP of less than 200 and 21.1% had an AFP above 200 (p = 0.185). An AFP value of above and below 400 was also investigated. An overall total of 216 patients (79.4%) had an AFP value of less than 400 and 56 patients (20.6%) had a raised AFP level of above 400. In the first time-category, 76% of patients had an AFP of less than 400 and 24% more than 400. In the second time category, 82.3% of patients had an AFP of less than 400 and 17.7% more than 400 (p = 0.199). Generally seen, a total of 116 patients (42.6%) had no elevated AFP (less than 7) and only 156 (57.4%) had a raised AFP (more than 7) level in the serum. In the first time-interval before 2018, 39.2% of patients had a normal AFP level and 60.8% of patients had a positive/ raised AFP level. In the second interval, 45.6% of patients had a normal AFP value and 54.4% a raised AFP level (p = 0.289).

Concerning the Child-Pugh scoring system, a total of 116 patients (42%) were classified as Child-Pugh A. 65 patients (23.6%) were classified as Child-Pugh stage B and 26 (9.4%) as stage C. 69 patients (25%) had no cirrhosis. When comparing the

two time-periods, non-cirrhotic patients increased from 17.2% to 31.8%. Child-Pugh A decreased from 43% in the first time-period to 41.2% in the second, stage B from 29.7% to 18.2% and stage C from 10.2% to 8.8% respectively (p = 0.020).

The majority of patients (40.6%) were classified as BCLC stage A at the time of diagnosis. 22.1% of all patients were categorized as BCLC-B, 25% as BCLC-C and 12.3% as BCLC-D. No major differences were observed between the two time-categories for BCLC stage A (41.1% in the first time-category and 39.9% in the second). Even though the percentage of patients diagnosed as BCLC-A stayed similar over time, significant changes were observed for BCLC-B, C and D between the two time-categories. BCLC stage B decreased from 25% in the first group to 19.6% in the second, BCLC stage C increased from 18% to 31.1% and the percentage of patients classified as BCLC-D at time of diagnosis decreased from 15.6% to 9.5% (p = 0.051).

Regarding the ALBI score, 30.6% of HCC patients were staged as ALBI grade 1, 54.6% as ALBI grade 2 and a further 14.8% of patients as ALBI grade 3. In the first time-period, only 14.6% of patients were classified as ALBI grade 1. This percentage increased to 43.9% in the second time-period. 65.9% of patients were staged as ALBI grade 2 in the first time-interval and 45.3% in the second time interval. 19.5% were ALBI grade 3 in the first time-period and 10.8% in the second (p < 0.001).

A total of 192 (72%) of all patients within this specific cohort received liver biopsies. Liver biopsies were performed more frequently during the period of 2018-2023, compared to 2012-2017. The rate increased from 65% to 77.6% within the respective time-categories (p = 0.028). Of the 192 patients who underwent a liver biopsy, 36.3% had grade 1 HCC, 42% had grade 2 HCC and 13% had grade 3 disease. There were no noteworthy changes over time (p = 0.196). At the time of diagnosis, 46% of all patients had unifocal disease and 54% had multifocal tumours. Here also, no significant change was evident between the two time periods (p = 0.345). The median size of space-occupying lesions was 4.5 cm (SD 3.7). The median size of tumour lesions was 4.5 cm (SD 3.9) in the first time-period and remained 4.5 cm (SD 3.5) in the second time-period (p = 0.433).

The extend and spread of disease was further evaluated by looking at the presence or absence of portal-vein thrombosis, distant metastases, macrovascular invasion and enlarged lymph-nodes (> 2 cm). 20.4% of patients presented with portal-vein thrombosis around the time of diagnosis, 9.8% had concomitant extra-hepatic metastases, 21% had macrovascular invasion and 15.1% had enlarged lymph-nodes. 17.3% of patients had portal-vein thrombosis in the first time-category and 23% in the second ($p = 0.246$). 7.1% of patients had distant metastases in the first time-interval and 12.2% in the second ($p = 0.158$). 17.3% of patients had macrovascular invasion in the first time period and 24.3% in the second ($p = 0.156$). 18.3% of patients had enlarged lymph-nodes at the time of diagnosis in the first period and 12.4% in the second ($p = 0.181$). None of these parameters showcased a remarkable change between the two time-intervals.

Concerning comorbidities, 12.3% of patients had concomitant coronary artery disease. No significant change was seen over time ($p = 0.345$). An overall total of 61.2% of patients also suffered from arterial hypertension. No significant change over time was noted for arterial hypertension ($p = 0.378$). 7.3% also had peripheral arterial disease, with no remarkable change between the two time-periods ($p = 0.589$). A total of 10.7% of patients had accompanying chronic renal insufficiency. Altogether, 31.9% of all patients had diabetes mellitus. Before 2018, 29.7% of patients suffered from diabetes and 33.8% in the second time-period ($p = 0.466$). The mean body mass index (BMI) for all patients was 28 (SD 4.5). The median BMI in the first time-category was 27.8 (SD 4.53) and 27.4 (SD 5.32) in the second ($p = 0.871$).

Various management options are available to treat different stages of HCC. In this patient population, a total of 7 OLT´s were performed on HCC patients before 2018 and 6 liver transplants were performed between 2018 and February 2013 ($p = 0.580$). The first-line therapies were documented for a total of 275 patients. Overall, 10.2% of all HCC patients underwent a partial hepatectomy as first-line treatment, 16.7% received ablation (RFA/MWA), 31.3% received TACE, to 16.7% of patients Tyrosine-kinase Inhibitors were prescribed, 9.5% received Immunotherapy and 12.4% received best supportive care.

