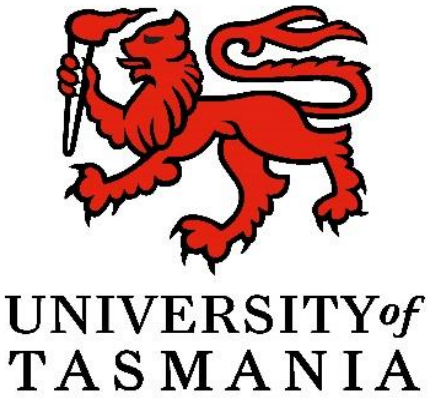

The Demographic and Clinical Characteristics of Primary Liver Cancer Patients in Tasmania

by

Thi Thu Hoa Nguyen

Menzies Institute for Medical Research

College of Health and Medicine

Submitted in fulfilment of the requirements for the degree of Master of Medical Science

University of Tasmania, Australia

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Declaration of Originality

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Statement of Co-Authorship

The following people and institutions contributed to the studies of undertaken as part of this thesis:

Candidate: Hoa Thi Thu Nguyen; Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia

Author 1: Dr. Barbara de Graaff; Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia

Author 2: Prof. Andrew J. Palmer; Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia; Melbourne School of Population and Global Health, University of Melbourne, Victoria, Australia

Author 3: Dr. Fiona Cocker; School of Medicine, University of Tasmania, Australia

Author 4: Dr. Kwang Chien Yee; Royal Hobart Hospital, Hobart, Tasmania, Australia; School of Medicine, University of Tasmania, Australia

Author 5: Mr. Brian Stokes; Tasmanian Cancer Registry, University of Tasmania, Hobart, Tasmania, Australia

Author 6: Dr. Karen Wills; Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia

Author 7: Dr. Michael Braude; Department of Gastroenterology and Hepatology, Monash University, Melbourne, Victoria, Australia

Author 8: Dr. Cristina Moldovan; Consultant Medical Oncologist, Icon Cancer Centre Hobart, Tasmania, Australia

Contribution of work by co-authors for each paper:

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Author contributions:

Designed study: Candidate, Author 1, Author 2, Author 3, Author 4, Author 5

Ethics approval processes: Author 1, Author 2, Author 3

Reviewed coded cause of death differences: Author 4, Author 7, Author 8

Analysed the data: Candidate

Interpreted the data: Candidate, Author 1

Wrote the manuscript: Candidate

Revised the manuscript: Candidate, Author 1, Author 2, Author 3

We, the undersigned, endorse the above stated contribution of work undertaken for each of the manuscripts contributing to this thesis:

Signed:

Hoa Nguyen	Dr. Barbara de Graff	Prof Alison Venn
Candidate	Primary Supervisor	Director of
Menzies Institute for Medical Research	Menzies Institute for Medical Research	Menzies Institute for Medical Research
University of Tasmania	University of Tasmania	University of Tasmania
Date: March 2021	March 2021	March 2021

Statement of Ethical Conduct

The research investigations conducted for this thesis abide by the ethical requirements of the University of Tasmania Human Research Ethics Committee. Ethics approval was gained through applications H0016958.

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List of Abbreviations

AASLD	American Association for the Study of Liver Diseases
ABS	Australian Bureau of Statistics
AFP	Alpha fetoprotein
AIHW	Australian Institute of Health and Welfare
ASR	Age standardize rate
BCLC	Barcelona Clinic Liver Cancer
BMI	Body mass index
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CI	Confidence Intervals
COD-URF	Cause of Death Unit Record File
CT	Computerised tomography
DAA	Direct-acting antiviral agents
DMR	Digital Medical Record
DOH	Department of Health
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
HCC	Hepatocellular carcinoma
IARC	International Agency for Research on Cancer
ICD-10	International Classification of Diseases and Related Health Problems 10th Revision
ICD-O3	International Classification of Diseases for Oncology, 3rd Revision
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NOS	Not otherwise specified

PLC	Primary liver cancer
PPID	Projected Person Identifier
SA2	Area of Usual Residence
SACC	Standard Australian Classification of Countries
SHR	Subdistribution hazard ratios
SVR	Sustained virological response
TCR	Tasmanian Cancer Registry
US	United States
WHO	World Health Organization

Abstract

Primary liver cancer (PLC) is the sixth most common cancer globally, and is the fourth leading cause of cancer mortality, accounting for 8.2% of all cancer deaths in 2018. Despite advances of new diagnostics and treatments, survival time of PLC patients remains poor, particularly in the absence of targeted screening programs to increase rates of early diagnosis. In Australia, both incidence and mortality rates of PLC have increased substantially, in contrast to the improved outcomes that have been observed for almost all other cancers.

The risk factors associated with PLC include chronic hepatitis B (CHB), chronic hepatitis C (CHC), diabetes, alcohol related liver disease, and non-alcoholic fatty liver disease (NAFLD). Demographic and epidemiological changes are impacting incidence of PLC in Australia, for example, the migration of CHB patients from high hepatitis B prevalence countries, and the increasing rates of obesity and diabetes. Understanding these changing risk factors and the impact on survival is important because it will help to inform healthcare policy for appropriate allocation of resources for prevention, targeted screening/surveillance and treatment. The aims of this Masters' research program are to describe the demographic characteristics, risk factors and survival time for all PLC cases in Tasmania (Study 1: Chapter 3) and to investigate the level of agreement for cause of death data between the Australian Bureau of Statistics (ABS) and Tasmanian Cancer Registry (TCR), along with medical specialist opinions and its impact on cause-specific survival (Study 2: Chapter 4).

Over a nine year period between 2007 and 2015, there were 293 PLC cases identified by using linked administrative data between the datasets. Hepatocellular carcinoma (HCC) (51.9%) and cholangiocarcinoma (20.5%) were the main types reported. Three-quarters of all PLC cases were male, and the average age was 70 years. For cases with a public hospital admission, 43% did not have a risk factor for PLC identified. Of those who did, the most common were cirrhosis (37%), chronic viral hepatitis (35%), diabetes (27%), and alcohol-related liver disease (23%). The mean age at diagnosis for all cases was 69.6 years, with a median survival time of 6.2 months. The 1-,3- and 5-year relative survival rates were 38.3%, 12.8%, and 6.7% respectively.

The linked PLC cases provided the opportunity to compare specific causes of death between the TCR and ABS. Conflicting records of cause of death were recorded for almost half of all PLC, with 20 cases had non-PLC underlying causes of death from the TCR dataset and 42 cases from the ABS dataset. These cases were independently reviewed by medical specialists with expertise in PLC. Concordance of cause of death data was estimated using Kappa statistics, and the impact on cause-specific survival time was explored using a competing risk framework. The overall concordance regarding causes of death data was minimal between the ABS and TCR (Kappa=0.35), moderate between the ABS and medical practitioners (Kappa=0.61), and strong agreement (Kappa=0.87)

between the medical practitioners were observed. These results reflect a greater level of agreement between medical practitioners than between coding agencies. Overall, cause-specific survival time was similar across the TCR, ABS and medical practitioners by sex, place of residence and country of birth, however, a small difference was observed for the type of liver cancer between the ABS, TCR and medical practitioners. As liver cancer is a low survival cancer, such results may be different to cancers with better survival such as breast cancer.

This thesis has made many distinct contributions including reporting the epidemiology of PLC in Tasmania and characterising the risk factors specific to this setting. These results support the need for surveillance to increase the rate of early detection of HCC in high risk patients. In turn, this will improve the very poor survival of PLC cases in Australia. This is the first study that has evaluated the impact of different coded causes of death on estimates of cause-specific survival for liver cancer cases.

Chapter 1. Introduction

This chapter provides the outline of this thesis, beginning with the definition of PLC and its subtypes (Sections 1.1 and 1.2). The incidence, mortality, demographic profile and risk factors of PLC worldwide is presented in Sections 1.3-1.7. Following this, the stage, methods and surveillance of PLC are presented in Sections 1.8 and 1.9. The context of PLC in Australia is discussed in Section 1.10. The need for PLC research in Tasmania is in Section 1.11. Finally, the aims and structure of the thesis are presented in Sections 1.12 and 1.13.

1.1. Primary liver cancer

Cancers of the liver can be classified as primary and secondary types. PLC arise from liver cells: hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma or hepatoblastoma[1, 2].

Secondary liver cancer is common and is metastases from tumours elsewhere in the body. The focus of this thesis is PLC, and as such all references to "liver cancer" refer to PLC.

1.2. Types of liver cancer

There are five main types of PLC, each named for the type of cell from which the cancer develops. Each of these types of PLC will now be described.

1.2.1. Hepatocellular carcinoma

HCC also known as hepatoma, is the most common type of PLC. HCC development starts in the hepatocytes, the predominant cell type in the liver, and accounts for 85-90% of all PLC worldwide[1, 3]. HCC mostly occurs in the setting of cirrhosis (i.e., scarring of the liver), a condition often related to chronic liver diseases including CHB and CHC infections, alcohol related liver disease, NAFLD, and ingestion of the fungal aflatoxin B1[1, 2, 4]. These risk factors are discussed in Section 1.7 below.

The incidence and mortality of HCC are discussed in Sections 1.3 and 1.4.

1.2.2. Cholangiocarcinoma

Cholangiocarcinoma, also known as bile duct cancer, develops from the biliary epithelium, and it can be divided to extrahepatic (75%-80%) and intrahepatic cholangiocarcinoma (20%-25%)[1]. These two types have different risk factors, presentation, prognosis, and treatment. However, only intrahepatic cholangiocarcinoma is considered as a PLC based on the anatomical location in the liver, and as such, this thesis only includes this type of cholangiocarcinoma.

Cholangiocarcinoma is the second most common PLC subtype globally, accounting for 10-15% of cases[5-8]. It is more common in Asian countries, with the highest incidence rates observed in Thailand (22.9 per 100,000 persons)[9], followed by China (7.5 per 100,000 persons) and South Korea (5.6 per 100,000 persons)[10]. Cholangiocarcinoma is rare in European countries and the US, but there is evidence of an increasing trend in incidence from 0.1/100,000 to 2.0/ 100,000 in some Western countries[7, 8].

1.2.3. Angiosarcoma

Angiosarcoma is a very rare type of PLC that forms in the lining of the hepatic blood vessels or lymphatic vessels[11, 12]. About 0.1-2.0% of PLC cases in Australia are hepatic angiosarcomas. This form is predominantly observed in patients aged between 60 and 80 years[11, 12]. This rare cancer tends to progress very quickly and has a poor prognosis as it is readily carried by the blood flow, easily metastasizes to distant areas, and has a high rate of recurrence rate[12].

1.2.4. Hepatoblastoma

Hepatoblastoma is a very rare type of PLC that develops from the primitive cell lines including foetal or embryonic stage hepatocytes[13]. It affects children during the first three years of life, and it appears as an abdominal mass in the liver[13]. Whilst the aetiology of hepatoblastoma is unknown, several genetic abnormalities have been identified as risk factors including Beckwith-Wiedemann syndrome, familial adenomatous polyposis, hemihypertrophy[14].

1.2.5. Fibrolamellar carcinoma

Fibrolamellar carcinoma is a distinct histological variant of HCC that typically affects young adults (10-35 years old) without sex predilection. The aetiology remains unknown but unlike HCC, this form is not associated with the risk factors of HCC such as cirrhosis, CHB, CHC[15]. Fibrolamellar carcinoma is characterized by a large, solitary, firm tumour that is well differentiated, with a dense fibrotic background in the liver. It accounts for 1-9% of all HCC[16].

1.3. Incidence

According to 2018 Global Cancer Statistics, PLC was the sixth most diagnosed cancer and the second leading cause of cancer mortality[17]. Annually, an estimated 840,000 new cases are diagnosed, and 780,000 deaths occur[17]. The incidence and mortality rates of PLC vary greatly, reflecting the uneven distribution of its risk factors, which are discussed in Section 1.7.

Low-and middle-income countries experience the greatest burden of PLC, where nearly 85% of PLC are diagnosed[17, 18] and the age standardize rate (ASR) incidence in is typically greater than 20 per

100,000 persons, e.g. countries in Eastern Asia, South-Eastern Asia, and Sub-Saharan Africa with incidence rates greater than 20/100,000 include: Mongolia: 93.7/100,000; China: 18.3/100,000; Vietnam: 23.2/100,000; Laos: 22.4/100,000; Thailand: 21.0/100,000, Gambia: 23.9/100,000; and Guinea: 21.8/100,000[17]. Although China bears more than half of all PLC cases globally due to its large population, Mongolia has the highest PLC rate in the world, with 117.0/100,000 for males and 74.1/100,000 for females[17].

In contrast, lower ASR incidence rates are reported in high income countries, such as Australia (5.7/100,000), the US (6.8/100,000), and in many European countries, the rate is less than 10 per 100,000 persons[17]. That said, these low rates have been increasing in recent years. For example, over the last 30 years in the US, ASR of PLC incidence has tripled from 1.6 to 4.9 per 100,000 persons between 1975 and 2005[19]. Similarly, in Australia, ASR incidence increased by more than 300% between 1982 and 2015, from 1.38/100,000 to 5.7/100,000[4, 20]. These increasing trends are related to changes in risk factors including CHB, CHC, alcoholic liver disease, and non-alcoholic fatty liver disease which is associated with type 2 diabetes and obesity[18, 21].

In contrast, incidence rates have declined in most Asian countries. The most notable reason for this is the reduction of CHB, the predominant risk factor for PLC in this region, due to introduction of an effective CHB vaccination of newborns in 2000 and a decline in the rates of HCC in younger age groups[18]. Additionally, the rates have declined in Asian countries by reducing exposure to aflatoxin B1 levels in the population, especially in China and Thailand[21, 22].

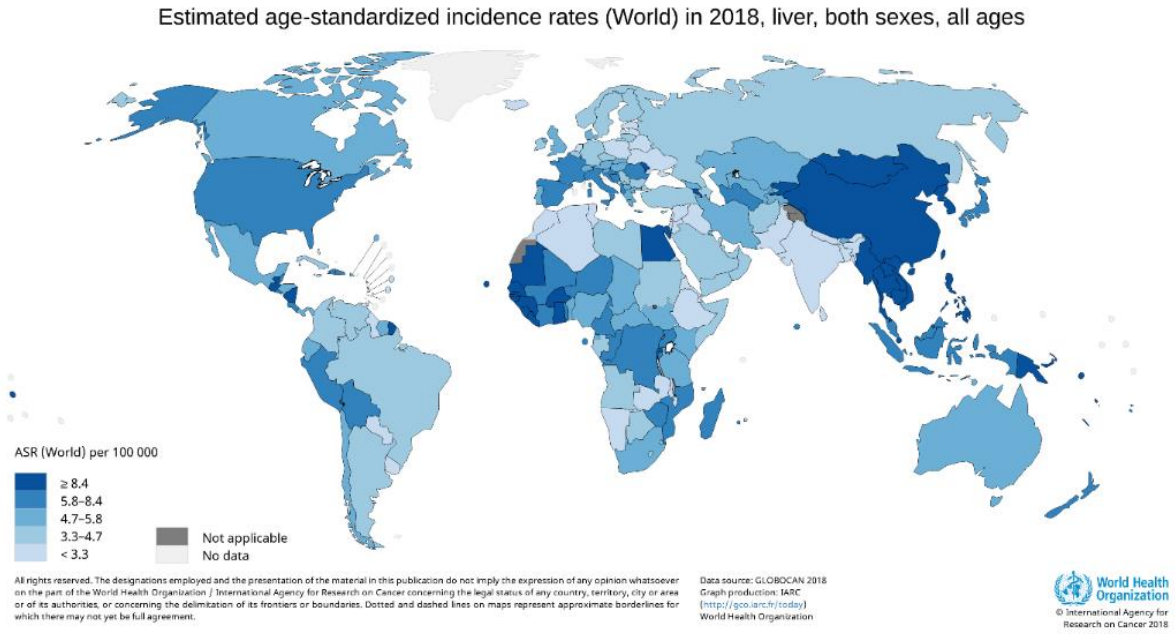


Figure 1: The region-specific ASR incidence rates by sex for liver cancer in 2018[17]

1.4. Mortality

PLC is the sixth leading cause of cancer mortality worldwide, with an estimated 782,000 deaths in 2018[17]. Many countries reported PLC as the fastest growing cause of any cancer death[17, 18].

The highest ASR mortality rates were reported for Asian countries (Mongolia: 75.4/100,000; Vietnam: 23.2/100,000; Thailand: 20.9/100,000)[17], and Egypt (31.8/100,000)[17], followed by some Sub-Saharan countries (Guinea: 19.5/100,000; Liberia 15.4/100,000; and Ghana: 15.4/100,000)[17]. Reflecting incidence rates, ASR mortality rates for high income countries were substantially lower: US: 4.9/100,000; Italy: 5.7/100,000; France: 6.3/100,000)[17].

The prognosis of PLC is poor, with low survival rates despite advances in treatment[2, 4, 23]. Many studies have found survival time is significantly longer in patients who are diagnosed at early stages and receive immediate treatment[23]. Treatments such as transplant or resection in these patients can achieve a 5-year survival rate of 70%[23]. For patients diagnosed at an advanced stage of PLC, palliative care is frequently the only treatment option, with median survival time less than one year[2, 23].

The five-year net survival for PLC has increased from 11.9% between 1995-2000 to 14.5% between 2004-2009 globally based on a study using 187 population-based registries and 36 countries[24].