42 patients (32.8%), out of all patients diagnosed with HCC within the first time-category underwent RFA and 17 (11.5%) in the second category ($p < 0.001$). The number of MWA's performed increased; with this procedure only being done 3 times in the first time-period and 14 times in the second ($p = 0.014$). In other words, a total of 17 patients (6.2% of all patients) underwent MWA.

Out of the 276 HCC patients, 102 received TACE as part of their treatment regime. A decrease in the number of patients receiving TACE was noticeable, with 70 patients (54.7%) in the first time-period and 32 (21.6%) in the second time-period ($p < 0.001$).

Around 2018, Immunotherapy started playing an increasingly important role in the treatment of HCC patients with advanced disease. A total of 52 patients received Immunotherapy of which only 10 (7.8% of all patients within time-interval) was in the first time-period and 42 (28.4%) in the second time-period ($p < 0.001$).

62 patients out of all patients in this cohort received Sorafenib as first line treatment, 35 of which was in the first time period and 27 in the second ($p = 0.071$).

During the whole course of treatment, a total of 110 patients received systemic medical therapy as part of their treatment regime. Within the first time-period, 28.9% of patients received systemic therapy during their course of treatment. This percentage increased within the second time-period, where 49.3% of patients received systemic therapy ($p < 0.001$).

Table 5 *Descriptive parameters comparing the two time-periods, created by author*

		Time period 1 2012-2017 (N=128)	**Time period 2 2018-2023 (n=148)**	
Variable		N (%)	N (%)	*p-value*
Age	Mean ± STD	73 ± 8.6	71 ± 8.5	*0.042*
Sex	Male	109 (85)	127 (86)	
	Female	19 (15)	21 (14)	*0.878*
BMI	Mean ± STD	28 ± 4.5	28 ± 5.3	*0.871*
Liver cirrhosis	Present	106 (83)	101 (68)	
	Absent	22 (17)	47 (32)	*0.005*
Aetiology	Alcohol	69 (59)	70 (53)	
	Viral	28 (24)	27 (21)	
	NASH	15 (13)	28 (21)	
	Other	6 (5)	7 (5)	*0.353*
Ascites	Present	28 (22)	41 (28)	
	Absent	98 (78)	106 (72)	*0.283*
Child-Pugh	No cirrhosis	22 (17)	47 (32)	
	A	55 (43)	61 (41)	

	B	38 (30)	27 (18)	
	C	13 (10)	13 (9)	*0.020*
BCLC stage	A	53 (41)	59 (40)	
	B	32 (25)	29 (20)	
	C	23 (18)	46 (31)	
	D	20 (16)	14 (10)	*0.051*
ALBI score	Grade 1	18 (15)	65 (44)	
	Grade 2	81 (66)	67 (45)	
	Grade 3	24 (20)	16 (11)	*< 0.001*
Grading	0/negative	10 (13)	6 (5)	
	1	30 (38)	40 (35)	
	2	28 (35)	53 (47)	
	3	11 (14)	14 (12)	
	4	1 (1)	0 (0)	*0.196*
Focality	Unifocal	55 (43)	72 (49)	
	Multifocal	73 (57)	76 (51)	*0.345*
SOL (size in cm)	Mean ± STD	5.7 ± 3.9	5.4 (3.5)	*0.433*
Up-to-seven	≤7	62 (49)	72 (49)	
	>7	65 (51)	76 (51)	*0.978*
Macrovascular invasions	Present	22 (17)	36 (24)	
	Absent	105 (83)	112 (76)	*0.156*
Enlarged lymph-nodes (>2cm)	Present	23 (18)	18 (12)	
	Absent	103 (82)	127 (88)	*0.181*
Coronary artery disease	Present	13 (10)	21 (14)	
	Absent	112 (90)	127 (86)	*0.345*
Hypertension	Present	80 (64)	87 (59)	
	Absent	45 (36)	61 (41)	*0.378*
Diabetes	Present	38 (30)	50 (34)	
	Absent	90 (70)	98 (66)	*0.466*
AFP	Raised (>7)	76 (61)	80 (54)	
	Normal	49 (39)	67 (46)	*0.289*
First-line Therapy	Surgical	15 (12)	16 (11)	
	Interventional	74 (58)	58 (40)	
	Systemic	14 (11)	58 (40)	
	None	25 (20)	15 (10)	*< 0.001*
OLT	Yes	7 (5.5)	6 (4)	
	No	121 (94.5)	142 (96)	*0.580*
Resection	Yes	16 (12.5)	11 (7)	
	No	112 (87.5)	137 (93)	*0.158*
RFA (first-line)	Yes	42 (33)	17 (12)	
	No	86 (67)	131 (89)	*< 0.001*
MWA (first-line)	Yes	3 (2)	14 (9.5)	
	No	125 (98)	134 (90.5)	*0.014*
TACE (first-line)	Yes	70 (55)	32 (22)	
	No	58 (45)	116 (78)	*< 0.001*
Immuno-therapy	Yes	10 (8)	42 (28)	
	No	118 (92)	106 (72)	*< 0.001*

Abbreviations: STD, standard deviation; BMI, body mass index, SOL, space-occupying lesion, AFP, alpha-fetoprotein, OLT, orthotopic liver transplantation, RFA, radiofrequency ablation, MWA, microwave ablation, TACE, trans-arterial chemoembolization

7.1. Overall survival outcomes

The median survival time for patients below the age of 70 years was 18.7 months (95% CI 12.7-24.7) and for patients above the age of 70, the median survival time was 22.2 months (95% CI 16.8-27.6, p = 0.163). (See *Table 6* and *7* for all survival outcome data.)

At the time of data collection, only 85 out of 236 (36%) males diagnosed with HCC were still alive and14 out of 40 (35%) females. The median survival time for men was 21.6 months (95% CI: 17.9-25.3), 16.5 months for women (95% CI: 9.5-23.4) and the median overall survival time for both sexes was 20.5 months (95% CI: 16.8-24.2, p = 0.842). The median overall survival time in months was 21.9 (95% CI: 16.9-26.8) in the first time-period and 20.2 (95% CI: 15.7-24.6) in the second time-period (p = 0.841).

When patients who underwent OLT were removed from the analysis, 263 remained of whom 224 were male and 39 were female. The median survival time for both males and females were 19.4 months (95% CI: 15.9-22.9). In the group before 2018, the median survival time in months was 19.4 (95% CI: 14.6-24.2). In the group from 2018 onwards, the median survival time was 18.7 months (95% CI: 14.9-22.9, p = 0.902).

The OS was calculated for a number of different variables. Of the 263 patients with HCC who did not undergo an OLT, 68 patients had no liver cirrhosis and 195 had liver cirrhosis present at the time of diagnosis. The survival time for those without cirrhosis was 22 months (95% CI: 8.7-35.3) and those with cirrhosis had a survival time of 18.9 months (95% CI: 15.7-22.2, p = 0.151). Patients without cirrhosis had a median survival time of 22 months (95% CI: 8.7-35.4) in the first time-period and a median OS of 16.1 months (95% CI: 4.1-28) in the second. Patients with cirrhosis had a median survival time of 18.9 months (95% CI: 12.1-25.6) in the first time period (before 2018) and a median OS of 18.7 months (95% CI: 2.1-14.7) in the second (p = 0.170).

The data for underlying aetiology was captured for a total of 219 patients who did not undergo an OLT. Patients with alcohol as underlying cause had the shortest survival time of 16.5 months (95% CI: 12.9-20.1). Those with viral hepatitis had the longest median survival time of 27 months (95% CI: 14.9-39.2). Patients with NASH had a median survival time of 26.2 months (95% CI: 15.1-37.4) and those with other causes had a median of 19.7 months survival time (95% CI: 0-53.7).

When the survival time of all patients in the cohort was calculated, those with underlying alcoholic liver disease had a median survival time of 18 months (95% CI:14.2-22), those with viral hepatitis 32.1 months (95% CI:15.9-48.4), those with underlying NASH 38 months (95% CI: 18.4-59) and those with other causes 19.7 months (95% CI: 0-53, p = 0.004).

The median survival time for patients with grade 0 ascites was 24.2 months (95% CI: 19.7-28.6), for grade 1 ascites 6.7 months (95% CI: 1.9-11.3) and grade 2 ascites 6.8 months (95% CI: 0.0-13.7, p < 0.001).

According to the Child-Pugh classification, the median survival time for patients staged as Child-Pugh A was 27 months (95% CI: 19.4 – 34.6). For Child-Pugh stage B, the median survival time was 14.6 months (95% CI: 10-19) and 2.6 months (95% CI: 0.17-5) for Child-Pugh C, as described in *Figure 2*. Those without cirrhosis had a median survival time of 22 months (95% CI: 8.4-35.7, p < 0.001).

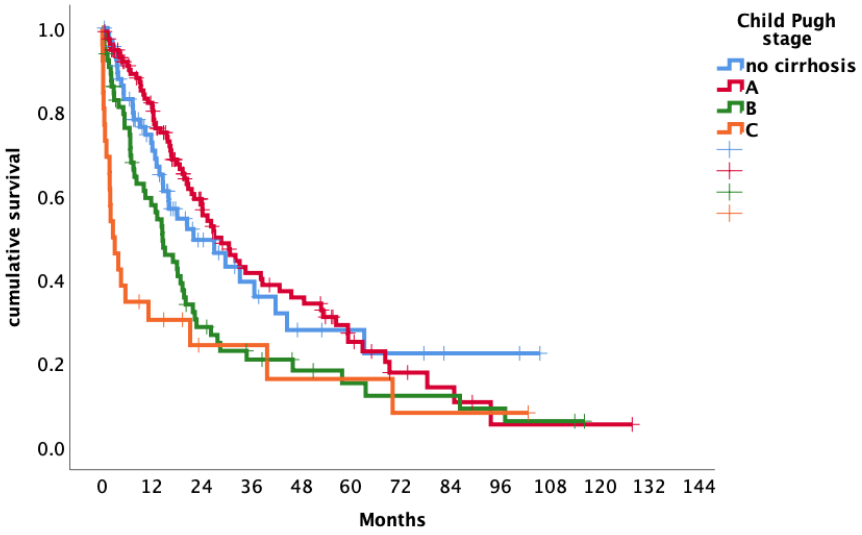

Figure 2 *Survival time of all patients including OLT according to Child-Pugh score, created by author*

Patients with BCLC-A had a median survival time of 34.9 months (95% CI: 16.1-53.6), those with BCLC-B had 24.2 months (95% CI: 15-33.4) survival time, BCLC-C had 10 months (95% CI: 7.3-12.8) and BCLC-D a median of 1.8 months (95% CI: 1.2-2.4) survival time (p < 0.001). (See *Figure 3*)