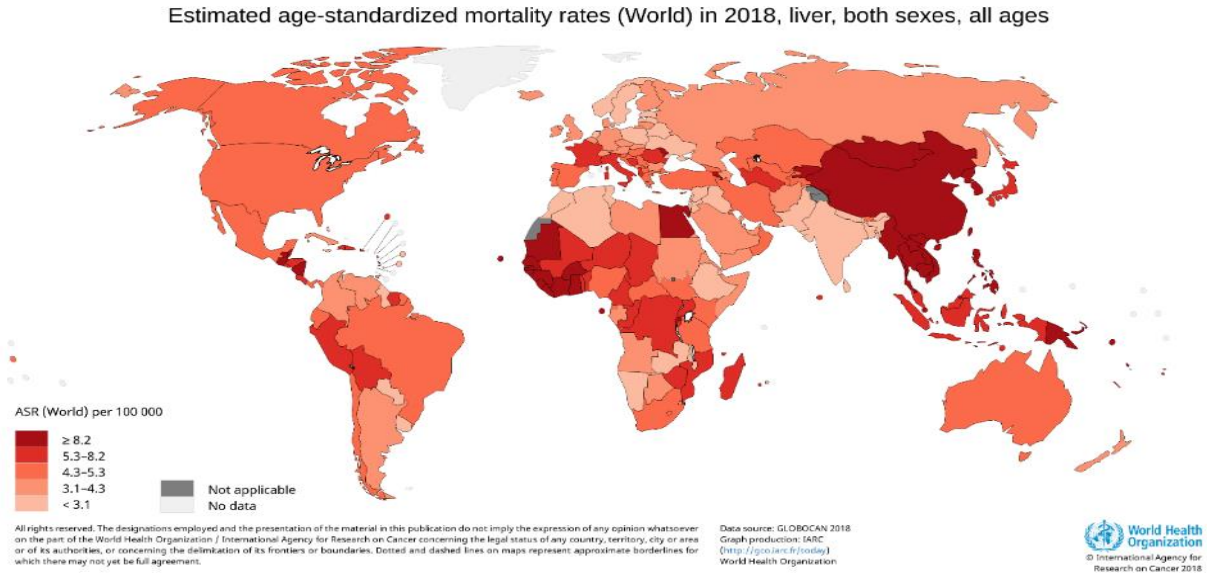


Figure 2: The region-specific ASR mortality rates by sex for liver cancer in 2018[17]

1.5. Data sources

Cancer registries are the core source of data on cancer globally, even though the International Association of Cancer Registries (IACR) estimated that cancer registries cover only 21% of the world's population[25]. The population coverage and quality of cancer registries vary by locations,

states and countries, are more commonly established in high income countries and are often not an integral part of middle and low income countries' cancer data collection and reporting infrastructure. In addition, the availability and quality of death certificate information vary widely, especially in low and middle income countries where either poor quality data or a complete absence of death registrations occur. The cause of death data sources are described in more detail in section 4.2, Chapter 4.

1.6. Demographic profile of liver cancer patients

1.6.1. Sex disparities

Globally, almost all countries report PLC incidence and mortality rates in males that are two to three times higher than rates in females[17] (Figure 3). The greatest sex disparities in incidence are observed in Samoa with a male to female ratio of 6.9 (17.3/100,000 in male and 2.5/100,000 in female), and French Guiana (6.7; 15.5/100,000 in men and 2.3/100,000 in women)[17]. Intermediate disparities in incidence are observed in China: 3.0 with 27.6/100,000 for males and 9.0/100,000 for females; Australia: 3.0 with 8.6/100,000 for males and 2.9/100,000 for females[17]. Exceptions to this, in which only marginal disparities are observed include Bolivia: 0.9 with 5.6/100,000 for males and 6.7/100,000 for females and in Tunisia: 0.9; 2.5/100,000 for males and 2.7/100,000 for females[17].

Although the reason for this difference is not completely understood, it is partly explained by higher levels of androgen in males, which promotes development of HCC[26]. In contrast, higher levels of estrogen in females may inhibit HCC development through its anti-inflammatory effects. Further, CHB, CHC, alcohol consumption is more prevalent in males, contribute to higher rates of HCC[26].

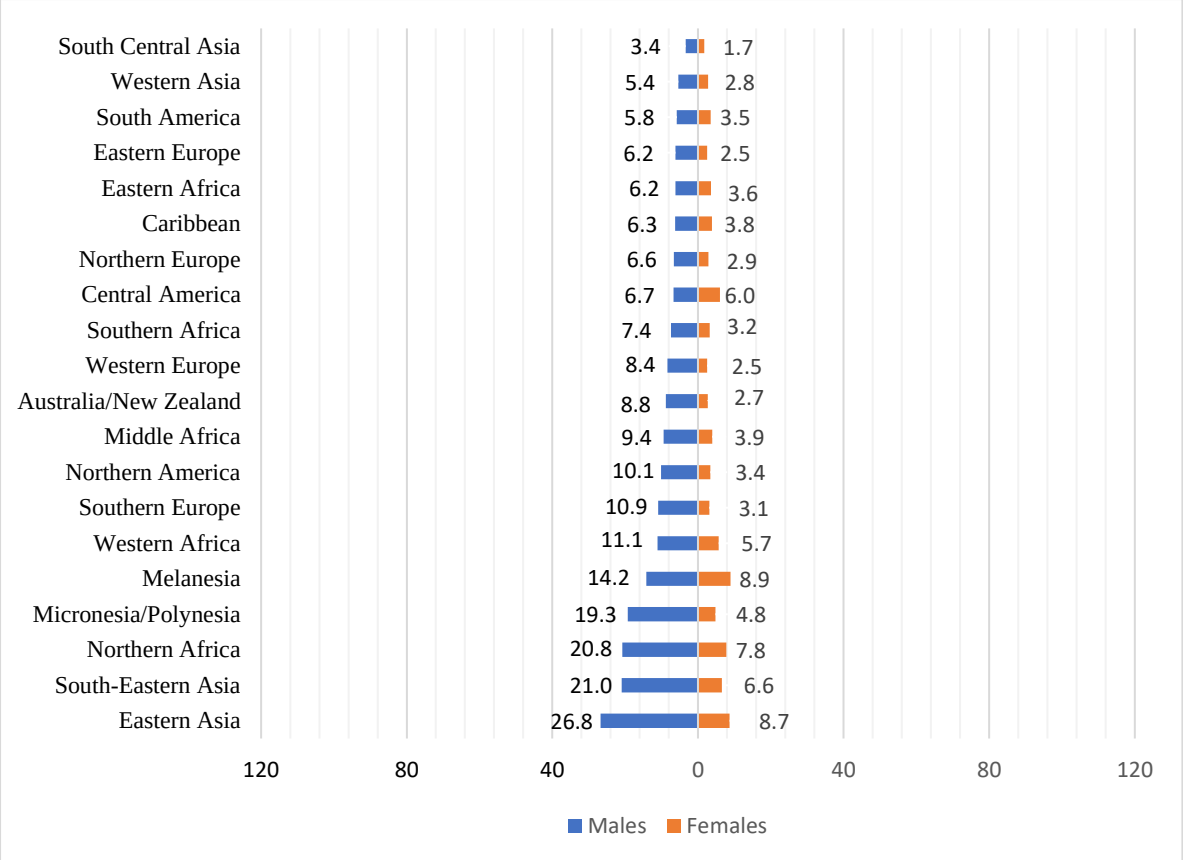


Figure 3: Region specific incidence age-standardized rates by sex for cancers of the liver in 2018[17]

1.6.2. Age

PLC incidence rates increase with age in all populations, with the highest incidence among those aged 70 years and older. In countries with lower incidence rates such as the US and many European countries, the incidence rates are generally very low before age of 40 and then gradually increase with age. In high incidence countries of East Asia and Africa, PLC incidence rates increase until age of 55 years and then plateau until age of 70 years. This is likely due to the high rates of CHB in these countries, many of which occur through vertical transmission at birth[27, 28].

1.6.3. Ethnicity

HCC incidence and mortality also vary between different ethnic groups. For example, in the US the incidence and mortality rates were highest in the American Indian/Inuit groups (incidence 15.2 per 100,000 persons; mortality 11.9 per 100,000 persons), followed by Asian and Pacific Islanders (incidence 13.5 per 100,000 persons; mortality 9.8 per 100,000 persons). The lowest rates were reported for non-Hispanic whites (incidence 6.3 per 100,000 persons; mortality 5.5 per 100,000 persons)[29]. Regarding survival time between different ethnicities, 5-year survival is highest in Asian and Pacific Islanders (27.1%) and lowest in American Indian/Inuit (16.2%), and African American

groups (16.3%) [29]. Differences in the prevalence of risk factors (CHB, CHC, alcoholic liver disease, non-alcoholic fatty liver disease) account for much of the observed variation in liver cancer rates, and to some degree, the disparities in access to high quality care[21, 22, 29, 30].

1.7. Risk factors of liver cancer

There are several factors associated with the risk of developing PLC including cirrhosis of the liver, CHB infection, CHC infection, NAFLD, obesity, type 2 mellitus, and smoking[4, 31]. As HCC is the main type of PLC (making up to 70 - 90% of total numbers), the following will focus on its risk factors.

1.7.1. Cirrhosis

Cirrhosis is severe scarring of the liver due to risk factors including viral hepatitis, excessive consumption of alcohol and NAFLD. In response to chronic liver injury caused by these risk factors, nodules within the liver develop, which are surrounded by fibrous bands. In turn, this frequently leads to portal hypertension and liver cancer[32]. More than 80% of PLC occurs in the setting of cirrhosis[33-35]. This condition is characterised by scarring of the liver and usually occurs when the liver is damaged over an extended period. It is referred to as the end-sate of chronic liver disease[34-36] and is strongly associated with HCC with one US-based cohort study in the reporting 95% of HCC patients had a diagnosis of cirrhosis[33].

1.7.2. Chronic hepatitis B infection

CHB is considered is one of the most common risk factors for PLC. Overall, almost 50% of cases of PLC are attributable to CHB infections and CHC infection[37]. The virus acts as a mutagenic agent which causes chromosomal rearrangement and increases genomic instability[38]. Through integration of DNA into the host genome in hepatocytes, the virus has been clearly linked to the development of HCC with the risk of developing HCC is higher among CHB patients compared to people who are not infected[39].

CHB affects almost 3.5% of the world population and results in 887,000 deaths[37]. Asian and sub-Saharan African countries have the highest prevalence of CHB, accounting for 68% of cases. The annual incidence from CHB to HCC is 2-8%[38, 40]. Most viral transmissions in high prevalence CHB countries occur via vertical transmission, either perinatally or soon after birth. In contrast, in lower prevalence countries the main transmission routes are through blood and bodily fluid contacts such as injecting drug use, sexual contact, and tattooing[37].

Vaccination against HBV for all newborns and high-risk groups is recommended by the World Health Organization (WHO)[37]. By the end of 2016, 186 countries had introduced universal hepatitis B

vaccination programs to their national immunization campaigns[37]. This has effectively reduced the risk of HCC, with many countries reducing the prevalence of HBV across younger age groups, especially in Eastern Asian countries[37, 41].

WHO recommends the use of oral treatments including tenofovir or entecavir. These treatments do not cure CHB infection, but it suppresses the replication of the virus[37]. However, even with the known benefits of CHB vaccinations and treatments, the risk of developing HCC cannot be eliminated. Thus, lifelong surveillance programs for patients with CHB must be continued.

1.7.3. Chronic hepatitis C infection

About 1% of the world population is estimated to have CHC, with the crude incidence of 23.7 per 100,000 persons[37]. CHC accounts for nearly 400,000 deaths every year, mostly due to CHC-related cirrhosis and HCC[37]. The regions most affected are Eastern Mediterranean, with the incidence rate of 62.5/100,000, and the European Region (61.8/100,000), followed by African counties (31.0/100,000), and South-East Asia (14.8/100,000)[37]. The Western Pacific region recorded the lowest rate of 6.0/100,000[37]. Among CHC patients, the risk of developing cirrhosis after 20 years varies between studies and areas but is estimated to be 10-15% for males and 1-5% for females[42, 43].

The HCV transmissions route is associated with direct percutaneous exposure to blood, via blood transfusions, needle sharing by intravenous drug users, the primary route in high income countries. In contrast, in low- and middle-income countries, the main transmission mechanisms are contaminated blood transfusions and unsafe medical procedures[37].

Although no vaccines for the CHC have been developed, the discovery of direct-acting antiviral agents (DDAs) such as sofosbuvir have revolutionised treatment. Over the last five years, DAAs have largely replaced previous treatments using pegylated interferon: which was characterised by low uptake and serious adverse events[44]. DAAs are highly effective, with approximately 95% of patients achieving a sustained virological response (SVR), i.e., a cure. However, DAAs are very expensive and access to treatment is lacking in many countries. SVR has shown to reduce the risk of HCC in CHC patients[44].

1.7.4. Alcohol related liver disease

Alcohol-related liver disease occurs in the context of alcohol overconsumption. Clinic presentations range from fatty liver/hepatic steatosis to alcoholic hepatitis, fibrosis, cirrhosis, and leading to HCC[45]. The International Agency for Research on Cancer (IARC) has categorised alcoholic drinks as “carcinogenic to humans” and likely to increase the risk of PLC[46]. Some guidelines consider consumption of more than 40g of alcohol per day at risk of developing liver disease[47].

Alcoholic liver disease is a more prominent PLC risk factor in high income countries such as the US and across Europe. The highest per capita alcohol consumption (21.3g/day) has been reported for Europe and the lowest (1.2g/day) in the Middle East and Northern Africa, with a global average of 15.1g/day[48]. High levels of alcohol consumption increase the relative risk of developing HCC by 3-10 times[49]. In addition, alcohol acts synergistically with other risk factors such as CHB, CHV, and tobacco use to increase the risk of PLC [46, 49].

1.7.5. Non-alcoholic fatty liver disease

NAFLD can result in liver damage particularly if fat accumulation in the liver progresses with inflammation[50, 51]. NAFLD is part of Metabolic Syndrome characterized by insulin resistance and being overweight or obese[50, 52]. In the general population, the global prevalence of NAFLD is estimated at 21% and expected to increase to 100 million in 2030[52]. Prevalence is increasing, particularly in low- and middle-income regions such as Asia and Africa due to rapid lifestyle and dietary changes in these areas[53].

Prevalence is highest in the Middle East and South America (more than 30%), followed by Asian countries (estimate of 27%) and European countries with an average of 23.71%)[53]. Whilst HCC due to NAFLD is less commonly observed than other aetiologies, the increasing global prevalence of obesity is expected to contribute to increased prevalence of NAFLD associated HCC in the coming decades. In contrast to other liver diseases, NAFLD can lead to HCC without cirrhosis, similar to CHB infection

The mean annual rate of progression in non-alcoholic steatohepatitis (NASH) (the extreme form of NAFLD) to fibrosis was 41% and HCC incidence among NAFLD cases is 0.44 per 1,000 person-years. Although PLC cases related to NAFLD are less common compared to other factors, the impact may be substantial in the context of the increasing prevalence trends of obesity, diabetes and metabolic syndrome observed globally[51].

1.7.6. Aflatoxin

Aflatoxin is a mycotoxin produced by the Aspergillus flavus and Aspergillus parasiticus moulds that contaminates peanuts, wheat, soybeans, ground nuts, corn, and rice[54]. Cultivation and storage in moist, warm environments can lead to the growth of this fungus[54]. The most potent aflatoxin B1 has been classified as a group 1 human carcinogen by IARC[54-57]. Between 4.6-28.2% of all HCC cases are attributable to aflatoxins globally[57]. It is more common in warmer and tropical countries such as sub-Saharan Africa and East Asia. Further, many countries, such as Australia have strict rules in place governing testing of imported at-risk food products for aflatoxins[58].

1.7.7. Obesity and Type 2 Diabetes

Obesity is a condition in which excess body fat has accumulated to an extent that may have negative health effects. Obesity is defined as a body mass index (BMI) more than 30kg/m^2. The WHO estimated that there were 650 million obese adults (13%) in 2016[59]. Obesity has been shown in many studies to independently increase the risk of developing HCC, largely due to metabolic syndrome and its hepatic manifestations (i.e., NAFLD)[59, 60]. For example, a report in European Prospective Investigation into Cancer and Nutrition found obesity was attributable to 16% of HCC cases in Europe[60, 61]. Further, a systematic review of BMI and HCC risks in Western populations found obesity was independently associated with a two-fold of HCC-related mortality compared to those with normal BMI[62].

Type 2 diabetes is related to an increased risk of developing HCC, usually in those who have other risk factors such as CHB, CHC patients. Globally, there were an estimated 392 million people (6% in 2015) with type 2 diabetes, making up 90% of all cases of diabetes[63]. Type 2 diabetes occurs mainly because of obesity, overweight and lack of physical activities[64]. Some studies have found patients with type 2 diabetes have about a 2-3 times higher risk of developing HCC compared to those without diabetes[21, 65].

1.8. Diagnosis of liver cancer

1.8.1. Tumour makers

Alpha fetoprotein (AFP) is a biomarker protein that can be measured in the blood and is widely used in surveillance programs for HCC[27]. As the sensitivity of this measure (approximately 60%) and specificity (80% at the cut-off level of 10-20ng/mL[66]) is limited, this test is carried out in conjunction with abdominal imaging such as ultrasound, CT and MRI. AFP levels greater than the healthy reference range can occur in the context of pregnancy, hepatitis, and jaundice[67]. Due to the limitations of this test, AFP is used as a sign of HCC, often in combination with liver ultrasound, for surveillance of HCC for high-risk patients.

1.8.2. Liver ultrasound

Liver ultrasound is a useful, real-time, non-invasive test that can be used for screening patients at high-risk and in the diagnosis of PLC[3, 68]. It is used to assess the structural integrity of the liver and features of portal hypertension[3, 68, 69]. Ultrasound may be indicated in people with abnormal liver function tests; symptomatic presentations with abdominal pain, jaundice[3, 68, 69].

The sensitivity of liver ultrasound to detect PLC ranges between 51-71% and specificity ranges between 80-100%[70-72]. Importantly, ultrasound is dependent on operator expertise and is of limited

effectiveness in obese patients. It is usually performed at 6 months intervals for screening high-risk patients[73-76].

1.8.3. CT scan

Computerised tomography (CT) is a medical imaging procedure that uses x-ray measurements to produce detailed, cross-sectional pictures of the body. It helps to feature the tumour and to determine if it is spreading[70, 77].