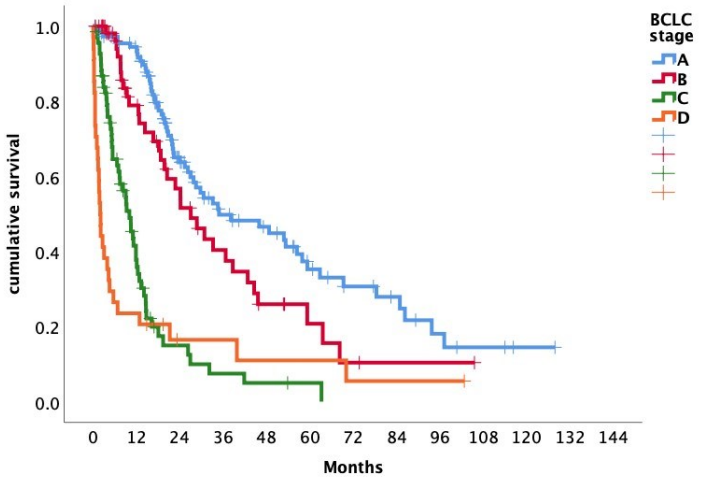

Figure 3 *Survival time of all patients including OLT according to BCLC, created by author*

When looking at the survival time of patients (OLT patients removed) graded as ALBI 1, the median survival time was 19.4 months (95% CI: 17-21.8). For patients classified as ALBI grade 2, the median survival time was 17 months (95% CI: 10.9-23.2) and 19.7 months (95% CI: 11-28.4) for ALBI grade 3 (as shown in *Figure 4*). No significant change over time for survival of the various ALBI grades was seen (p = 0.660).

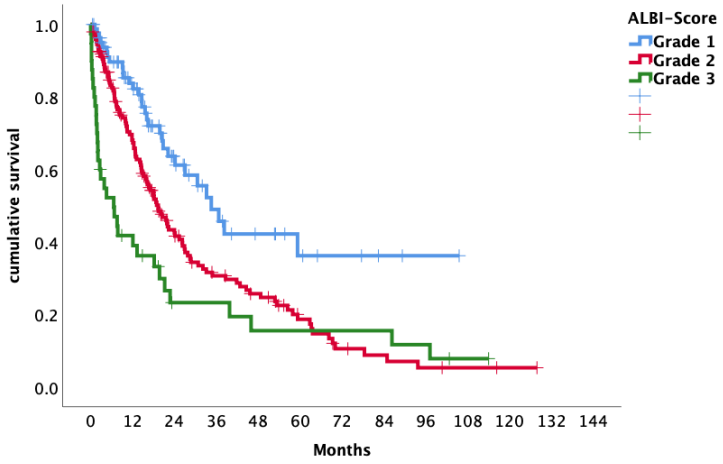

Figure 4 *Survival time of all patients including OLT according to ALBI score, created by author*

Patients with an AFP serum level of below 200, had a median survival time of 26 months (95% CI: 18.8-33.7). Those with an AFP above 200 had a median survival time of 7 months (95% CI: 2.6-11.4, p < 0.001). Patients with an unelevated AFP level

(below 7) had a median survival time of 33 months (95% CI: 22.2-44.1) and those with a raised AFP above 7 had a 14-month median survival time (95% CI: 10.7-17.4, $p < 0.001$).

Patients with unifocal lesions had a median survival time of 22.4 months (95% CI: 14.9-29.9) and those with multifocal tumours, a 16.2 month (95% CI: 11.1-21.3, $p = 0.007$) survival time.

The median survival time for those who fulfilled the Up-to-seven criteria was 29.7 months (95% CI: 18.9-40.6). Those with more than seven points (larger/multiple lesions) had a median survival time of 11.8 months (95% CI: 9.5-14.2, $p < 0.001$).

The median survival time of patients without MVI's was 24.2 months (95% CI: 18.8-29.6) and those with MVI's, 5.4 months (95% CI: 3.2-7.5, $p < 0.001$).

With regards to comorbidities, patients without hypertension had a median survival time of 19.7 months (95% CI: 14.9-24.6) and those with a median survival time of 20.7 months (95% CI: 16-25.5, $p = 0.88$). Patients without chronic kidney disease, had a median survival time of 20.7 months (95% CI: 17-24.5) and those with chronic kidney disease, a 15.6 month (95% CI: 8.7-22.5) median survival time ($p = 0.310$). Patients with comorbid coronary artery disease had a median survival time of 19.3 months (95% CI: 2.1-36.6) and those without 20.7 months (95% CI:16.8-24.7, $p = 0.463$). Those suffering from diabetes mellitus had a median survival time of 20.2 months (95% CI: 16.2-24) and those without, 21.2 months (95% CI:15-27.5, $p = 0.605$). Patients with a normal BMI below 25 had a median survival time 19.8 months (95% CI: 13.6-26) and those with a BMI above 25 had a median survival time of 24.2 months (95% CI: 18.7-29.6, $p = 0.676$).

Concerning survival and first line treatments for all patients, those who underwent surgical therapy had an overall median survival time 63.2 months (95% CI: 40.9-85.6). Patients who received interventional treatment had a median survival time of 29 months (95% CI: 22-35.4) and those who were treated with systemic therapy had a median survival time of 11.8 months (95% CI: 9.7-14). Those who did not receive any treatment had a 2 month (95% CI: 1-3) overall survival time ($p < 0.001$).

Table 6 *Descriptive statistics and univariate analysis of patients diagnosed at Klinikum Klagenfurt between 2012 and 2023, created by author*

			Overall survival (months)		P-value
Variable		**N=276**	**Median**	**95% CI**	**(log rank)**
Age	<70	104	18.7	12.7-24.7	
	≥70	172	22.2	16.8-27.6	0.163
Sex	male	236	21.6	17.9-25.3	
	female	40	16.5	9.5-23.4	0.842
Liver cirrhosis	Present	207	20.2	1.6-16.9	0.262
	Absent	69	22	8.4-35.7	
Aetiology	Alcohol	139	18	14.2-22	
	Viral	55	32.2	15.9-48.4	
	NASH	43	38.7	18.4-59	0.004
	Other	13	19.7	0-53.7	
Ascites	Present	69	7.4	1.5-13.3	
	Absent	204	26.2	21.5-31	< 0.001
Child-Pugh	No cirrhosis	69	22	8.4-35.7	
	A	116	27	19.4-34.6	
	B	65	14.6	10.1-19	< 0.001
	C	26	2.6	0.2-5	
BCLC	A	112	34.8	15.8-53.9	
	B	61	27	17.9-36.2	
	C	69	10	7.3-12.8	< 0.001
	D	34	1.9	1.3-2.6	
Focality	Unifocal	127	27	19-35.1	
	Multifocal	149	17.1	11.6-22.5	0.002
Up-to-seven	≤7	141	33.1	17.9-48.4	
	>7	134	11.8	9.6-14.1	< 0.001
SBL	Present	23	9.1	3.8-14.4	
	Absent	252	22	17.9-26.5	< 0.001
Macrovascular invasion	Present	58	5.3	3.2-7.6	
	Absent	217	26.9	21-32.8	< 0.001
Lymph-node enlargement (>2cm)	Present	41	6.8	1.9-11.8	
	Absent	230	24.2	18.9-29-5	< 0.001
CRP	Raised	120	11.8	8.6-15.1	
	Normal	152	32.2	23.4-40.9	< 0.001

Coronary artery disease	Present	34	19.4	2.1-36.6	
	Absent	239	20.7	16.8-24.7	0.463
Chronic kidney disease	Present	29	15.6	8.7-22.5	
	Absent	243	20.7	17-24.5	0.310
Hypertension	Present	167	20.7	16-25.5	
	Absent	106	19.7	15-24.6	0.880
Diabetes mellitus	Present	88	20.2	16.2-24.1	
	Absent	188	21.2	15-27.5	0.605
BMI	<25	75	19.8	13.6-26	
	≥25	168	24.2	18.7-29.6	0.676
AFP	Raised (>7)	156	14.6	10.3-18.9	
	Normal	116	34.6	22.8-46.3	< 0.001
ALBI score	Grade 1	83	34.6	26-43.1	
	Grade 2	148	19.2	15.1-23.6	
	Grade 3	40	6.6	1-12.2	< 0.001
First-line therapy	Surgical	31	63.2	40.9-85.5	
	Interventional	132	28.7	22-35.4	
	Systemic	72	11.8	9.7-14	
	None	40	2	1.1-3.1	< 0.001
ASA	Yes	59	26.9	14.6-39.1	
	No	217	19.8	16.2-23.4	0.264

Abbreviations: BCLC, Barcelona-Clinic Liver-Cancer Staging, CRP, C-reactive protein, BMI, body mass index, AFP, alpha-fetoprotein, ALBI, albumin-bilirubin score, SBL, sclerotic bone lesions, ASA, acetylsalicylic acid

Table 7 *Results of multivariable Cox regression analysis of prognostic factors in patients with HCC diagnosed at the Klinikum Klagenfurt between 2012 and 2023, created by author*

		Overall survival		
Variable		**HR**	**95%CI**	**p-value**
Up-to-seven	in	1		
	out	1.6	1.0-2.5	0.047
Aetiology	alcohol	1		
	viral	1.14	0.6-2.4	
	NASH	0.7	0.3-1.5	
	other	0.8	0.4-1.9	0.183
Ascites	Absent	1		
	Present	1.7	1.1-2.7	0.017
AFP	Normal	1		
	Raised (>7)	1.5	1-2.3	0.024
Focality	Unifocal	1		

	Multifocal	1.2	0.8-1.8	0.430
Sclerotic Bone Lesion	Absent	1		
	Present	0.9	0.4-1.6	0.448
Macrovascular invasions	Absent	1		
	Present	2.2	1.4-3.5	0.001
Enlarged Lymph-nodes (> 2cm)	Absent	1		
	Present	2	1.3-3.3	0.003
CRP	Normal	1		
	Raised	1.6	1-2.3	0.007
ALBI score	Grade 1	1		
	Grade 2	1	0.6-1.9	
	Grade 3	1	0.6-1.7	0.878

Abbreviations: BCLC, Barcelona-Clinic Liver-Cancer Staging, CRP, C-reactive protein, BMI, body mass index, AFP, alpha-fetoprotein, ALBI, albumin-bilirubin score, SBL, sclerotic bone lesions, ASA, acetylsalicylic acid

7.2. Analysis of HCC patients without cirrhosis

As mentioned above, the number of patients diagnosed with HCC, where no liver cirrhosis was present increased from the first time-interval (< 2018) to the second (≥ 2018). A more in-depth look at the specific characteristics of this patient group was taken, in order to better understand why this phenomenon occurred.

An overall total of 69 patients had no liver cirrhosis at the time of HCC diagnosis, of which 58 (84.1%) were male and 11 (15.9%) were female. The median age of diagnosis within this population group was 74 years (SD 8.8), compared to 72 years (SD 8.6) in patients with liver cirrhosis.