CT scan is used following a lesion identified on liver ultrasound to confirm the diagnosis of HCC by radiological criteria. The sensitivity and specificity of CT are 63-76% and 87-98%, respectively[70, 77, 78]. Due to the increased risks of developing cancer from the ionising radiation from CT scans, this method is generally not used for regular screening for PLC[70, 78].

1.8.4. MRI scan

An MRI (magnetic resonance imaging) is a test that uses powerful magnets and radio waves to create detailed cross-sectional pictures of the body[79]. MRIs are increasingly being used to diagnose PLC/HCC due to the high sensitivity (77-90%) and specificity (84-97%), respectively[70, 77, 78]. This investigation is often used as a supplementary to CT scans for diagnosis of PLC[70, 77]. The high costs and time associated with MRIs limit the usefulness of this approach for screening[70, 77].

1.8.5. Biopsy

A liver biopsy involves taking a small sample of cells from the affected area for examination of liver histology[80, 81]. It has traditionally been the gold standard approach for assessing liver scarring and for diagnosis of PLC. However, this approach carries a substantial risk of bleeding, iatrogenic injury, and complications[80, 82, 83]. Further, the insertion of a needle into a tumour, the risk of dislodging a cell along the needle path is high[83]. With the advances and availability of imaging techniques, biopsy is now used for less than 5% of HCC diagnoses. Liver biopsy is indicated only when there is uncertainty regarding the results of the AFP test, ultrasound, CT scan/ MRI scans[80, 82, 83].

1.8.6. Staging of liver cancer

The stage of PLC involves describing the size of the tumours, the location and spread to other parts of the body[84]. Staging is carried out to inform the treatment plan. Several staging systems have been proposed in HCC management, but there is no globally accepted system. In this thesis, the Barcelona Clinic Liver Cancer (BCLC) staging system is used as it is currently the most widely used internationally as well as in Australia[2]. This system contains four components: the size, number or

spread of the tumour; Child-Pugh score; presence of portal hypertension and the Eastern Cooperative Oncology Group (ECOG) performance scale[84].

The BCLC staging system[84]

0 (very early stage)	Single tumour less than 2 cm; the liver is working normally without portal hypertension (Child-Pugh A)
A (early stage)	Single tumour of any size or up to 3 tumours less than 3 cm; the liver is working well (Child-Pugh A or B)
B (intermediate stage)	Many tumours in the liver; single tumour > 5cm, the liver is working well (Child-Pugh A or B)
C (advanced stage)	The tumour has grown into one of the main blood vessels of the liver, or spread to the lymph nodes or other body organs; the liver is still working well (Child-Pugh A or B)
D (end-stage)	Child-Pugh C with any size tumour

Child-Pugh score[84, 85]

The Child-Pugh score is a system for scoring how well the liver is functioning. The system includes the following five factors: bilirubin levels; albumin levels; prothrombin time; ascites; and encephalopathy[84]. Each measure is scored from 1-3, and based on that score, people fall into 1 of 3 categories of the ECOG scale.

A	5-6 points; liver is working well, and cirrhosis is less advanced
B	7-9 points; Liver is working moderately well
C	10-15 points; Liver is not working well, and cirrhosis is advanced

The Eastern Cooperative Oncology Group (ECOG) scale[86, 87]

The ECOG scale is a measure used to assess the level of functioning in terms of the daily living abilities of the patients. It is scored from 0 to 5 as follows.

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

1.9. Surveillance of liver cancer

The WHO's definition of screening is "the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests which can be applied rapidly and easily to the target population"[88]. It is the repeated usage of the screening test at regular intervals to detect disease in latent or asymptomatic patients, for a disease for which an intervention has the potential to alter its course[88].

The outcomes for PLC patients are highly dependent on the stage at which it is detected. If detected early, HCC is potentially curable[2, 21, 89]. Early identification of small tumours with subsequent treatment has a 5-year survival rate of 50-70%[41, 90, 91]. In contrast, management of patients diagnosed with advanced tumours is palliative[2, 92]. Many studies have identified the effectiveness of HCC surveillance programs[93].

Many international liver societies recommend surveillance of HCC for high risk populations. For example, the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend surveillance every 6 months, consisting of ultrasound ± AFP for high risk patients (cirrhosis patients and subgroups of CHB patients)[74, 94].

In the Australian context, a consensus statement was published in late 2020 by PLC specialists with evidence-based recommendations[95]. This paper states it is now a priority to institute HCC surveillance strategies in Australia for high-risk patients, with the aim of identifying tumours at early stages. The authors recommend surveillance should occur 6-monthly using liver ultrasound and ± AFP in[95]:

People with cirrhosis (any aetiology)

Non-cirrhosis patients with CHB infection in:

- Asian men older than 40 years
- Asian women older than 50 years
- People born in sub-Saharan Africa older than 20 years
- Aboriginal and Torres Strait Islander people older than 50 years

1.10. The context of primary liver cancer in Australia

1.10.1. Incidence and mortality

PLC is estimated to be the fourth most common digestive tract cancer and the third most common digestive tract cancer mortality in Australia in 2018[2]. In Australia there are an estimated 2,215 new cases of PLC and 2,088 PLC deaths annually[2]. Incidence in males is 3.4 times higher than for females, and PLC mortality is 2.4 times higher than females in Australia[2].

Whilst PLC is a relatively rare cancer in Australia, both the incidence and mortality rates have been increasing in recent years. Between 1982 and 2014, ASR incidence increased by over 306% (from 1.8/100,000 persons to 7.4/100,000 persons), and ASR mortality by 184% (from 2.3/100,000 persons to 6.6/100,000 persons)[20]. These trends are in contrast to stable incidence rates for most other cancers, along with their decreasing mortality rates. Whilst this has occurred in the context of improved diagnostic imaging and therapeutic options, the survival time of PLC patients has increased but

remains poor (5 year relative survival rate was 18%[2]). This is lower compared to 5 year relative survival time for all cancer combined (69%)[2].

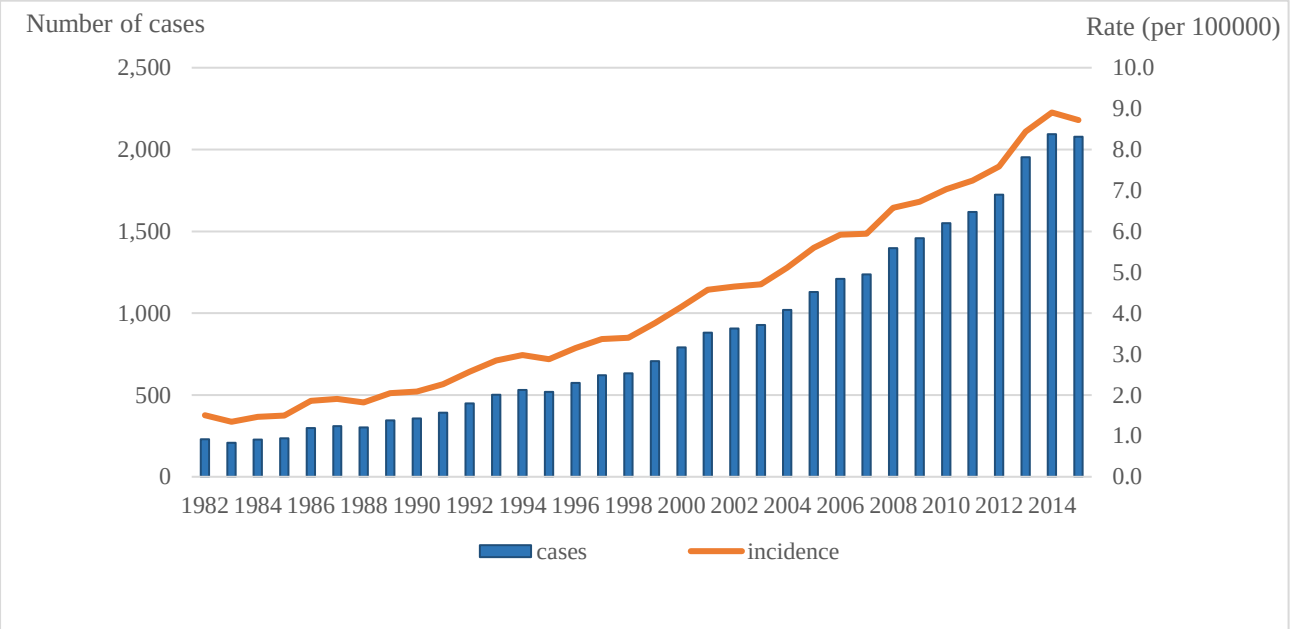


Figure 4: Incidence trends of liver cancer in Australia from 1982-2015[2]

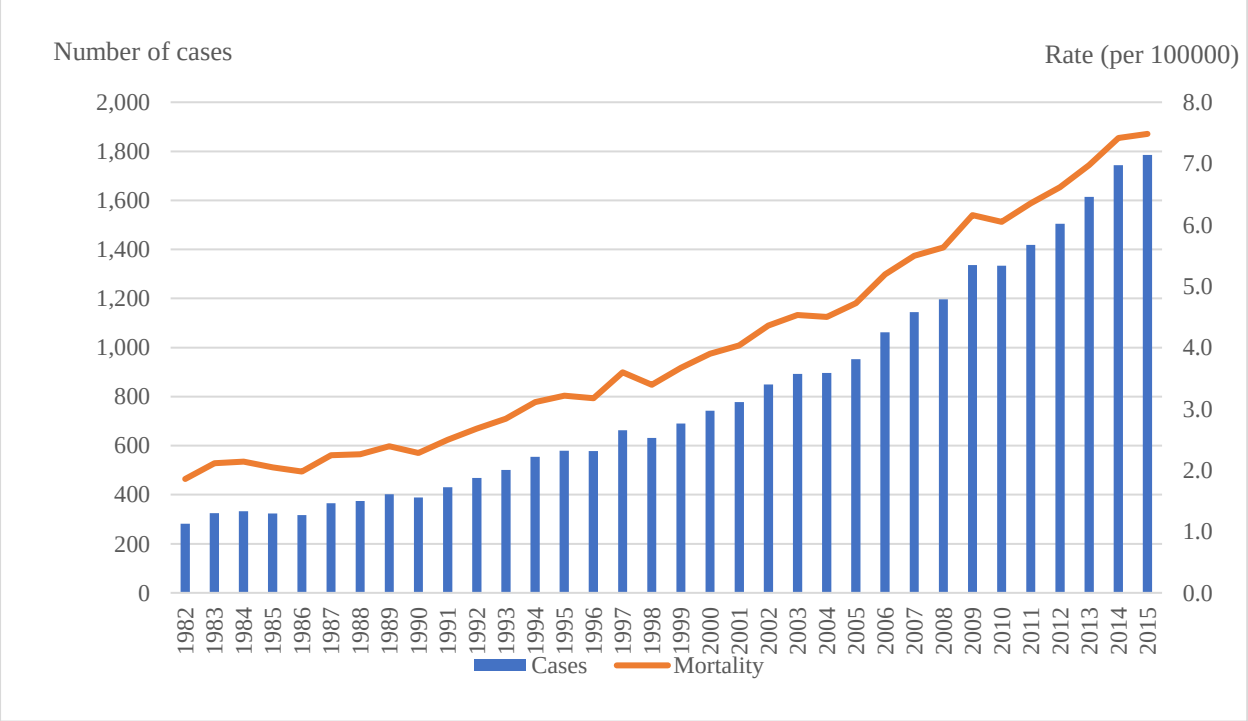


Figure 5: Mortality trends of liver cancer in Australia from 1982-2015[2]

The most common subtype of PLC in Australia is HCC, accounting for 68% of all PLC cases, followed by cholangiocarcinoma type with 21%[2]. The 5-year relative survival rate is highest in HCC patients (22%), whereas lowest in unspecified group (9.5%). These patients belong to this

'unspecified group' when the type of PLC was not specified as the diagnosis were at an advanced stage, and further investigation to identify the type of PLC is often unwarranted as it will have no impact on treatment[2].

1.10.2. Risk factors for liver cancer in Australia

Chronic Hepatitis B

CHB is one of the most common risk factors for PLC. In Australia, there were an estimated 233,947 people living with hepatitis B in 2017[96]. Of those, 90,027 cases (38%) were born in Asia and 26,241 (21%) were Aboriginal and Torres Strait Islanders. The prevalence of Hepatitis B has reduced in younger age groups (under 30), reflecting the impact of the universal infant hepatitis B vaccination program since 2000[96]. Across the 233,947 individuals estimated to be living with CHB, approximately 64% have been diagnosed[96]. Among those, just 18% received regular monitoring, and 8% received antiviral treatment[96].

Chronic hepatitis C

At the end of 2017, there were an estimated 10,537 hepatitis C notifications[96]. Notifications of hepatitis C infections have decreased from 52.6 to 44.2 per 100,000 population between 2008 and 2017[96]. The main route of transmission of CHC in Australia is sharing of injecting equipment in the context of injecting drug use[96]. The highest of hepatitis C notification rates are seen in the Northern Territory (58.0 per 100,000), and lowest in Tasmania (48.6 per 100,000)[96].

Other risk factors

Other risk factors identified in Australia include alcoholic liver disease, obesity, NAFLD and tobacco use[2]. A study in Victoria, Australia has found that alcoholic liver disease was present in 39% of their cohort, and 14% with fatty liver disease[97].

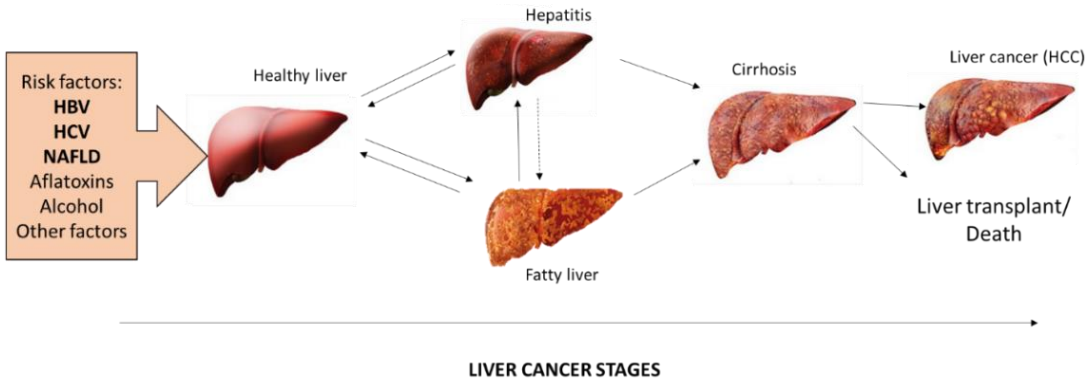


Figure 6*:* Liver cancer stages[98-101]

1.11. What is the need for primary liver cancer research in Tasmania?

In Australia, the incidence and mortality of most cancers have decreased in recent decades. In contrast, both the incidence and mortality of PLC have increased substantially[20, 102], and this is projected to continue in the coming decades[2, 17].

This increased burden is associated with increased prevalence of the key risk factors for PLC in Australia: sequelae of excessive alcohol use, CHB, and increasingly NAFLD[2]. Understanding the demographic characteristics of people diagnosed with PLC is required to develop strategies to reduce the burden of PLC. For example, different approaches are required to raise awareness of liver health for patients from different countries and cultures: a one size fits all strategy will not work. To date, the demographic characteristics of PLC cases in Tasmania have been unknown.

In addition, survival of different types of PLC in Tasmania has been unknown. Investigating local data is important in prevention, management and in guiding healthcare policy and research. Thus, understanding the epidemiology of PLC and the factors affecting their survival time is very important as it will have implications for targeting and informing strategies of effective health service to reduce the burden of this cancer in Tasmania.

To provide a comprehensive picture of liver cancer in Tasmania, the quality of cause of death data derived from the TCR and ABS is also investigated. Other studies have shown different cause of death leading to a difference in survival[103, 104]. To-date, no research has been published for PLC examining a) the level of agreement between different agencies coding deaths and medical practitioners, and b) the impact these differences may have on cause-specific survival estimates.

1.12. Aims of this research

The aims of the studies contained in this thesis are:

- To determine the characteristics and survival time of PLC in Tasmania by subtypes; and
- To estimate the accuracy of cause of death data and the impact on cause-specific survival

The second aim arose from the work undertaken for the first aim. Almost half of all PLC cases were found to have a conflicting cause of death recorded in different datasets. In response, study 2 was undertaken to explore this in the context that previously published studies have reported that cause of death data may be inaccurate and that this can lead to imprecise cause-specific survival estimates[103, 105, 106].

1.13. The structure of the thesis

The thesis contains five chapters. The first chapter provides background to understand about PLC, including the descriptions of subtypes of PLC, the incidence and mortality of PLC globally, the demographic profile, risk factors of PLC, the PLC context in Australia, the diagnostic approaches of PLC, staging of PLC and the need for this study.

Chapter 2 describes the methodology used in the two studies.

Chapter 3 presents a draft paper of Study 1 “Characteristics and survival of primary liver cancer patients in Tasmania by subtypes: A data linkage study”.

Chapter 4 presents the draft paper of Study 2 “Accuracy of cause of death data: A case study based on primary liver cancer”.

Chapter 5 discusses and summarises the whole thesis and offers suggestions for future PLC research.

This thesis is part of a larger study that will develop a patient-centred intervention to support increased participation in liver cancer surveillance. The studies included in this Master’s thesis will provide critical information on the epidemiology for diagnosis of PLC in Tasmania and will be used to inform the development of the future surveillance intervention. As such, the primary aim is to determine characteristics and survival time of PLC in Tasmania and the accuracy of PLC data in Tasmania.

Chapter 2. Methods

This chapter provides a brief overview of the study methods, and these are further detailed within Chapters 3 and 4.