With regards to aetiology, 7 patients (15.2%) were known with alcoholic liver disease, 14 patients (30.4%) had underlying viral hepatitis, 23 (50%) had NASH and 2 patients (4.3%) were classified as other. When compared to patients with liver cirrhosis, 64.7% of patients had underlying alcoholic liver disease, 20.1% had viral hepatitis, 9.8% had NASH and 5.4% of patients were classified as other ($p < 0.001$).

The largest percentage of patients were staged as BCLC-A (42%). 21.7% was classified as BCLC-B, 34.8% as BCLC-C and 1.4% as BCLC-D. The majority of patients (92.8%) did undergo a liver biopsy of which most patients (47.7%) had grade 1 disease. 40% of patients had grade 2 disease and 12.3% grade 3.

Only 47.1% of patients without cirrhosis had a raised AFP (above 7) compared to 60.8% of patients with cirrhosis who had a raised AFP level ($p = 0.047$).

56.5% of patients without cirrhosis had an unifocal lesion and 43.5% had multifocal lesions, compared to patients with cirrhosis where only 42.5% had unifocal lesions and 57.5% had multifocal lesions (p = 0.043). The median space-occupying lesion size was 5.3 cm (SD 3.4) in non-cirrhotic patients, compared to 4 cm (SD 3.7) in cirrhotic patients. 11 patients (15.9%) had portal-vein thrombosis at the time of diagnosis, 9 patients (13%) had distant/ extra-hepatic metastases, 13 patients (18.8%) had MVI's, and 13 patients (18.8%) had significantly enlarged lymph-nodes (> 2 cm). Patients without liver cirrhosis, predominantly had lesions restricted to one lobe of the liver (68.1%).

With regards to comorbidities in HCC patients without cirrhosis, 14.5% of patients had accompanying coronary artery disease, 73.9% had hypertension, 13% had atrial fibrillation, 10.1% had cerebrovascular insufficiency, 10.1% had peripheral artery disease and 10.3% had chronic kidney disease. For the incidence of coronary artery disease there was no statistically significant difference between cirrhotic and non-cirrhotic patients (p = 0.553). Patients with cirrhosis had a lower incidence of hypertension (56.9%, p = 0.012). 30.4% of patients without cirrhosis had accompanying diabetes mellitus and 32.4% of patients with cirrhosis (p = 0.765).

Patients without liver cirrhosis had a median BMI of 28.1 (SD 4.8) and those with liver cirrhosis had a median BMI of 27.3 (SD 5.1, p = 0.690).

36.2% of these patients were taking Acetylsalicylic acid at the time of diagnosis, 24.6% of patients were on Metformin, 16.7% were on other oral antidiabetic drugs, a further 7.2% on Insulin, 24.6% were on an ACE-Inhibitor and 30.4% on a Beta-blocker.

Regarding first line therapy, 23.2% of non-cirrhotic patients underwent surgical intervention compared to 7.3% in cirrhotic patients. 33.3% of non-cirrhotic patients received interventional therapy as first-line treatment compared to 52.9% of cirrhotic patients. 39.1% of non-cirrhotic patients received systemic medical treatment compared to 21.8% of cirrhotic patients. Only 4.3% of non-cirrhotic patients received no treatment (supportive care only), compared to 18% of cirrhotic patients (p < 0.001).

The Fibrosis-4 score was calculated for all non-cirrhotic patients to estimate the severity of fibrosis. Out of the 69 patients, 6 (8.7%) had mild fibrosis, 24 (34.8%) had moderate fibrosis and 39 (56.5%) had severe fibrosis.

Out of the 69 patients without liver cirrhosis, 36 also had no elevated AFP levels in the serum. 33 (91.7%) of these patients were male and 3 (8.3%) were female. The median age of diagnosis within this particular group was 73.5 years (SD: 9.5).

As for staging, 61.1% of patients was classified as BCLC-A at diagnosis, 19.4% as BCLC-B and another 19.4% as BCLC-C. The majority of patients (88.9%) did undergo a liver biopsy and 67.6% had grade 1 disease. 26.5% had grade 2 HCC and 5.9% had a grade 3 tumour. Most patients (72.2%) had a unifocal lesion, with a median diameter of 5 cm (SD 3). 55.6% patients obtained 7 or less points for the Up-to-seven score.

With regards to spreading of disease, 5.6% of patients had distant metastases present at the time of diagnosis, 11.1% of patients had macrovascular invasions, 5.6% had lymph-node enlargement (>2 cm) and 83.3% had unilobular disease. 33.3% of patients did have a significantly raised CRP and the median AFP value was 3.325 (SD 1.54).

As for comorbidities in patients without cirrhosis and a negative AFP value, 13.9% also had coronary artery disease, 72.2% had hypertension, 16.7% had atrial fibrillation, 8.3% had cerebrovascular insufficiency, 8.3% had peripheral artery disease and 11.1% had chronic kidney insufficiency. Concerning medical treatment, 36.1% were taking Acetylsalicylic acid at the time of diagnosis, 11.1% oral anticoagulants, 16.7% were on Metformin, 2.8% were administering Insulin, 19.4% Levothyroxine, 27.8% of patients were on an ACE-Inhibitor and 22.2% on a Beta-blocker.

With regards to first-line treatment, 25% underwent ablation (RFA/MWA), another 25% received TACE, 22% underwent resection, 19.4% received Immunotherapy, 5.6% of patients were placed on a Tyrosine-kinase Inhibitor and 2.8% received supportive care.