2.1. Study design

To address the aims of this Master's thesis, a retrospective study design is adopted using linked health administrative datasets. The datasets include:

- Tasmania Cancer Registry (custodian: Tasmanian Department of Health (DOH))
- Tasmanian Emergency Department Presentations (custodian: Tasmanian DOH)
- Tasmania Public Hospital Admissions (custodian: Tasmanian DOH)
- Tasmania Coded Cause of Death (custodian: Australian Bureau of Statistics)

2.2. Participants

In Australia, cancer registration is mandatory in all States and Territories. For Tasmania, the TCR is responsible for collecting, coding and reporting incidence, mortality and survival time for all malignant neoplasms within the state[107].

The participants in this study were defined as any individual aged 18 years or older with a confirmed PLC (ICD-10 code of C22.*) diagnosed in Tasmania between 1/1/2007 and 31/12/2015.

2.3. Data Linkage process

From the year 2013, the TCR used radiological and clinical diagnoses for HCC (coded as 81703-Hepatocellular carcinoma). Then from the year 2017, according to changes in coding rules in other states, cases with 8003 (Malignant neoplasm) were coded as HCC. As a result, the number of tumours coded to 81703 dropped substantially. Changes in TCR staff and lack of documentation of coding rules would have impacted the number of tumours coded to 81703 from 2013 onwards. The flowchart below describes the processes for all stages of the preparation of linked data.

These detailed steps were described in the method of Chapter 3.

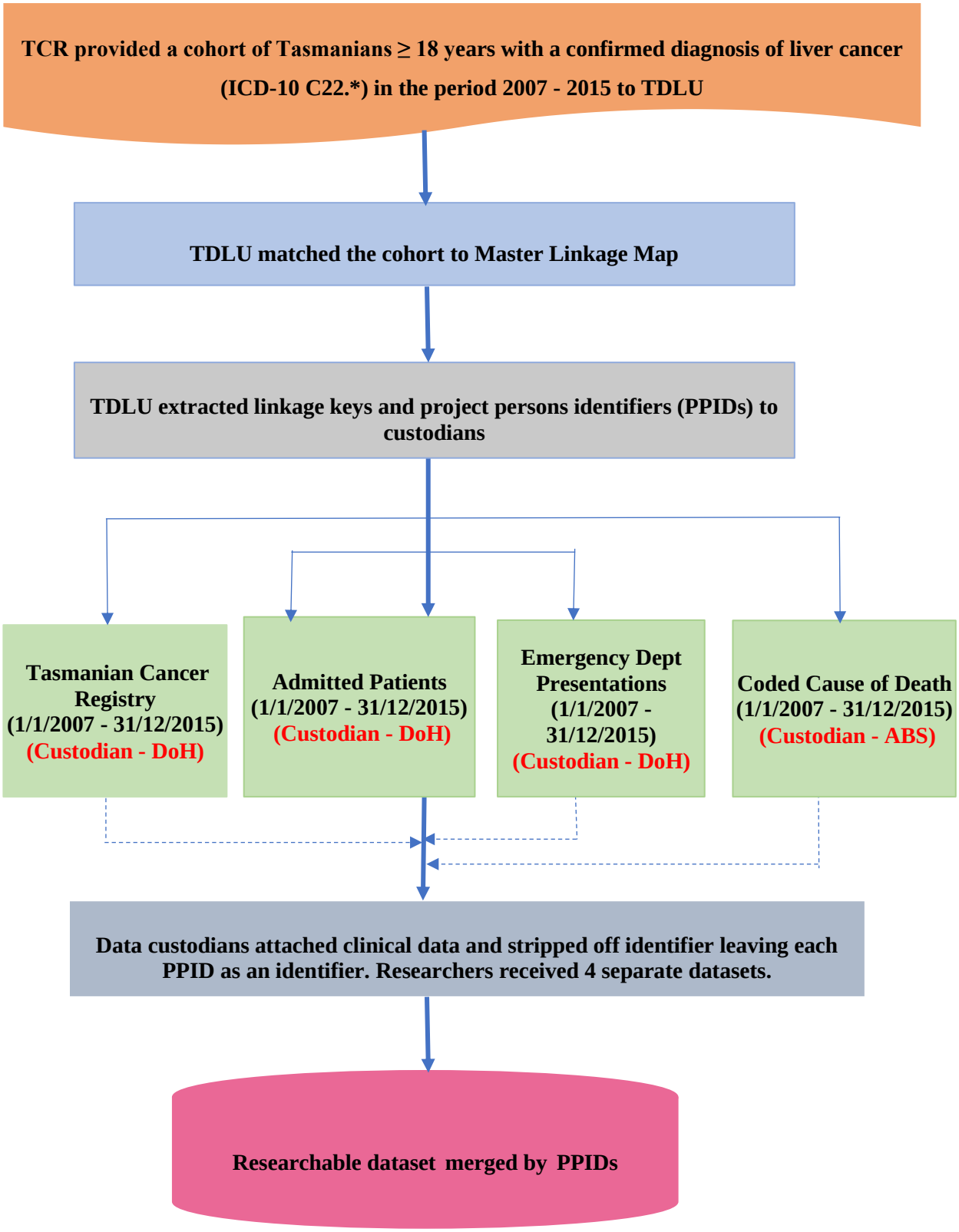


Figure 7: Data linkage process

2.4. Diagnostic coding of liver cancer

The International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) is a standard that is used to code for all health conditions, including in this context, PLC and its subtypes[108]. This version has been used for coding in the Australian health system since 1997[4]. The codes used to identify cases were:

- C22.0 Liver cell carcinoma
- C22.1 Intrahepatic bile duct carcinoma
- C22.2 Hepatoblastoma
- C22.3 Angiosarcoma
- C22.4 Other sarcomas of liver
- C22.7 Other specified carcinomas of liver
- C22.8 Malignant neoplasm of liver, primary, unspecified as to type
- C22.9 Malignant neoplasm of liver, not specified as primary or secondary

The International Classification of Diseases for Oncology, 3rd Revision (ICD-O3) is an extension of the ICD coding standard for tumour diseases. There is a formal agreement between the International Association for Cancer Registries, the International Agency for Research on Cancer, and the WHO that registered cancer cases should be coded according to the ICD-O3[84]. It is a dual classification system, including topography and morphology of tumours[84]. Thus, each cancer case in the TCR was coded by trained registry staff according to the ICD-O3, based on the information gathered from medical records. For PLC, the relevant ICD-O3 codes are:

Topography codes (indicate the site of origin of a neoplasm)[84]

- C22.0 Liver
- C22.1 Intrahepatic bile duct

Morphology codes record the type of cell that has become neoplastic and its biologic activity. There are three parts to a complete morphology code: the first four digits indicate cell types (histology); the fifth digit indicates the behaviour, and the last digit indicates the grade of the tumour.

Morphology code	**ICD-O3 morphology code description[84]**
8000	Neoplasm, malignant
8010	Carcinoma, not otherwise specified (NOS)
8033	Pseudosarcomatous carcinoma
8140	Adenocarcinoma, NOS
8160	Cholangiocarcinoma
8162	Klatskin tumor
8170	Hepatocellular carcinoma, NOS
8173	Hepatocellular carcinoma, spindle cell variant

8180	Combined hepatocellular carcinoma and cholangiocarcinoma
8890	Leiomyosarcoma, NOS
8970	Hepatoblastoma
9120	Hemangiosarcoma
9680	Malignant lymphoma, large B-cell, diffuse, NOS
Behaviour code	**ICD-O3 behaviour code description[84]**
0	Benign
1	Uncertain whether benign or malignant Borderline malignancy Low malignant potential Uncertain malignant potential
2	Carcinoma in situ Intraepithelial Noninfiltrating Non invasive
3	Malignant, primary site
Grade code	**ICD-O3 grade code description[84]**
1	Grade I Well differentiated, Differentiated, NOS
2	Grade II Moderately differentiated Moderately well differentiated Intermediate differentiation
3	Grade III Poorly differentiated
4	Grade IV Undifferentiated Anaplastic
9	Grade or differentiation not determined, not stated or not applicable

2.5. Data collection from each dataset

The variables collected four different sources are detailed in this table:

Table 1: Data collection from each dataset

Variables	Description
1. Tasmania Public Hospital Admissions (custodian: Tasmanian DOH)	
PPID	A project-specific, unique pseudo identifier that is supplied to researchers that refers to an individual with minimal risk of re-identification.
Date of Birth	Date
Sex	1 Male 2 Female 3 Indeterminate 9 Not stated/inadequately described
Date of Death	
Area of Usual Residence SA2	An SA2 is identifiable by a 9-digit fully hierarchical code. The SA2 identifier is a 4-digit code, assigned in alphabetical order within a Statistical area level 3. An SA2 code is only unique within a state/territory if it is preceded by the state/territory identifier.
Diagnosis related group version 7	A patient classification scheme which provides a means of relating the number and types of patients treated in a hospital to the resources required by the hospital, as represented by a code.
Procedure Code 1 to 50	Record and code all procedures undertaken during the episode of care. Procedures are derived from and must be substantiated by clinical documentation.
Procedure Block 1 to 50	The urgency related group major diagnostic block category into which the patient's emergency department diagnosis is grouped, as represented by a code.

Diagnosis Code 1 to 100	The category into which the patient's diagnosis and the associated Australian refined diagnosis related group falls, as represented by a code. The diagnosis codes must be valid codes from the current edition of the ICD-10.
2. Tasmania Cancer Registry (custodian: Tasmanian DOH)	
PPID	
Date of Birth	
Sex	
Country of birth	The country in which the person was born, as represented by a code according to the Standard Australian Classification of Countries 2016 (SACC).
Date of Death	The date of death of the person, expressed as DD MM YYYY
Age at Death	The age of death of the patient
Place of Death	The place of death of the patient
The Statistical area level 2 (SA2)	As described above
Date of Diagnosis	The date on which the patient was first diagnosed with cancer.
Age at Diagnosis	The age of patients when they were diagnosed
Primary Site ICD-O3	C22.0 Liver C22.1 Intrahepatic bile duct
Primary Site ICD-10	The subtypes of PLC record in TCR data
Morphology Code	As mentioned above
Basis of Diagnosis	The basis of diagnostic investigation of a person with cancer at the time of first presentation, as represented by a code. 1 Clinical Only 2 Clinical Investigation - (including diagnostic techniques i.e. x-ray, endoscopy, imaging, ultrasound and exploratory surgery) 4 Specific biochemical and/or immunological tests 5 Cytology or haematology - (examination of cells including fluids aspirated by endoscopy or needle, including peripheral blood & bone marrow aspirates) 6 Histology 7 Death Certificate Only - Information provided is from a death certificate. 9 Unknown
Spread	1 Localised to the tissue of origin (includes insitu breast and insitu melanoma) 2 Invasion of adjacent tissue or organs (includes subcut fat or muscle and organs adjacent to the primary cancer site) 3 Regional lymph nodes 4 Distant metastases 5 Not applicable. Applies to lymphatic and haemopoetic cancers. 9 Unknown
Cause of Death ICD-O3	
Cause of Death ICD-10	
3. Tasmanian Emergency Department Presentations (custodian: Tasmanian DOH)	
PPID	
Date of Birth	
Sex	
Country of Birth	

Area of Usual Residence SA2	
Type of Visit	The reason the patient presented to an emergency department, as represented by a code. 1 Emergency presentation 2 Return visit, planned 3 Pre-arranged admission 5 Dead on arrival
Diagnosis Classification Type	The type of classification used for recording emergency department diagnosis, as represented by a code.
Principal Diagnosis Code	The diagnosis established at the conclusion of the patient's attendance in an emergency department to be mainly responsible for occasioning the attendance following consideration of clinical assessment, as represented by a code.
Major Diagnosis Block	The urgency related group (URG) major diagnostic block category into which the patient's emergency department diagnosis is grouped, as represented by a code.
4. Tasmania Coded Cause of Death (custodian: ABS)	
PPID	
Date of Birth	
Sex	
URES_SA2	Australian Statistical Geography Standard code denoting the ceased usually resided. Usual residence refers to that address at which the deceased has lived or intends to live for a total of six months or more in a given reference year.
Date of Death	
Age at death	
Underlying cause of death	The disease or injury which initiated the train of morbid events leading directly to death. Accidental and violent deaths are classified according to the external cause, that is, to the circumstances of the accident or violence which produced the fatal injury rather than to the nature of the injury. Underlying cause is recorded as four digits.
RACS 1 to 20	A count of the number of causes recorded in the record axis data field after application of the ICD-10 coding rules and procedures for the selection of underlying and associated causes of death for mortality tabulation.

2.6. Data analysis

Study 1: Characteristics and survival of primary liver cancer patients in an Australian jurisdiction: A data linkage study.

Aim 1: Present demographic characteristics by subtypes of PLC patients in Tasmania (2007-2015): ANOVA were used to examine the differences in age at diagnosis. The log-rank test and Kaplan Meier method were used to compare median survival between subtypes, urban and rural residence and country of birth.

Aim 2: Estimate relative survival by PLC subtypes and demographic factors. The Ederer II method based on the algorithm developed by Dickman was used to estimate 1-,3- and 5- year relative survival

rates[109]. This method is commonly used for estimating patient survival for population based registries when specific cause of death is unknown. It was calculated as the ratio of the observed survival rate in the cohort relative to the expected survival rate taken from the Tasmania population over the same period.

Aim 3: Describe the prevalence of PLC risk factors among patients with PLC in Tasmania: A pre-defined list of risk factors for PLC was developed according to the ICD-10[108]. These risk factors codes were searched for during each patient's admission, discharge, examination as well as in the TCR and ABS datasets.

Specific details for the analyses used in this study are described in Chapter 3.

Study 2: Accuracy of cause of death data: A case study based on primary liver cancer

Aim 1: Investigate the level of agreement on cause of death between the ABS and TCR, along with medical practitioners' opinions: Cohen's kappa statistics were used to assess the concordance by chance alone between the different methods of ascertaining cause of death[110].

Aim 2: Measure the impact of different coding practices and resulting cause of death data on cause-specific survival: The cumulative incidence function was used to estimate deaths caused by non-PLC cases based on the final causes of death provided by the medical practitioners in the presence of competing risks[111]. This is preferred to the traditional Kaplan-Meier method or net survival as it provided the appropriate framework to analyse the interplay between deaths from liver cancer and other competing risk factors based on different coding practices.

Specific details for the analyses used in this study are described in Chapter 4.
All analyses were conducted with Stata 15 (Ver.15, College Station, Texas, USA).

2.7. Ethics

Ethics approval for this study was provided by the Tasmanian Human Research Ethics Committee (Ethics reference number is H0016958).

Chapter 3. Characteristics and survival of primary liver cancer patients in Tasmania by subtypes: A data linkage study

3.1. Abstract

Aims: Describe the demographic characteristics, risk factors and estimate survival time by subtypes for all PLC patients in Tasmania between 2007 and 2015.

Methods**:** Data for all PLC patients in Tasmania, Australia between 2007 and 2015 were obtained from the TCR and linked to public hospital inpatient data. Demographic characteristics and risk factors were examined using descriptive statistics. Median survival was estimated using log-rank test and the Kaplan-Meier method; relative survival time was estimated using the Ederer II method.

Results**:** 293 PLC cases were identified. HCC (51.9%) and cholangiocarcinoma (20.5%) represented the majority of cases, along with 24.9% of 'unspecified' cases. At least one risk factor was reported for 57.0% of cases, most commonly cirrhosis (37.2%), diabetes (26.7%), alcoholic related liver disease (22.5%) and viral hepatitis (16.7%). Mean age at diagnosis for all cases was 69.6 years (95% confidence interval (CI): 68.3 - 70.9), and median survival cases was 6.2 months (95% CI: 4.1-8.3). The 1-, 3- and 5-year relative survival rates were 38.3% (95% CI: 32.0-44.5); 13.8% (95% CI: 9.0-9.8) and 6.7% (95% CI: 2.9-13.0) respectively, with a trend toward increasing survival time over the reporting period.

Conclusions**:** HCC and cholangiocarcinoma were the main types of PLC reported in Tasmania. The identified risk factors can be used to inform interventions to improve early diagnosis. In turn, this would improve the poor survival outcomes for patients diagnosed with PLC.

Keywords**:** cholangiocarcinoma, hepatocellular carcinoma, liver cancer, risk factor, survival rate.

3.2. Introduction

PLC is the sixth most common cancer globally, accounting for 4.7% of cancer incidence[17]. It is the fourth leading cause of cancer deaths, accounting for 8.2% of all cancer deaths in 2018[17]. The predominant form of PLC is HCC, representing 75%-85% of all cases[2, 17, 21]. This is followed by intrahepatic cholangiocarcinoma (10%-15% of cases), and rare forms of PLC including hepatoblastoma and angiosarcoma[2, 17, 21].

The most common risk factors for PLC are chronic viral infections caused by the CHB and CHC. These viral infections lead to progressive liver scarring (cirrhosis), which is a common precursor for HCC and is present in 70%-90% of all HCC cases[2, 21]. Worldwide, 80% of PLC cases are attributable

to HBV and HCV infections[2]. More recently, NAFLD has emerged as a risk factor for HCC, particularly in high-income countries[64, 112]. NAFLD represents a spectrum of liver diseases, ranging from simple steatosis to decompensated cirrhosis[51]. Prevalence of NAFLD has increased in parallel with rates of obesity[53]. In the US, NAFLD-associated cirrhosis is now the second most common indication for liver transplant[113]. For cholangiocarcinoma, in addition to HBV and HCV, primary sclerosing cholangitis is a risk factor[2, 4]. Liver flukes are an important risk factor in Southeast Asian countries. This parasitic worm is ingested when eating raw or uncooked freshwater fish. They subsequently infect the liver, gallbladder and bile duct. Untreated, the infection can persist for the lifetime of the parasite: 25-30 years[114].

As HCC is the most common form of PLC, this is the primary focus of this research. HCC incidence and mortality rates vary markedly by region and country, reflecting the heterogeneity in the distribution and natural history of risk factors[2]. Globally, males consistently have incidence rates two-three times higher than females: partly explained by higher levels of androgen in males, which promotes development of HCC[2, 21]. In contrast, higher levels of estrogen in females may inhibit HCC through its anti-inflammatory effects. Further, CHB, CHC, and alcohol consumption are more prevalent in males and contribute to higher rates of HCC[2, 21].