8. Discussion

The incidence of Hepatocellular carcinoma in Austria is rising and continues to place a significant burden on healthcare systems worldwide. This study aimed to detect and analyse changes in the epidemiology of HCC within our study population at *Klinikum* Klagenfurt. By recognizing what transpired we hope to have a better understanding of HCC in our community and use this knowledge to improve prevention strategies and aid in better detection and treatment of HCC.

More patients in our cohort were diagnosed during the second time interval compared to the first, which proves that the incidence of HCC is also rising in our area. We were able to prove that the incidence of HCC remained higher in males compared to females and that there was no significant change in the ratio over time. Advanced age is known to be a risk factor for HCC. This was also true for patients in our study population with the median age of diagnosis being 72.5 years. It was however interesting to note that patients were on average 2 years younger when diagnosed with HCC in the second time-period.

Chronic underlying liver cirrhosis is known to be an important risk factor for HCC development. The majority of patients did have liver cirrhosis at the time of diagnosis, but interestingly enough, the proportion of patients without liver cirrhosis notably increased in the second time-category. Inversely, the number of patients with HCC and liver cirrhosis decreased over time.

Alcohol is known to be the predominant underlying cause of HCC in Austria and continued to be the number one cause of HCC in our cohort. Viral hepatitis was the second most common underlying aetiology of HCC and NASH the third. It has been proposed that alcohol-related liver disease is declining in Austria and that NAFLD/ NASH due to obesity and life-style diseases is increasing as the cause of HCC. Even though, statistically seen, the aetiology of HCC remained similar over time, an upward trend in the number of NASH cases was still evident in the second time-period. In a large, international meta-analysis conducted by Younossi et al., it was estimated that the global incidence of NAFLD is around 25.24% (95% CI: 22.10-28.65). [96] In a study conducted in New-south Wales, Australia that evaluated the epidemiological trends of HCC, it was also found that there was an increasing number of NAFLD/ NASH-related HCC cases occurring, although not statistically significant at the time. [97]

Another noteworthy finding was the fact that 42.6% of all patients diagnosed with HCC in our cohort did not have an elevated AFP level. Overall, only 24.3% of patients had an AFP level above 200 and only 20.6% of patients above 400. This emphasizes the fact the AFP cannot be used as a sole, reliable screening factor for HCC. Other studies have also proven that in about 40%-50% of HCC patients no elevated/ normal AFP levels were found. [98]

With regards to the staging and prediction of outcome, most patients were diagnosed as Child-Pugh A in our population. The number of non-cirrhotic patients increased over time and the number of patients classified as Child-Pugh stage B, decreased over time. Overall, most patients in our population were diagnosed as BCLC-A (early-stage disease). No significant changes over time were observed for this stage. Nonetheless, fewer patients were diagnosed with BCLC-B and more with BCLC-C in the second time-category, a decrease in terminally ill, BCLC stage D, patients were seen.

More liver biopsies were performed in our centre during the second time-period compared to the first. This was likely done to enable molecular categorization of tumours and thereby offer more targeted therapy. Most patients were diagnosed with grade 2 disease and no statistically significant changes were identified over time. There was also no difference between the two time-periods for parameters that measured the extent of spread.

We were not able to prove that comorbid life-style diseases were increasing in our study population, as there were no statistically significant changes between the two time-periods for hypertension, coronary artery disease or diabetes mellitus.

Many changes were observed in the approach to treating HCC. TACE was the most common first-line treatment modality used overall, but became more unpopular during the second time-interval. RFA was initially the most used first-line ablation technique, but MWA gained popularity over time. A rapid increased in the administration of Immunotherapy was also evident after 2018. There was a significant increase in the percentage of patients who received systemic therapy as part of their treatment regime during the second time-period.

The fact that less patients were staged as BCLC-B and more with BCLC-C in the second time-period caused a treatment migration away from TACE and lead to in increasing number of patients being treated with systemic therapy.

8.1. Survival

Generally, patients in our cohort survived between 19-22 months. It is important to note that despite major advances in the systemic medical management of HCC, there still was no significant change in the median survival time of patients between the two time-periods. Men however, had a longer survival time compared to women. Liver transplant

patients were later removed from the survival analysis in order to determine overall survival more accurately.

Although no improvement in the median overall survival time was seen between the two time-periods, survival time still improved compared to older data collected in Austria. In a study conducted at the Medical University of Vienna by Schöniger-Hekele et al., it was shown that HCC patients only had a median survival time of 8 months between 1991 and 1998. [99] Another study performed by Hucke et al. took an even more extensive look at the survival outcomes of all HCC patients in Austria. Here patients diagnosed between 1990-1999, had a mean survival time of 2.6 months (95% CI: 2.3-2.9) and those diagnosed between 2000-2009 had a 5.6-month survival time (95% CI: 5.1-6.1). In the group of patients that were diagnosed with HCC between 2010-2018, the overall survival improved significantly to 9.3 months ($p < 0.001$). [5] This still shows that the overall survival time did improve over the past 3 decades.

We took a closer look at the survival of patients without liver cirrhosis compared to those with cirrhosis. The median survival time of patients without cirrhosis was on average 2-3 months longer than those with cirrhosis. The survival time for cirrhosis vs. non-cirrhosis patients stayed the same in the respective time categories.

In terms of underlying aetiology, patients with viral hepatitis and NASH had the longest overall survival time. Patients with HCC related to alcohol use, performed the worst and had the shortest survival time. The Child-Pugh and BCLC staging systems correlated with OS/ survival time, as those staged as A had the longest survival. The ABLI score also correlated with overall survival time, as those with ALBI grade 1 had the longest survival time.