Whilst approximately 80% of the burden of PLC is observed in low and middle-income countries, Australia has experienced an increasing burden[2, 4, 17]. Between 1982 and 2014, ASR incidence increased by over 300% (from 1.8/100,000 to 7.4/100,000), and ASR mortality by almost 200% (from 2.3/100,000 to 6.6/100,000)[17]. These trends are in contrast to decreasing rates of most other cancers in Australia, with this trend expected to continue over coming decades[2, 18, 20]. Despite advances in treatment, the 5-year relative survival rate for Australians diagnosed with PLC is 18.1%[2].

Although recent population-level research on PLC has been conducted elsewhere in Australia[20, 30, 97, 115-117], in Tasmania this is limited to the TCR's annual report of incidence and mortality[107]. As risk factors for PLC vary by regions (e.g., migration from hepatitis endemic countries), understanding the burden in Tasmania has the potential to contribute to development of targeted local interventions. This study aimed to 1) present demographic characteristics by subtypes of PLC patients in Tasmania (2007-2015); 2) estimate relative survival by PLC subtypes and demographic factors; 3) describe the prevalence of risk factors for PLC in Tasmania.

3.3. Methods

A retrospective data linkage study was conducted using de-identified datasets from the TCR and inpatient admissions from Tasmanian public hospitals from 2007-2015.

Data sources

The cohort was provided by the TCR, a population-based registry responsible for collecting and reporting cancer incidence and mortality data The TCR is notified of all cancer diagnoses made in Tasmania by hospitals, pathology, and radiology laboratories.

All incident cases of PLC were defined according to the International Classification of Diseases for Oncology, Third Revision (ICD-O3)[84]. The ICD-O3 coded tumours were converted to ICD-10 (the International Statistical Classification of Diseases and Related Health Problems Tenth Revision). All tumours with a basis of diagnosis other than histology were classified as 'unspecified'. PLC subtypes were categorised into four groups according to ICD-10: HCC (C22.0), intrahepatic cholangiocarcinoma (C22.1) (referred to as cholangiocarcinoma in this study), PLC where the subtype was not specified (C22.9) ('unspecified'). As the number of each remaining type was <5, these cases were combined into 'other' (hepatoblastoma, angiosarcoma of liver, other sarcomas of liver, other specified carcinomas of liver).

Patient data was extracted from the TCR, including country of birth, place of residence, date of diagnosis, primary site ICD-O3, ICD-10 codes, basis of diagnosis, spread of disease, tumour grade, tumour size, cause and date of death.

De-identified administrative data for all admissions to Tasmanian public hospitals were linked to the TCR dataset (see Data Linkage Process below). For each admission, up to 56 ICD-10 codes were reported. As almost all of the TCR cohort had a public hospital admission, these codes were used to identify risk factors for PLC.

Place of residence was categorised as either urban or rural according to the Australian Statistical Geography Standard 2016[118]. Country of birth was coded based on the Standard Australian Classification of Countries 2016 and later categorized into Australian-born or overseas-born[119]. A more detailed breakdown by country or region was not reported to maintain anonymity for the small number of cases for which this was reported.

Data Linkage Process

The data linkage process was carried out in three steps. Firstly, the TCR identified the cohort as individuals aged 18 years and above with a confirmed PLC (ICD-10 code of C22.*) diagnosed between 1/1/2007 and 31/12/2015. Patient identifiers were provided to the Tasmania Data Linkage Unit for probabilistic linkage to identifiers from the Master Linkage Map. The Linkage Unit generated Project Person Identifiers (PPIDs) which were supplied to the data custodians for the extraction of data. Finally, data custodians provided the data to the researchers.

Ethical approval for this study was obtained by the University of Tasmania Human Research Ethics Committee.

Statistical analysis

Demographic characteristics were summarized using descriptive statistics. Differences in age at diagnosis were examined by ANOVA. Survival time was calculated from date of diagnosis until date of notified death: those cases that were alive on 31 December 2015 were censored in the survival analysis. Those with the date of death equal to the date of diagnosis were excluded from all survival tests.. The log-rank test and Kaplan Meier method were used to compare median survival between histologic subtypes, urban and rural residence and country of birth.

The 1-, 3- and 5-year relative survival rates were calculated using the Ederer II method, based on an algorithm developed by Dickman[109]. Relative survival was calculated as the ratio of the observed survival rate in the cohort relative to the expected survival rate taken from the Tasmania population from 2007 to 2015. Life table data for Tasmanians was taken from the ABS for 2007 to 2015[120]. Relative survival rates were estimated for all cases and between different subtypes of PLC. As recent studies have suggested improved survival time from 1982 to 2014[2, 97, 121], survival was estimated for 2007-2010 and 2011-2015 to assess for any differences.

A pre-defined list of risk factors for PLC was developed based on published literature. This included HBV[122], HCV[123], alcoholic related liver disease[124], NAFLD[125], diabetes[126], and cirrhosis[122].

Data was analysed using Stata 15 (Ver.15, College Station, Texas, USA). Any cell counts ≤5 cases were suppressed to prevent any possibility of identification. A p-value <0.05 was deemed statistically significant.

3.4. Results

Demographic characteristics

Between 2007-2015, 293 patients were diagnosed with PLC in Tasmania. Most were diagnosed with HCC (51.9%, n=152) and cholangiocarcinoma (20.5%, n=60) (Table 2). 24.9% (n=73) were reported as ‘unspecified’ which likely reflects these patients were diagnosed at an advanced stage when further investigation is unwarranted as it will not impact treatment. This assumption is based on discussions with clinicians and data custodians. The remaining cases were classified as ‘other’ (2.7%, n=8); owing to the small number in this group, we focused on the three more common forms (Table 2). Of the total cohort, 239 patients (81.6%) died during this study period. Mean age at diagnosis for all cases was 69.6 years (95%CI: 68.3-70.9). Breaking this down by subtype, mean age at diagnosis for HCC was 66.5 years (95%CI: 64.7-68.2), and for cholangiocarcinoma was 72.2 years (95%CI: 69.4-75.0) and for the unspecified group 74.2 years (95%CI: 71.6-76.8). Comparisons between ages at diagnosis showed a statistically significant difference between HCC and cholangiocarcinoma (p=0.001), and HCC and the unspecified group (p<0.001) (Table 2).

The majority of all PLC cases were male (74.1%, n=217). Whilst large majorities of HCC and unspecified cases were male, this was not observed for cholangiocarcinoma (53.3% male). Reflecting the population distribution[127], a greater number of cases across all types of PLC was observed for people living in urban settings (62.1%, n=182) compared to rural areas (37.9%, n=111). Country of birth information was available for 68.6% (n=201): of these over 83.1% (n=167) were born in Australia.

Regarding the basis of diagnosis, from 2007-2015, clinical investigation (e.g., imaging) was the main method (44.7%, n=131). Histology of the primary tumour was the second most common method (36.9%, n=108). Data on spread of tumour was available for 29.4% (n=86) of cases, of these 44.2% (n=38) had distant metastases, 24.4% (n=21) had either localised tumours or PLC with invasion of adjacent tissues/organs respectively. Similarly, for grade and size of tumour, 81.5% (n=238) and 82.9% (n=243) of the data was unavailable (Table 2).

Table 2: Demographic characteristics of liver cancer patients in Tasmania between 2007 and 2015

Variables	Total (n=293)	HCC (n=152)	Cholangiocarcinoma (n=60)	Unspecified (n=73)	Other (n=8)
Age at diagnosis (mean, 95% CI) [a]	69.6 (68.3-70.9)	66.5 (64.7-68.2)	72.2 (69.4-75.0)	74.2 (71.6-76.8)	69.2 (63.3-75.1)
Sex (n, %)					
Males	217 (74.1)	128 (84.2)	32 (53.3)	53 (72.6)	n/r n/r
Females	76 (25.9)	24 (15.8)	28 (46.7)	20 (27.4)	n/r n/r
Place of residence (n, %)					
Rural	111 (37.9)	63 (41.4)	22 (36.7)	20 (27.4)	6 (75.0)
Urban	182 (62.1)	89 (58.6)	38 (63.3)	53 (72.6)	n/r n/r
Country of birth (n, %)					
Australia born	167 (57.0)	69 (45.4)	44 (73.3)	49 (67.1)	n/r n/r
Overseas born	34 (11.6)	18 (11.8)	6 (10.0)	9 (12.3)	n/r n/r
Not stated/missing	92 (31.4)	65 (42.8)	10 (16.7)	15 20.5	n/r n/r
Basis of diagnosis (n, %)					
Clinical investigation	131 (44.7)	65 (42.8)	19 (31.7)	46 (63.0)	n/r n/r
Biochemical and/or immunological tests	8 (2.7)	n/r n/r	n/r n/r	6 (8.2)	n/r n/r
Cytology or haematology	18 (6.1)	9 (5.9)	8 (13.3)	n/r n/r	n/r n/r
Histology	108 (36.9)	68 (44.7)	33 (55.0)	n/r n/r	7 (87.5)
Death certificate only	20 (6.8)	n/r n/r	n/r n/r	16 (21.9)	n/r n/r
Unknown	8 (2.7)	n/r n/r	n/r n/r	n/r n/r	n/r n/r
Spread (n, %)					
Localised tumour	21 (7.2)	12 (7.9)	9 (15.0)	n/r n/r	n/r n/r
Invasion of adjacent tissue/ organs	21 (7.2)	9 (5.9)	6 (10.0)	n/r n/r	n/r n/r
Regional lymph nodes	6 (2.0)	n/r n/r	n/r n/r	n/r n/r	n/r n/r
Distant metastases	38 (13.0)	19 (12.5)	9 (15.0)	9 (12.3)	n/r n/r
Unknown	207 (70.6)	109 (71.8)	34 (56.7)	58 (79.5)	6 (75.0)
Grade (n, %)					
I (Well differentiated)	21 (7.2)	18 (11.9)	n/r n/r	n/r n/r	n/r n/r
II (Moderately differentiated)	15 (5.1)	6 (4.0)	9 (15.0)	n/r n/r	n/r n/r
III (Poorly differentiated)	18 (6.2)	8 (5.3)	8 (13.3)	n/r n/r	n/r n/r
Unknown	238 (81.5)	119 (78.8)	40 (66.7)	72 (98.6)	7 (87.5)

n/r: not reported due to small numbers (≤5), confidentiality or other concerns about the quality of the data

Prevalence of risk factors

During the study period, 88.1% (n=258) of cases had at ≥1 public hospital admission. For this group, 57.0% (n=147) had at least one or more risk factors reported in their hospital data. The mean number of risk factors was 1.3 (SD=1.4), with the most frequently reported being cirrhosis (37.2%, n=96), chronic viral hepatitis (35.0%, n=89), diabetes (26.7%, n=69) and alcohol-related liver disease (22.5%, n=58).

Table 3: Prevalence of risk factors of liver cancer patients by inpatient admission ICD-10 codes

	Risk factors	Total (n=258)		HCC (n=137)		Cholangiocarcinoma (n=51)		Unspecified (n=64)		Other (n=6)	
		n	%	n	%	n	%	n	%	n	%
1	Cirrhosis	96	(37.2)	72	(52.6)	n/r	n/r	20	(31.3)	n/r	n/r
2	Diabetes	69	(26.7)	45	(32.8)	8	(15.7)	14	(21.9)	n/r	n/r
3	Alcoholic related liver disease	58	(22.5)	44	(32.1)	n/r	n/r	14	(21.9)	n/r	n/r
4	Viral hepatitis	43	(16.7)	36	(26.3)	n/r	n/r	6	(9.4)	n/r	n/r
5	Chronic hepatitis C	38	(14.7)	32	(23.4)	n/r	n/r	n/r	n/r	n/r	n/r
6	Obesity	9	(3.5)	8	(5.8)	n/r	n/r	n/r	n/r	n/r	n/r
7	Chronic hepatitis B	8	(3.1)	7	(5.1)	n/r	n/r	n/r	n/r	n/r	n/r
8	Non-alcoholic fatty liver disease	6	(2.3)	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r
9	Had at least 1 risk factor	147	(57.0)	100	(73.0)	12	(23.5)	32	(50.0)	n/r	n/r

n/r: not reported due to small numbers (≤5), confidentiality or other concerns about the quality of the data

Survival time

Median survival time

Between 2007 and 2015, 81.6% (n=239) of patients were deceased in Tasmania, in which 46.1% (n=111) were reported with HCC, 24.6% (n=72) in the 'unspecified group', and 20.1% (n=50) with Cholangiocarcinoma. The remaining, 2.5% (n=6) belonged to the 'other' type of liver cancer.

For all PLC cases, median survival (n=260) was 6.2 months (95%CI: 4.1-8.3) (Figure 8). Cases excluded from this analysis included those diagnosed at death (8.4%, n=25) and eight cases that were classified as 'other' types of cancer.

Median survival was similar for HCC (8.8 months, 95%CI: 4.2-13.5) and cholangiocarcinoma (9.2 months, 95%CI: 6.2-12.1). For 'unspecified' cases, median survival was 2.7 months (95%CI: 1.8-3.6) (Figure 9), reflecting the nature of the grouping.

Median survival across all PLC cases was similar for males (5.9 months, 95%CI: 3.8-7.9) and females (8.1 months, 95% CI: 3.0-13.1), and for those residing in rural (8.2 months, 95%CI: 3.3-13.2) and

urban areas (4.7 months, 95%CI: 3.0-6.6). In terms of country of birth, median survival was 3.4 months (95%CI: 2.0-4.7) for those born overseas and 4.8 months (95% CI: 2.9-6.7) for people born in Australia. Between 2007-2010 and 2011-2015, a potential trend toward increasing median survival was observed, increasing from 5.7 months (95%CI: 2.7-8.6) to 6.8 months (95%CI: 2.1-11.5). The overlapping confidence intervals indicate no real difference was observed.

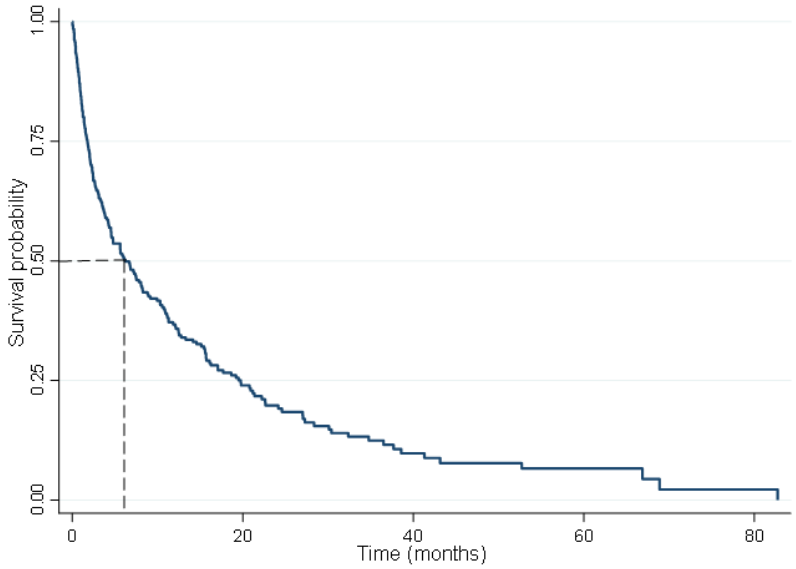


Figure 8: Kaplan-Meier survival curve for all liver cancer cases from the time of diagnosis between 2007 and 2015

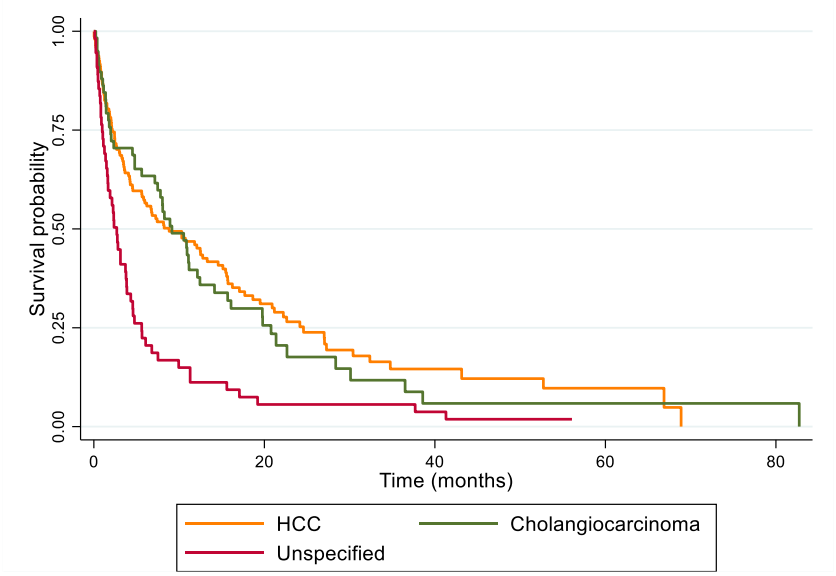


Figure 9: Kaplan-Meier survival curves for those diagnosed with liver cancer by subtypes

Relative survival rates

The 1-, 3- and 5-year relative survival rates for all cases across the study period were 38.3% (95%CI: 32.0-44.5); 13.8% (95%CI: 9.0-19.8) and 6.7% (95%CI: 2.9-13.0), respectively. A trend towards improved relative survival was observed for the 2011-2015 period compared with 2007-2010 for all cases as well as for each subtype (Table 4). Specifically, 1-year survival increased from 32.9% (95%CI: 23.9-42.3) to 42.4% (95%CI: 33.9-50.6), the 3-year survival from 10.7% (95%CI: 5.5-18.0) to 18.6% (95%CI: 10.5-28.7), and 5-year survival increased from 4.7% (95%CI: 1.5-10.8) to 13.5% (95%CI: 4.1-29.0). Again, the overlapping 95% CIs mean these results should be interpreted with caution.

Table 4: 1-, 3- and 5-year relative survival for patients diagnosed with liver cancer from 2007-2015

Relative survival rate	1 year	3 year	5 year
All cases (%, 95% CI)	38.3 (32.0-44.5)	13.8 (9.0-19.8)	6.7 (2.9-13.0)
Time period (%, 95%)			
2007-2010 (n=104 cases)	32.9 (23.9-42.3)	10.7 (5.5-18.0)	4.7 (1.5-10.8)
2011-2015 (n=156 cases)	42.4 (33.9-50.6)	18.6 (10.5-28.7)	13.5 (4.1-29.0)
Subtypes (%, 95% CI)			
HCC	47.4 (38.6-55.8)	16.0 (8.9-25.1)	11.6 (4.6-22.6)
Cholangiocarcinoma	41.6 (28.4-54.5)	13.8 (5.1-27.1)	6.4 (1.0-20.1)
Unspecified	12.0 (4.9-22.5)	6.6 (1.7-16.3)	0.0

3.5. Discussion

This study is the first to examine demographic characteristics, risk factors and survival time for PLC patients in Tasmania. Our results show a potential trend of higher relative survival across the study period from 2007 to 2015. However, PLC remains a low survival cancer, and in addition, almost 10% of cases were diagnosed only at time of death. Diagnosed early, curative treatment for PLC is possible. Our data clearly indicated that this is not occurring in the majority of cases, despite recommendations that people at high-risk of developing PLC should be regularly screened[128, 129].

This study investigated 293 PLC cases from 2007 to 2015. Our results highlighted that the most frequently occurring subtypes were HCC and cholangiocarcinoma. These results are similar to previous reports. A recent Australian report using cancer registry data reported HCC accounted for 67.6% of all liver cases, and cholangiocarcinoma 25.3%[2]; for HCC this is higher than our estimate for

HCC (51.9%). Recent work has demonstrated studies using Australian cancer registry data are likely to underestimate the number of HCC cases[107, 116]. For example, coding in the TCR, is based on the ICD-O3 topography code (C22.*) and morphology codes. In the absence of histologic data to accurately describe morphology, patients are coded as C22.*, and a morphology code of 80003 (neoplasm, malignant), i.e., unspecified. When changing from ICD-O3 to ICD-10, the C22.*, 80003 code is recoded as unspecified liver cancer (C22.9). This is likely to explain the differences in results. A recent Australian study highlighted this issue[107], with recoding of data resulting in 75.9% of cases originally coded as C22, 80003 morphology being recorded as HCC (C22.0, 81703 morphology).

As an example of these coding issues, a recent study using data from the Australian Cancer Database to assess incidence of HCC between 1982 and 2014 also reported data quality and registration methodology were heterogeneous[116]. These authors reported data from two different registries included relatively high rates (41% and 29%) of cases coded as C22.*, 80003 (unspecified type), with the remaining registries reporting this code for 0.5%-7.2% of cases. Based on the results of Hong[107], the authors adopted the assumption all unspecified cases were HCC in order to estimate survival time[116]. In our study, the rate of 'unspecified' liver cancer was relatively high (24.9%), and the mean age at diagnosis was significantly higher than for HCC. Therefore, we assume that the number of HCC cases has been underestimated due to coding practices.

In this study, cirrhosis was reported in 37.2% (n=96) of cases, viral hepatitis (not further specified) in 16.7% (n=43), HCV in 14.7% (n=38), and HBV in 3.1% (n=8) of cases. These results differ from those of a recently published study in Victoria[97]. This study reported on HCC patients, with 22.1% having HBV and 41.2% with HCV. This difference can be largely explained by the different rates of HBV in these jurisdictions, with 28.2/100,000 notifications in Victoria, compared with 9.5/100,000 in Tasmania in 2017[130]. To some degree, this difference is related to the different rates of migration in these states, with Tasmania having a lower rate of migrants from HBV endemic countries. This is not the case for HCV, with 31.0/100,000 notifications of HCV in Victoria, compared with 45.9/100,000 people in Tasmania in 2017[96]. Another difference observed was our study reported just 2.3% of cases had a recorded diagnosis of NAFLD, compared with 14.3% of cases in this Victorian study. This is in contrast to the prevalence of overweight and obesity, with 70.9% of Tasmanians and 68.3% of Victorians in these categories in the 2017-2018[131]. This difference, therefore, may be related to assessment and diagnosis, documentation and coding of NAFLD.

In our study, the overall median survival time from diagnosis was 6.2 months and the 5-year relative survival rate was 6.7% between 2007 and 2015. A recently published estimate of PLC survival in Australia reported median survival time increased from 2.1 months (95% CI: 1.6-2.6 months) to 12.1 months (95% CI: 11.2-13.0) during 2010-2014[116]. Whilst improved survival over time was observed, the large confidence intervals suggest this result should be interpreted with caution. Similarly, HCC

and cholangiocarcinoma cases had lower 5-year relative survival rates in our study with 11.6% and 6.4% respectively, compared to national data reporting 5-year survival over 2010-2014 for HCC as 22.1% and 9.0% for cholangiocarcinoma. Part of this difference may be related to the time periods: our data reflects 5-year survival over 2007-2015 as we had insufficient numbers of cases to conduct analyses of cancer subtypes for 2007-2010 and 2011-2015[2]. The other possibility is aetiology and risk factors. In Tasmania, due to low immigration rates, HCC related to non-cirrhotic hepatitis B is rare, which is reflected in our data. The survival of patients with HCC is dependent on tumour number, size and liver disease status. In our cohort, 37.2% had cirrhosis, which can limit treatment options and survival.

Previous Australian research has reported superior survival outcomes for patients born in Asia compared to those born in Europe or Oceania[30, 116, 121]. This disparity may be partly related to the majority of Asian-born patients originating from HBV endemic countries: it is possible that patients with HBV-related HCC may not have cirrhotic livers, and therefore more treatment options are available. Survival was not impacted by being born overseas, current policies that are resulting in increased migration to Tasmania, particularly from countries with high prevalence of HBV and HCV, may impact this[116, 130]. A such, it will be important to monitor health outcomes to prevent avoidable differences in the population.

Strengths and limitations

This study has several strengths. Data from the TCR with full coverage of the Tasmanian population was used and linked to Tasmanian public hospital admitted patient episodes which provided valuable and reliable data. A further strength was using ICD-10 coded data, which served as a useful tool for consistent classification of PLC by subtype. Notwithstanding this, several limitations must be noted. Firstly, a considerable proportion of unspecified cases may have resulted in an underestimation of the true proportion of each PLC subtype. A further limitation related to use of administrative admitted patient data pertaining to risk factors relates to ICD-10-AM coding. Whilst up to 56 ICD-10-AM codes for each patient admission are possible, typically the only codes recorded are those relevant to the admission. For example, a CHB patient admitted with a fractured femur is unlikely to have CHB recorded. Similarly, we expect that NAFLD was under-reported in our data, particularly in the context of the high rate of overweight and obesity in Tasmania. Therefore, we expect that we have underestimated the prevalence of risk factors such as cirrhosis NAFLD due to the completeness of the administrative dataset. Lastly, the datasets did not include any information on tumour size, which is of critical importance when considering survival.

3.6. Conclusions

In summary, this descriptive study identified HCC and cholangiocarcinoma as the main types of PLC in Tasmania. Whilst we observed an increasing survival trend, survival time remains poor. This emphasises the importance of prevention and early detection for people at high risk of developing PLC. Understanding of the most frequent risk factors for PLC in Tasmania can be used to support targeted screening to increase the rate of early diagnosis.

Chapter 4. Accuracy of coded cause of death data: A case study based on primary liver cancer

Chapter 3 provided information on the characteristics and survival time of liver cancer in Tasmania. Whilst undertaking this study, nearly half of all cases were found to have a conflicting cause of death recorded by the TCR compared to the ABS. Cause of death data is critical to estimate cause-specific mortality and survival time. Previously published studies have shown that inaccurate cause of death data can lead to less precise cause-specific survival estimates[103, 105, 106]. In response, Chapter 4 focuses on the level of agreement between the TCR, ABS and independent medical practitioners to determine causes of death and any impact on cause-specific survival.

4.1. Abstract

Background: Cause of death data from death certificates is important for understanding mortality related to cancers and their treatments. This information is coded and reported by the ABS. In addition to the information from death certificates, the TCR uses additional sources of information including medical records, pathology, and imaging services to report the underlying cause of death.

Aims: Using a cohort of PLC cases, the aims were to investigate the level of agreement for cause of death data between the ABS and TCR along with medical practitioners' opinions, secondly, estimate the impact of different coding practices and resulting cause of death data on cause-specific survival.

Methods: Causes of death were compared between the ABS and TCR, with discrepancies independently reviewed by specialist medical practitioners. Cohen's Kappa statistics were applied to evaluate the degree of concordance between the ABS, TCR and medical practitioners' opinions regarding cause of death. The cumulative incidence function was used to estimate cause-specific survival time in the presence of a competing risk framework according to sex, place of residence, country of birth, and type of PLC.

Results: A minimal level of agreement (Kappa=0.35) was observed when comparing the TCR and ABS cause of death data. Agreement between the TCR and medical practitioners was weak (Kappa=0.51), moderate between the ABS and medical practitioners (Kappa=0.61), strong (Kappa=0.87) between the medical practitioners. These results reflect a greater level of agreement between medical practitioners than between coding agencies. Overall, cause-specific survival time was similar across the TCR, ABS and medical practitioners by sex, place of residence and country of birth, however, regarding type of PLC, a small difference was observed.

Conclusions: Agreement between the TCR and ABS cause of death data was minimal. Interestingly, whilst both the ABS and medical practitioners coded cause of death using death certificate data,

agreement was only moderate. Overall, cause-specific survival time was similar across the TCR, ABS and medical practitioners, however, a small difference was observed for the type of PLC. As PLC is a low survival cancer, such results may be different to cancers with better survival such as breast cancer.

Keywords: primary liver cancer, hepatocellular carcinoma, competing risk, noncancer mortality.

4.2. Introduction

PLC has become the fourth leading cause of cancer mortality and is the sixth most frequently occurring cancer globally[17]. In Australia, the age-standardised incidence and mortality rates have increased substantially and are projected to continue to increase in the coming decades[2, 20, 89].

Cancer mortality data play an important role in the estimation of population-based mortality statistics and survival rates[132]. In turn, these data are used in medical research to develop and evaluate health policies and resource allocation decisions. Therefore, this information needs to be as accurate and complete as possible.

In Australia, a death must be registered with the jurisdictional Registry of Births, Deaths and Marriages as soon as possible[132, 133]. The registration is based on the death certificate completed by the attending medical practitioner or a coroner[132, 133]. This certificate includes information on the underlying cause of death and associated cause of death[132, 133]. According to the Australian Institute of Health and Welfare (AIHW), the *underlying cause of death* is defined as "the disease or injury which initiated the train of morbid events leading directly to death"[132]. The *associated causes of death* are all causes that contributed to the death, other than the underlying cause of death [132].

Coding Cause of Death by the Australian Bureau of Statistics

The information from death certificates is provided to the ABS on a monthly basis for coding based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)[108]. It enables comparison of mortality statistics over time and between different areas. This process produces the national Cause of Death Unit Record File (COD-URF)[84], the mortality dataset including all national information on causes of death registered in Australia from the ABS. The information from this dataset is the major source of Australian cancer mortality and survival data published by the AIHW[132]. For this study, cause of death from the COD-URF was referred to as the ABS dataset.

Coding Cause of Death by the Tasmanian Cancer Registry

The Registries of Births, Deaths and Marriages also report death certificate data to jurisdictional cancer registries[132]. Each of death is then recorded in the TCR dataset can include: five causes of

death, eight antecedent causes of death, and two other important conditions recorded at the time of death.

TCR staff then access the Digital Medical Record (DMR) of each public hospital patient and review the cause of death data in the death certificate in the context of the patient's DMR. In addition, the TCR receives cancer notifications from pathology, and radiology laboratories. All documentation provided to the TCR is reviewed to further refine the cause of death data in the TCR database.

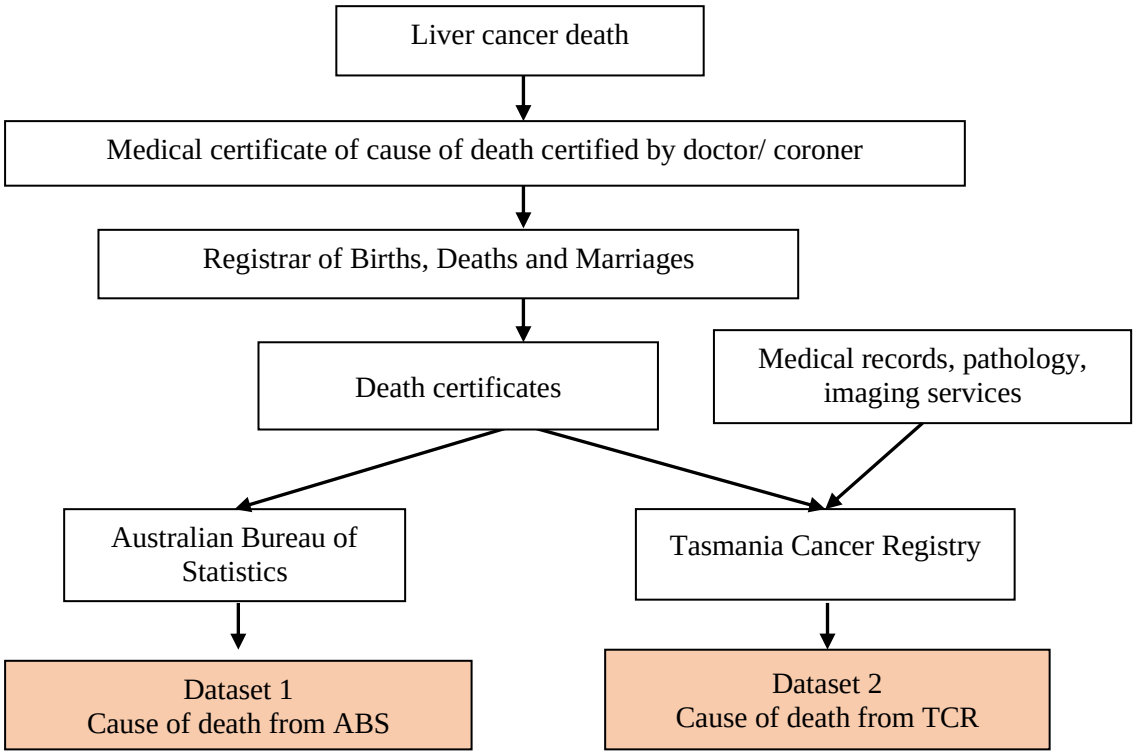
The TCR uses the International Classification of Diseases for Oncology, Third Edition (ICD-O3)[84] for coding the site (topography) and morphology of all cases to determine the underlying cause of death and associated cause(s) of death. For the purposes of comparing between different geographic areas of Australia, all causes of death data are converted the ICD-10[108].

A study estimating survival for Tasmanian patients diagnosed with PLC was conducted. Data on cancer notifications, date and cause(s) of death were taken from the TCR and ABS datasets. We compared these data and identified the cause of death differed in 112 cases (48.3%). Whilst this is not an issue when estimating all-cause mortality, it is important when considering cause-specific mortality.

Several studies have identified that inaccuracies of cause of death information obtained from death certificates[103, 134-137]. For example, a study in the US reported that 50.8% of reviewed death certificates had errors regarding the cause of death[134]. To our knowledge, no studies have investigated this issue in Australia.

The primary aim of this study was to investigate the level of agreement on cause of death between the ABS and TCR, along with medical practitioners' opinions. The secondary aim was to understand the impact of different coding practices and resulting cause of death data on cause-specific survival. We used PLC cases as a case study.

Figure 10: The process of recording the cause of death in ABS, TCR [107, 132, 138]



4.3. Methods

Data sources

The cohort was defined as all PLC notifications to the TCR between 01/01/2007 and 31/12/2015, aged >=18 years, and deceased. The ABS dataset provides each patient's information on date of birth, sex, date of death, age at death, underlying cause of death and up to 20 associated cause of death. Linkage to the ABS's COD-URF was undertaken by the Tasmanian Data Linkage Unit using probabilistic linkage [107].

The records of the underlying cause of death in the TCR dataset with the ABS dataset and information from death certificates were compared. For cases in which a discrepancy was identified, an Excel spreadsheet was developed for review independently by medical practitioners. This deidentified spreadsheet included:

1. ABS data (1 underlying cause of death and up to 8 associated causes of death)

2. TCR data (date of birth, sex, age at death, morphology code, topography code, ICD-10 code, underlying cause of death)

3. Information from death certificates (including up to five causes of death, the disease or condition directly leading to death; up to 8 antecedent causes, and other significant conditions, contributing to the death but not related to the disease, injury or condition causing it).

Three specialist medical practitioners were involved in reviewing this information, including two hepatologists/gastroenterologists (referred as medical practitioner 1 and medical practitioner 2) with expertise in PLC. Where discrepancies remained, a third reviewer, a medical oncologist (referred as medical practitioner 3) made the final determination of the cause of death based on the group of information from the ABS, TCR and death certificates. Each practitioner independently reviewed the available data.

Statistical analysis

Descriptive statistics were used to describe the characteristics of the cohort. Cohen's Kappa statistics were applied to evaluate the degree of concordance between the ABS, TCR and medical practitioner's judgement regarding causes of death[110]. Cohen's kappa statistics were used to assess the degree of agreement by chance alone between the different methods of ascertaining cause of death. Values range from 0 to 1; 0 represents no agreement and 1 perfect agreement the interpretation of Cohen's Kappa is interpreted as follow [110].