Slightly more patients presented with multifocal lesions compared to unifocal. Those with unifocal tumours had a better overall survival rate. The Up-to-seven score is often used in our centre to determine eligibility for liver transplantation. Here we could prove that those who fulfilled the criteria had a significantly longer survival time.

Patients who underwent resection as part of their treatment plan had the best survival rate. Generally, those with early-stage disease undergo a partial hepatectomy and therefore would naturally have a longer survival time. The survival time of patients who received ablation was in the proximity of those who underwent a resection. Patients on Immunotherapy seem to have had better outcomes compared to those on traditional Tyrosine-kinase Inhibitors.

8.2. HCC without cirrhosis:

The most significant discovery in our study was the fact that the incidence of HCC in patients without liver cirrhosis is rising. We investigated the characteristics of this specific patient group in more detail.

HCC patients without liver cirrhosis were on average 2 years older at the time of diagnosis, compared to those with cirrhosis. The male to female ratio stayed unchanged in the group of patients without cirrhosis, compared to our general HCC population and compared to cirrhotic patients alone. A marked difference in the underlying aetiology between cirrhotic and non-cirrhotic patients was detected. Here, the primary cause of HCC was NASH in the first place, viral hepatitis in the second place and underlying alcoholic liver disease in the last place. This stands in contrast to our general population group where alcoholic liver disease was the leading cause of HCC. In patients with liver cirrhosis, alcohol was the main underlying cause of HCC, viral hepatitis was in the second place and NASH third.

Haung et al. described the global epidemiology of HCC related to NAFLD. In their review it was also mentioned that patients with underlying NAFLD tended to be older at the time of diagnosis, compared to patients with viral hepatitis as underlying cause. [100] In a meta-analysis by Stine et al., 34% of patients with NASH-induced HCC had no underlying evidence of liver cirrhosis. [101] In our patient population without liver cirrhosis, half of the patients had underlying NASH.

The majority of patients were diagnosed as BCLC-A, similar as in our collective patient group. In the group without liver cirrhosis, more patients were diagnosed as BCLC-C compared to patients with cirrhotic, but less non-cirrhotic patients were staged as BCLC-D compared to cirrhotic patients.

Nearly all patients without liver cirrhosis did undergo a liver biopsy and most patients had grade 1 HCC. A larger proportion of patients had grade 1 disease compared to the general cohort and compared the cirrhotic patients alone. A higher percentage of patients without cirrhosis had unifocal lesions, as opposed to those with cirrhosis, where more patients had multifocal lesions.

In patients without liver cirrhosis, 52.9% had a normal/unelevated AFP level, compared to 39.2% of patients with liver cirrhosis. This suggests that AFP levels are even less sensitive in non-cirrhotic patients. In a review done by Desai et al., it was also found

that AFP levels were only elevated in 31-67% of non-cirrhotic cases, compared to 63-84% in cirrhotic patients. [102]

The median size of the space-occupying lesions was 5.3 cm (SD 3.4), compared to the smaller median of 4.5 cm (SD 3.5) in the collective HCC group and 4 cm (SD 3.7) in patients with cirrhosis.

A higher percentage of patients without cirrhosis suffered from comorbid hypertension, compared to patients with cirrhosis. Patients without cirrhosis had slightly less chances of developing portal vein thrombosis, but the percentage of patients with distant metastases were slightly higher compared to the general cohort. Desai et al. reported that 25% of non-cirrhotic patients had distant metastases at the time of diagnosis. [102] This is however more than the 13% we found in our study.

Another group of patients were identified, namely those without cirrhosis and an unelevated AFP level. The underlying aetiology was similar to those without cirrhosis, where alcoholic liver disease was now the least common cause. An even larger proportion of patients were staged as BCLC-A, grade 1 disease on histology and had unifocal lesions, compared to the group solely without cirrhosis. Out of all groups, this cohort had the fewest patients with distant metastases and the most patients with unilobular disease.

9. Conclusion

Hepatocellular carcinoma remains a major cause of concern in our society. The incidence continues to rise globally despite efforts being made to prevent HCC. This is also true in our specific cohort.

Changes in the epidemiology of HCC are noticeable over the past decade. More patients are being diagnosed without underlying liver cirrhosis than before. This group of patients was particularly interesting as it demonstrated a different aetiological pattern compared to our general HCC cohort.

NASH secondary to lifestyle diseases played a bigger role in the development of HCC without cirrhosis compared to alcohol use. This should alert health-care practitioners and policymakers to shift prevention strategies in this direction.

We were able to observe a clear trend that the number of NASH cases increased in our general study population. NASH remains an important upcoming risk factor for

HCC and is already one of the leading causes of HCC in the USA. In about 20-30% of NASH induced HCC, no evidence of liver cirrhosis is found. [26]

Even though major advances have been made in the medical management of HCC, the overall survival time of patients did not improve between the two time-periods. Patients are often still only diagnosed at a late stage of disease which leads to a shorter survival time. From this study, it is therefore evident that more effort should be made, with regards to active disease prevention. It also emphasizes the need for appropriate screening and surveillance programs in at risk patient-groups and highlights the fact that AFP alone is not a reliable screening tool as almost half of the patients did not have an elevated AFP level.

In light of these findings, one could ask the question if there is a need for new screening techniques and prevention strategies as we have proven that the epidemiology of HCC in our population is changing.

Strengths and limitations:

This study was limited by the fact that data was collected in a retrospective manner, therefore errors in documentation could have potentially led to incorrect data collection. This study was however strengthened by the fact that a clear population group and inclusion criteria was established.

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