Value of Kappa	Level of Agreement	% of Data that are reliable
0-0.20	None	0-4%
0.21-0.39	Minimal	4-15%
0.40-0.59	Weak	15-35%
0.60-0.79	Moderate	35-63%
0.80-0.90	Strong	64-81%
Above 0.90	Almost Perfect	82-100%

The cumulative incidence function was used to estimate deaths caused by non-PLC cases based on the final causes of death provided by the medical practitioners in the presence of competing risks [111]. The cumulative incidence function curves and the subdistribution hazard ratios (SHRs) were generated to describe the incidence of death over time from the event of interest (liver cancer) and the competing risk of death (other causes of death)[111, 139]. Estimates for the cumulative incidence of death after notification of PLC were undertaken according to sex; place of residence (urban/rural) according to the Australian Statistical Geography Standard 2016 [118]; type of PLC based on the TCR data according to the ICD-10 codes for HCC with the code C22.0, cholangiocarcinoma with the code C22.1 and unspecified types - C22.9 (these cases belonged to this group as the subtype was not specified). The patients in this group tend to be diagnosed at an advanced stage, when further investigation to identify the type of PLC is often unwarranted as it will have no impact on treatment decisions. Other rare

forms of PLC were excluded due to small numbers (≤5) (included C22.2 hepatoblastoma, C22.3 angiosarcoma of liver, C22.4 other sarcomas of liver, C22.7 other specified carcinomas of liver) [108]. Country of birth was coded according to the Standard Australian Classification of Countries 2016 [119]. Due to the small number of patients being born in overseas countries, this was reported as either Australian or overseas born. Where the underlying cause of death was recorded as PLC, this was considered as the event of interest; other causes of death were considered as competing risks.

Data were analysed using Stata 15 (Ver.15, College Station, Texas, USA). Any cell counts ≤5 cases were suppressed to prevent any possibility of identification. A p-value less than 0.05 was deemed statistically significant.

Ethical approval for this study was obtained by the University of Tasmania Human Research Ethics Committee (H0016958).

4.4. Results

Between 2007 and 2015, 293 patients were diagnosed with PLC in Tasmania, of which 239 were deceased. Among these patients, seven cases were not matched between the ABS and TCR datasets (i.e., there were six cases marked as deceased in the TCR but not in the ABS and in turn, one case marked deceased in the ABS but not found in the TCR). These patients were excluded in the agreement analysis as the data provided no potential for comparison. Finally, 232 deceased cases with matches in the TCR and ABS datasets were included in the study.

For all included cases, the majority were male (74.6%, n=173), most resided in urban areas (62.9%, n=146) and over two-thirds were born in Australia (68.1%, n=158). Based on the TCR data, the most common cause of death was HCC (46.1%, n=107), followed by cholangiocarcinoma (21.1%, n=49) while the remaining 30.6% (n=71) were reported as having an unspecified type of PLC. The remaining cases were combined into ‘other’ (C22.2 hepatoblastoma, C22.3 angiosarcoma of liver, C22.4 other sarcomas of liver, C22.7 other specified carcinomas of liver). Table 5 shows the characteristics of all included cases.

Table 5: Characteristics of deceased cases among liver cancer patients in Tasmania (2007-2015)

Characteristics		Number	%
		232	100
Discrepancies in cause of death		112	48.3
Sex	Males	173	74.6
	Females	59	25.4
Place of residence	Rural	86	37.1
	Urban	146	62.9
Country of birth	Australian born	158	68.1
	Overseas born	30	12.9
	Not stated/ Missing	44	19.0
Type of PLC	HCC	107	46.1
	Cholangiocarcinoma	49	21.1
	Unspecified type	71	30.6
	Other types	5	2.2

Agreement between the ABS, TCR and medical practitioners

Agreement for all cases

The comparisons regarding the underlying cause of death by the ABS, TCR and medical practitioners were conducted in three stages. Firstly, the 232 ABS and TCR causes of death were reviewed, with discrepancies identified in 48.3% (n=112) of cases: a minimal level of agreement (Kappa=0.35, $p<0.001$) (Table 6).

The 112 discrepancies were then reviewed independently by medical practitioners 1 and 2. Of these cases, 16 (17.0%) discrepancies remained and were further reviewed by medical practitioner 3 to achieve a consensus. Interrater reliability between the TCR and final consensus from the medical practitioners showed weak agreement (Kappa=0.51, $p<0.001$) and between the ABS and medical practitioners' moderate agreement (Kappa=0.61, $p<0.001$).

The highest interrater reliability was observed between medical practitioners 1 and 2 (Kappa=0.87, $p<0.001$). This reflects a greater consistency between these experts when deciding the underlying cause of death. Although showing similar trends of agreement across the different comparisons, the Kappa statistics revealed more robust outputs than the percent agreement.

Table 6: The agreement between the ABS, TCR and the medical practitioners regarding underlying cause of death of liver cancer patients in Tasmania (N=232)

Comparison	Agreement frequency (%)	Kappa statistics
ABS-TCR	120 (51.3%)	0.35*
TCR-Medical practitioners	150 (64.7%)	0.51*
ABS-Medical practitioners	168 (72.4%)	0.61*

* Significant difference with $p<0.001$

Cumulative incidence of cause-specific deaths

The cumulative incidence of death after being diagnosed with PLC is presented according to (1) sex (males/females), (2) place of residence (urban/rural), (3) country of birth (Australia/overseas), and (4) type of PLC (Unspecified type/ HCC/Cholangiocarcinoma) (Table 7). The calculations from the three different sources of information-the TCR, ABS and the medical practitioners-returned many similar SHR results. First, the cumulative incidence of death (with females as the reference group) was trending towards being higher in males compared with females (Figure 11-2A). The SHRs were across the datasets: 0.74 (95%CI: 0.52-1.1) based on the TCR data; 0.77 (95%CI: 0.53-1.12) based on the ABS data; and 0.74 (95%CI: 0.51-1.01) based on the medical practitioners' data.

Second, the cumulative incidence of death with urban as the reference group was largely similar for rural and urban residence, with each of the three datasets providing similar results (Figure 11-2B): the SHRs being 0.90 (95%CI: 0.68-1.20), 0.93 (95%CI: 0.69-1.26), and 0.93 (95%CI: 0.69-1.25), respectively from the TCR, ABS and medical practitioners data.

Interestingly, the different estimations based on the three datasets (i.e., cause of death datasets from the TCR, ABS and consensus from the medical practitioners), consistently showed that the cumulative incidence of death was higher in patients born in Australia than those overseas-born (Figure 11-2C), with the SHRs being 0.68 (95%CI: 0.57-0.82) based on the TCR data, 0.63 (95%CI: 0.52-0.77) based on the ABS data, and 0.69 (95%CI: 0.58-0.83) based on the medical practitioner's data. All these estimates were statistically significant ($p<0.001$).

Lastly, the type of PLC was the only factor that contributed to inconsistent estimates in the SHRs (Table 7) and survival time across the datasets (Figure 11-2D). The SHRs (reference group: 'Unspecified type') were 0.48 (95% CI: 0.33-0.70) and 0.50 (95% CI: 0.33-0.77) for HCC and Cholangiocarcinoma groups respectively based on the TCR's data. The SHRs based on ABS's data were similar with 0.45 (95% CI: 0.31-0.67) and 0.40 (95% CI: 0.26-0.63) for HCC and Cholangiocarcinoma respectively, and for the medical practitioners' data the SHRs were 0.64 (95% CI: 0.42-0.96) and 0.69 (95% CI: 0.44-1.08) for HCC and Cholangiocarcinoma respectively. The cumulative incidence of death was highest in cases with unspecified PLC in all datasets. This largely reflects the nature of this unspecified group, i.e., diagnosed at an advanced stage with no subsequent clinical investigations conducted to inform treatment. However, while significant differences were found when estimating the SHRs in the ABS and TCR datasets, the estimation based on the medical practitioner's data was not statistically significant ($p=0.11$) between the patients with Cholangiocarcinoma and HCC.

Table 7: Hazard Ratios by sex, place of residence, country of birth, and type of liver cancer from the ABS, TCR, Medical Practitioners' data

Variables		Tasmanian Cancer Registry SHR (95%CI)	Australian Bureau of Statistics SHR (95%CI)	Medical Practitioners SHR (95%CI)
Sex	Males (Ref) Females	0.74 (0.52-1.1)	0.77 (0.53-1.12)	0.74 (0.51-1.01)
Place of residence	Urban (Ref) Rural	0.90 (0.68-1.20)	0.93 (0.69-1.26)	0.93 (0.69-1.25)
Country of birth	Australia born (Ref) Overseas born	0.68 (0.57-0.82) ***	0.63 (0.52-0.77) ***	0.69 (0.58-0.83) ***
Type of liver cancer	Unspecified type (Ref) HCC Cholangiocarcinoma	0.48 (0.33-0.70)*** 0.50 (0.33-0.77)**	0.45 (0.31-0.67)*** 0.40 (0.26-0.63)***	0.64 (0.42-0.96)* 0.69 (0.44-1.08)

Note: *** p<0.001; ** p<0.01; * p<0.05

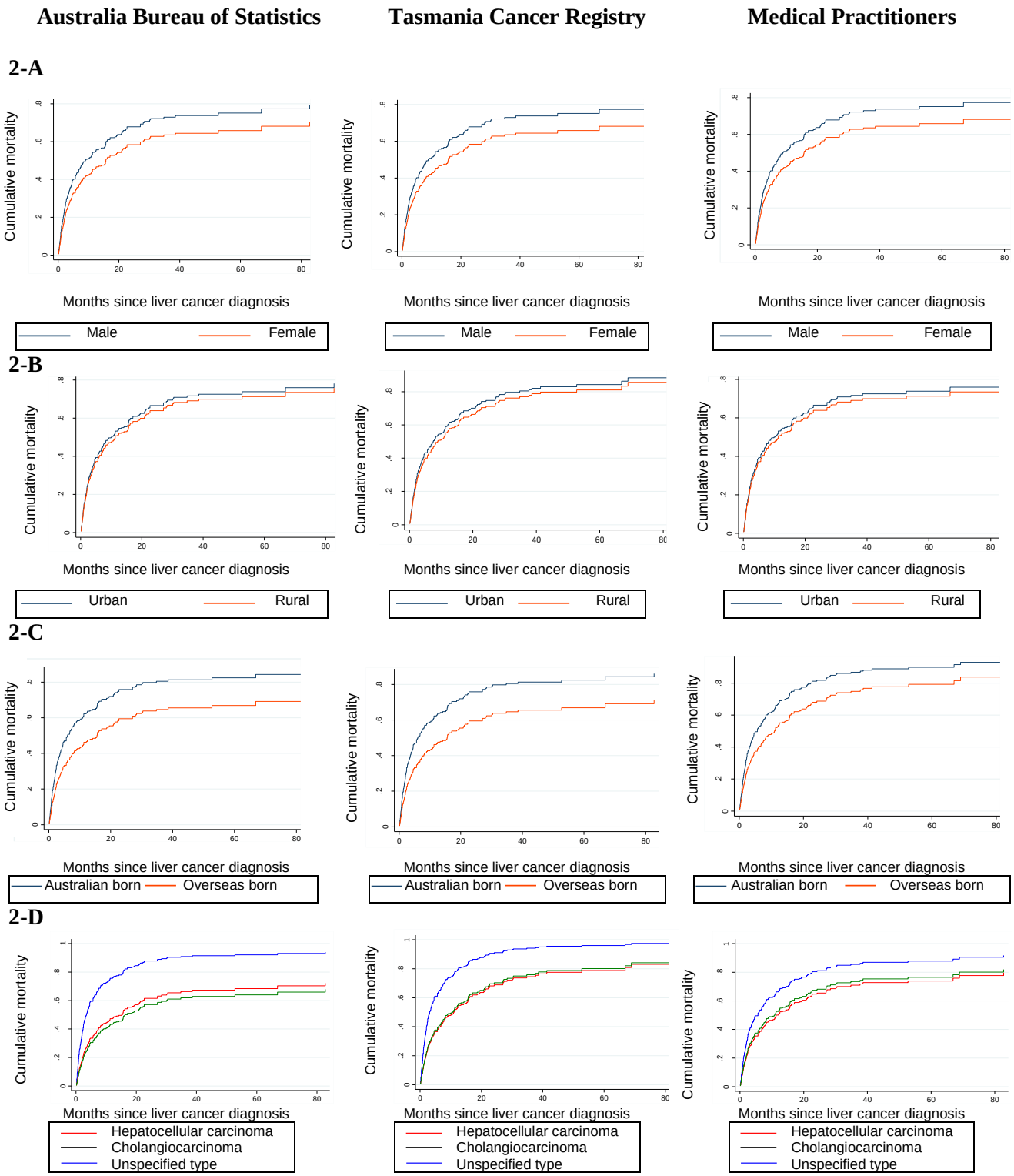


Figure 11: Cumulative incidence function curves illustrate deaths from liver cancer patients and other reasons by gender (2-A), place of residence (2-B), country of birth (2-C), and type of liver cancer (2-D) from ABS, TCR, Medical Practitioners' data

4.5. Discussion

Cause of death data derived from death certificates is of critical importance to fully understand mortality related to cancers and their treatments. This study describes both the processes of recording the cause of death and the impact on cause-specific survival using a competing risk framework for a cohort of PLC patients.

Our results showed the overall concordance between the ABS and TCR was minimal (Kappa=0.35, with discrepancies present for nearly half of the cases). When cause of death was based on death certificates only, the results between the ABS and specialists showed moderate agreement (Kappa=0.61). The discrepancies identified between the TCR and ABS were largely due to the additional sources of information used by the TCR, that is, the DMR, pathology and imaging services, to conclude the underlying cause of death.

To the best of our knowledge, no previous studies have been published on the accuracy of cause of death data and the impact on survival estimates for PLC. A study using a similar approach to ours but looking at breast cancer cases, compared cause-specific survival time from death certificates with coded cause of death from the Geneva Cancer Registry. This Registry codes cause of death based on death certificate data along with all available clinical information. The authors reported a high level of agreement (Kappa = 0.82), with 8.8% of cases misclassified. Overall cause-specific survival time was not affected, but differences were observed for some groups such as patients aged over 80 years[103].

In our study, there were 71 cases diagnosed with a morphology code of 8003 (Neoplasm, malignant) based on the ICD-O3[84]. In the absence of histology data to accurately describe the morphology of a tumour, the TCR coded cases as C22.*, with the 8003 morphology code recorded as unspecified liver cancer (C22.9). For cases coded as unspecified liver cancer (54 cases/71 cases), a high rate of discrepancies between the TCR and ABS regarding the cause of death was observed. The coding methods of these patients partly contributed to the minimal agreement between the ABS and TCR. A Victorian study [117] highlighted the issue of PLC cases being coded as ‘unspecified liver cancer’ due to missing morphology code. This study reported that following a review of the medical records, 75.9% of these ‘unspecified liver cancer’ cases were subsequently recoded as HCC. However, we did not have access to the medical records from public hospitals in Tasmania or results from pathology and imaging laboratories in this study. Thus, we could not draw strong conclusions regarding the accuracy of coded causes of death data from TCR.

Our results using the competing risks framework did not identify sex or rurality to have an impact on the cumulative incidence of death. We did, however, observe that the cumulative incidence of death was highest in cases with unspecified liver cancer. This is in-line with clinical practice that patients

diagnosed at an advanced stage of PLC often do not undergo further investigations, and therefore histology data are not available.

In contrast to our results, a US study reported cumulative incidence of breast cancer deaths was overestimated due to misclassification of the cause of death[104]. Comparisons of mortality between breast and PLC using a competing risk framework require careful consideration. Breast cancer is associated with substantially longer survival in both the US and Australia (5 year survival 91.3%[140] and 90.8%[4] respectively) compared to PLC (5 year survival 19.2%[140] and 18.5%[2] respectively). Additionally, breast cancer patients are generally younger than PLC patients, with incidence highest for breast cancer patients between the ages 70-74[141] and for PLC patients between the ages 80-84[89].

In turn, breast cancer cases have a higher risk of death from other causes of death in comparison to PLC cases. In our study, the majority of PLC cases died from the event of interest (liver cancer) in all three datasets (89.2% for the TCR, 78.0% for the ABS, and 74.6% based on the consensus from medical practitioners). Meanwhile, in the breast cancer study, the number of deaths due to the event of interest (breast cancer) represented a small proportion of all deaths (12.2%)[104]. These different results suggest that the cumulative incidence function may not show substantial impacts on cause-specific survival for cancers with short survival time such as PLC.

Strengths and Limitations

The use of linked health data is useful as a means of studying many health conditions, outcomes and service provision in a cost-effective manner[142]. In our study, the TCR provided access to high quality data, based on using probabilistic linkage methods to reduce potential errors[107]. The cumulative incidence function was used to estimate deaths caused by noncancer events in the presence of competing risks. This method is preferred to the Kaplan-Meier or net survival methods, which usually overestimates the absolute risk of cause-specific survival and ignores competing causes[111, 139, 143]. The competing risk methods provided the appropriate framework to analyse the interplay between deaths from PLC and other competing risk factors based on different coding practices[139, 143, 144].

A limitation of this study was that we could not draw strong conclusions regarding the accuracy of cause of death data from the TCR or ABS. Access to patients' digital medical records would be required for this. Future research should focus on better understanding of coding practices and the accuracy of the different approaches. Cause-specific survival estimates have been shown to provide lower survival rates compared to all cause estimates for breast cancer[145]. In this context, robust cause of death data will support more accurate cause-specific survival estimates for patients and clinicians. Whilst this may not be as relevant for low survival cancers such as liver PLC, this may be particularly useful for cancers with longer survival and earlier age at diagnosis such as breast cancer.

4.6. Conclusions

This is the first study that has evaluated the impact of different coded causes of death on estimates of cause-specific survival for PLC cases. Agreement between the TCR and ABS cause of death data was minimal, weak between the TCR and medical practitioners, and was only moderate between the ABS and medical practitioners. The cumulative incidence of deaths were similar across the TCR, ABS, and medical practitioners. However, it was different according to the type of PLC, reflecting a need for more cohesive reporting and coding practices that will ultimately improve funding allocation. Lastly, whilst there were no differences observed for cause-specific survival across these datasets, a small difference was observed regarding type of PLC. As PLC is a low survival cancer, such results may be different to cancers with better survival such as breast cancer.

Chapter 5. Summary and future directions

5.1. Preface

This thesis presents the demographic characteristics, risk factors and survival time for all PLC cases diagnosed in Tasmania between 2007 and 2015. Secondly, the results of a study investigating the level of agreement for causes of death between the ABS, TCR and medical specialists are reported. The impact on cause-specific survival is presented and discussed. This chapter provides a synopsis, conclusions, and suggestions for future directions.

5.2. Summary of the thesis

Chapter 1 provides an overview of the epidemiology and clinical perspectives of PLC. More specifically, the global epidemiology of PLC is presented, and the methods of diagnosis, staging, and surveillance are discussed. This chapter then focuses on the epidemiology of PLC in Australia, the rationale for conducting PLC research in Tasmania, and the aims of this thesis are presented.

Chapter 2 describes the methods used in the studies reported in Chapters 3 and 4. Much of this Master's project has used linked administrative data: the linkage methodologies are described in this chapter, along with the study design, selection of 'participants', cancer and death coding practices in the TCR, and the analysis methods used in both studies. This chapter summarises the main methods used in these studies, whilst more specific information about the methods of each study are included in Chapters 3 and 4.

Chapter 3 (Study 1) is a retrospective data linkage study using de-identified datasets from the TCR and inpatient admissions from Tasmanian public hospitals. This study describes the demographic characteristics, risk factors and relative survival time for subtypes of PLC in Tasmania between 2007 and 2015. Over the study period, there were 293 primary PLC cases identified. HCC (51.9%) and cholangiocarcinoma (20.5%) were the main types reported. Three-quarters of all PLC cases were male, and the average age was 70 years. For cases with public hospital admissions, 43% did not have a risk factor for PLC identified. Of those who did, the most common were cirrhosis (37%), chronic viral hepatitis (35%), diabetes (27%), and alcohol-related liver disease (23%). The mean age at diagnosis for all cases was 69.6 years, with a median survival time of 6.2 months. The 1-,3- and 5-year relative survival rates were 38.3%, 12.8%, and 6.7%. Understanding the most frequent risk factors for PLC in Tasmania can be used to support targeted surveillance to increase the rate of early diagnosis.

Whilst undertaking the study reported in Chapter 3, it was identified that nearly half of all cases had different causes of death recorded by the TCR compared with the ABS. Chapter 4 (Study 2) reports

on a study developed to investigate this issue. The aim was to identify consensus for causes of death, and to understand how coding impacts causespecific survival estimates. For the 48.3% (112/232) of cases in which a discrepancy was identified, independent reviews were conducted by medical specialists with expertise in PLC. Concordance of cause of death data was estimated using Kappa statistics, and the impact on cause-specific survival time was explored using a competing risk framework. The overall concordance regarding cause of death data was minimal between the ABS and TCR (Kappa=0.35). Moderate agreement (Kappa=0.61) between the ABS and medical specialists was identified.

Whilst the cumulative incidence of cause-specific survival estimates were similar across the TCR, ABS, and medical practitioners, when assessing this in the context of region of birth, the SHRs were higher for cases born in Australia compared to those born overseas. This result is in-keeping with other Australian studies[116, 121], and is related to differing aetiologies. For example, Australian-born PLC patients are more likely to present with cirrhosis due to alcoholic liver disease; in contrast, Asian born patients are more likely to present with PLC related to chronic hepatitis B with or without cirrhosis. In turn, the latter patient group are more likely to be eligible for treatments such as liver resection[97]. A recent Australian consensus statement has supported surveillance for high risk patients, including those with cirrhosis, to increase the rate of early diagnosis[95]. Whilst this would reduce the difference in survival across these groups, further work is required to understand the acceptability and uptake of surveillance from the perspectives of patients and health care providers.

In addition, differences were observed when estimating SHRs for the type of PLC. Using "Unspecified" cases as the reference group, statistically significant differences were observed for HCC and cholangiocarcinoma based on the TCR and ABS data. No significant difference was observed for the medical practitioners' data. In order to understand how different coding practices may over or underestimate cause-specific survival, the accuracy of cause of death data would need to be assessed. This could be done using patients' digital medical records to better understand the complexities of each individual's health. In addition, these results highlight the need for more cohesive reporting and coding practices that will ultimately improve understanding of survival of cancers.

5.3. Integrated conclusions of the thesis

Survival of PLC remains poor in Tasmania, with a 5 year survival rate of just 6.7% over 2007 to 2015. This is due to the high number of cases that were diagnosed at late stages (almost 10% of cases at time of death, 24.9% at an advanced stage).

In contrast is the Japanese experience, with a 5 year survival rate of 40.4% for HCC patients diagnosed between 1998 and 2009[146]. This improved survival is largely related to the stage of the

tumours at diagnosis, with more than 60% diagnosed at early stages[146, 147]. This has occurred in the context of a nationwide PLC surveillance program that was developed in the 1980s for high risk patients. This program includes ultrasound and measurement of three tumour markers included AFP, the lens culinaris agglutinin-reactive glycoform, and des-gamma-carboxy prothrombin, every 3-4 months for patients with CHB and CHC-associated cirrhosis, and every 6 months for patients with nonviral cirrhosis, and patients with CHB and/or CHC (without cirrhosis)[146-148].

Many international liver societies recommend surveillance of HCC for high risk populations. For example, the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend surveillance every 6 months, consisting of ultrasound ± AFP for high risk patients (cirrhosis patients and subgroups of CHB patients)[74, 94].

In the Australian context, a consensus statement was published in late 2020 by PLC specialists with evidence-based recommendations[95]. This paper states it is now a priority to institute HCC surveillance strategies in Australia for high-risk patients, with the aim of identifying tumours at early stages. The authors recommend surveillance should occur 6-monthly using liver ultrasound and ± AFP in[95]:

People with cirrhosis (any aetiology)

Non-cirrhosis patients with CHB infection in:

- Asian men older than 40 years
- Asian women older than 50 years
- People born in sub-Saharan Africa older than 20 years
- Aboriginal and Torres Strait Islander people older than 50 years

A small number of Australian studies have demonstrated the effectiveness of HCC surveillance every 6 months for high risk patients to increase early detection and improve survival[97, 149]. Our results support the need for surveillance to increase the rate of early detection of HCC in high risk patients. In turn, this will improve the very poor survival outcomes for people diagnosed with HCC in Australia.

5.4. Future directions

Identification of barriers and enablers for liver cancer surveillance

Despite Australian recommendations since 2005[150] to screen high risk patients, uptake and adherence remain poor. A recent population-based study of patients diagnosed with HCC in Victoria, Australia reported that 40% were participating in surveillance at the time of diagnosis[97]. For patients living with CHB, only 27% adhered to surveillance on a six monthly basis[151]. However, the reasons for such low participation are not well understood in Australia. Internationally, several studies have reported on

multiple barriers to surveillance from the perspective of primary care providers, including failure to identify the clinical need for surveillance for high risk patients, insufficient knowledge of risk factors, indications for surveillance and time intervals, along with competing clinical concerns[152, 153]. Other studies have reported on barriers from patients' perspectives, such as knowledge deficits regarding their risk, difficulty with scheduling processes of tests and appointments, costs of liver imaging and transportation barriers[154]. In addition health care system barriers such as a lack of guidelines for surveillance have also been reported to be a barrier[153, 155]. As these studies were conducted in countries with health systems that differ greatly to Australia's, it is important to understand the local barriers and enablers impacting patients, health care providers, and health care system.

The findings of the current study suggest that better understanding of the barriers and enablers of regular participation in surveillance for high-risk patients is required. This will support the development of a more acceptable and effective surveillance strategy.

Determination of pathways to diagnosis of liver cancer and associations with survival

As the thesis findings provide a large descriptive picture of the PLC in Tasmania, more challenging research directions are also opened. PLC is frequently diagnosed at a late or end stage, resulting in very poor outcomes for patients. Characterisation of the pathways to diagnosis, time between first presentation to a medical professional and clinical diagnoses, reasons for emergency department presentations and inpatient admissions before the diagnosis of PLC should be understood. As no such study has been published in Australia, research on these pathways to diagnosis will be the first step to understanding why most PLC patients are diagnosed at late stages. In turn, this information can be used to inform the development of a surveillance strategy.

Develop a strategy/program to support increased participation in regular surveillance for those at risk and liver cancer patients

The effectiveness of HCC surveillance programs is largely accepted and has been recommended for high risk patients by multiple international professional bodies and in guidelines[3, 23, 73, 74, 156]. However, their effectiveness in clinical settings is hampered by multiple barriers[152-155]. Additionally, there have been three well established national screening programs for breast, bowel, and cervical cancers in Australia[157-159]. Whilst HCC screening will need to be targeted to high-risk individuals, valuable lessons from these programs should be considered. Based on the results from suggestions above, it is now of critical importance to work with patients and clinicians to develop appropriate surveillance programs to increase the rate of early diagnosis of PLC and eventually improve patient survival.

Assess the cost effectiveness of HCC surveillance

As noted, effectiveness of HCC surveillance for high risk patients has been demonstrated in a number of studies. More specifically, it has been shown to increase the rate of early diagnosis, and ultimately improve survival in Australia[97, 149]. However, no evidence of the cost effectiveness of HCC surveillance has been published for Australia. As surveillance programs are costly to government(s), it is essential to provide such information that can be used in decision making. Therefore, a thorough cost effectiveness evaluation of clinically effective surveillance programs will be required before implementation can occur, to ensure it is financially justified at the population level.

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Appendix A: A publication co-authored by the candidate

Nguyen ALT, **Nguyen HTT**, Yee KC, Palmer AJ, Blizzard CL, de Graaff B. A Systematic Review and Narrative Synthesis of Health Economic Evaluations of Hepatocellular Carcinoma Screening Strategies. Value in Health. 2021.

I co-authored the paper in which I helped with data acquisition, data analysis and interpretation, provision of study materials or patients.

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A Systematic Review and Narrative Synthesis of Health Economic Evaluations of Hepatocellular Carcinoma Screening Strategies

Anh Le Tuan Nguyen, MSc, Hoa Thi Thu Nguyen, BSc, Kwang Chien Yee, MBBS, BMedSci, FRACP, PhD, Andrew J. Palmer, MBBS, BMedSci, PhD, Christopher Leigh Blizzard, PhD, Barbara de Graaff, PhD

ABSTRACT

Objectives: Many economic evaluations of hepatocellular carcinoma (HCC) screenings have been conducted; however, these vary substantially with regards to screening strategies, patient group, and setting. This review aims to report the current knowledge of the cost-effectiveness of screening and describe the published data.

Methods: We conducted a search of biomedical and health economic databases up to July 2020. We included full and partial health economic studies if they evaluated the costs or outcomes of HCC screening strategies.

Results: The review included 43 studies. Due to significant heterogeneity in key aspects across the studies, a narrative synthesis was conducted. Most studies reported using ultrasound or alpha fetoprotein as screening strategies. Screening intervals were mostly annual or biannual. Incidence, diagnostic performance, and health state utility values were the most critical parameters affecting the cost-effectiveness of screening. The majority of studies reported HCC screening to be cost-effective, with the biannual ultrasound + alpha fetoprotein standing out as the most cost-effective strategy. However, few studies considered the utilization rate, and none considered the diagnostic performance of ultrasound in the context of central adiposity. Computed tomography and magnetic resonance imaging were also evaluated, but its cost-effectiveness was still controversial.

Conclusions: Although many studies suggested HCC screening was cost-effective, substantial limitations of the quality of these studies means the results should be interpreted with caution. Future modeling studies should consider the impact of central adiposity on the precision of ultrasound, real-world utilization rates and projections of increased HCC incidence.

Keywords: cost-effectiveness, hepatocellular carcinoma, primary liver cancer, screening, surveillance

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Introduction

Primary liver cancer (PLC) is the sixth most commonly occurring cancer in the world[1] and third most common cause of cancer mortality.[2-4] In Australia, from 1982 to 2014, the age standardized incidence and mortality rate of this cancer increased by 306% and 184%, respectively.[5] Meanwhile, the age standardized incidence and mortality rate mortality rates for colorectal, lung, breast, and all cancers combined decreased during the same period.[5] PLC is the fastest increasing cause of cancer mortality in this country.[6]

Furthermore, incidence is expected to increase in the future.[7,8] Two main drivers are the trajectory of chronic hepatitis B virus (HBV) infections and increasing prevalence of obesity and nonalcoholic fatty liver disease (NAFLD).[9] HBV is strongly oncogenic,[10] and is endemic in many East Asian and Sub-Saharan Africa countries.[11] As such, the increasing numbers of people migrating to Australia from these countries is projected to contribute to increasing incidence of PLC.[12] Furthermore, NAFLD is associated with an increased risk of PLC, and is now the second most common indication for liver transplant in the United States.[13]

PLC places a substantial economic burden on the Australian health system, with an estimated annual cost of AUD50.2 million for patients admitted to hospitals in 2012.[14] The costs associated with hepatocellular carcinoma (HCC), the most common PLC form (accounts for 80% of all cases),[15] have also been reported for the United States and Canada. The average annual cost per patient with HCC in the United States was $147 000 in 2016,[16] and the extrapolated net cost (ie, difference between the mean costs for patients with HCC and matched controls without HCC) to the whole Canadian population was $25 million annually in 2009, and these costs are likely to rise.[17]

Globally, HCC represents the fifth most common cancer in men and seventh in women.[3,4] Timing of HCC diagnosis is critical to patient outcomes. Patients diagnosed in early stages have more treatment options available and improved outcomes than those diagnosed at later stages, for whom palliative care is often the only option.[18,19]

However, HCC is infrequently detected early.[17,20-22] Late diagnosis is partly related to the lack of HCC symptoms in the early stages.[23-25] Additionally, the cost of diagnostic tests and low awareness of the disease among primary care physicians have been cited as factors contributing to delayed diagnosis.[21,26] Further complicating this is the fact that HCC can develop in the absence of risk factors (eg, cirrhosis) and in patients with normal liver histology.[27-29] Between 30% to 50% of HBV-related HCC cases occur in the absence of cirrhosis.[15,30] Additionally, up to 90% of HBV carriers worldwide are unaware of their HBV status.[31] An Australian study reported only 26% of people newly diagnosed with HCC were at early stages.[32] Similar results have been published in the United States and Austria, with less than 20% of HCC cases diagnosed at early stages.[33,34]

HCC screening (or surveillance) for high-risk populations is recommended as a method for early detection of the disease by many authors[4,8,22,35-37] and professional bodies.[38-41] The recommended screening approach is ultrasound ± alpha-fetoprotein (AFP) at regular intervals for high-risk patients (cirrhotic or noncirrhotic chronic HBV/hepatitis C virus [HCV] carriers).

Many economic evaluations of HCC screening have been conducted; however, these vary substantially with regard to intervention, patient group, and setting. To our knowledge, one systematic review on the health economic aspects of HCC screening has been published in 2012.[36] This review only included full economic evaluations and outcomes were limited to quality-adjusted life years (QALYs). Since then, several health economic evaluations of screening have been published. The aim of this article is to present the current knowledge and narratively synthesize the published data.

Methods

This review was conducted in accordance with the PRISMA Protocol.[42] The study protocol was registered on Prospero (CRD42019130358). The studies selection followed the PICO model (Patients: high HCC risk; Intervention: HCC screening strategies; Comparison: alternative screening strategies or nonscreening; Outcomes: cost/effectiveness of strategies).

Search Strategy

The review was performed using published guideline.[43] The initial search was carried out in April 2019 and a further search was performed in July 2020 in PubMed, Embase, Scopus, Cochrane, Econlit, Centre for Review and Dissemination, and cost-effectiveness analysis registry. Searches were also conducted on grey literature (Open Grey and Google Scholar) to capture additional studies. Search strategies were developed in consultation with a research librarian and the economic concepts were based on a published filter.[44,45] Details of the search strategies are in the Supplemental Materials 1 found at https://doi.org/10.1016/j.jval.2020.11.014.

Study Selection

Studies were included if they were full/partial health economic analyses that evaluated the costs or outcomes of HCC screening strategies. The outcomes were health economic measures: QALYs, quality-adjusted life expectancy (QALEs), health-state utility values (HSUVs), life expectancy, and life years (LYs). Studies published in English, German, French, Italian, and Vietnamese were included. Studies were excluded if they were reviews, meta-analyses, letters, editorials, conference abstracts, or studies of other PLC types (eg, angiosarcoma, cholangiocarcinoma) or HCC treatment.

Titles and abstracts were independently screened by 2 reviewers (A.N. and H.N.). Full texts of accepted abstracts and those in need of further clarification were reviewed for the second stage. Any discrepancies arising that could not be resolved during the systematic search among 2 reviewers (A.N. and H.N.) were decided through discussion with the third reviewer (B.dG.).

Quality Assessment of Studies

The reporting quality of the accepted articles were assessed against the 24-item Consolidated Health Economic Evaluation Reporting Standards checklist.[46] For items fulfilled, a score of "1" was given, otherwise a "0" was given. A percentage was calculated to compare scores between studies. The denominator was calculated by summing the number of applicable items per study, and the numerator by summing the scores. Studies were deemed to be of high (>75%), moderate (50%-75%), or low (<50%) reporting quality. Although use of the Consolidated Health Economic Evaluation Reporting Standards checklist is most appropriate for studies published subsequent to publication of the checklist, we applied this to all studies as it provides a benchmark for study comparisons. A.N. conducted the quality assessment, and a 10% random selection of articles was reviewed by B.dG. to check for agreement.

Synthesis of Results

The initial intention, as per the protocol, was to conduct a meta-analysis. As significant heterogeneity in key aspects across the studies was identified (including the economic evaluation methods, patient groups, screening interventions, time horizons, perspectives, outcome measures, and health systems), a narrative synthesis was conducted following published guidance.[47]

Results

Search Outcomes

Figure 1 illustrates the study selection process. The searches yielded a total of 6748 studies. After removing 2268 duplicates, another 4342 records were excluded by title and abstract screening; 138 full texts were assessed, and the remaining 43 articles were included.

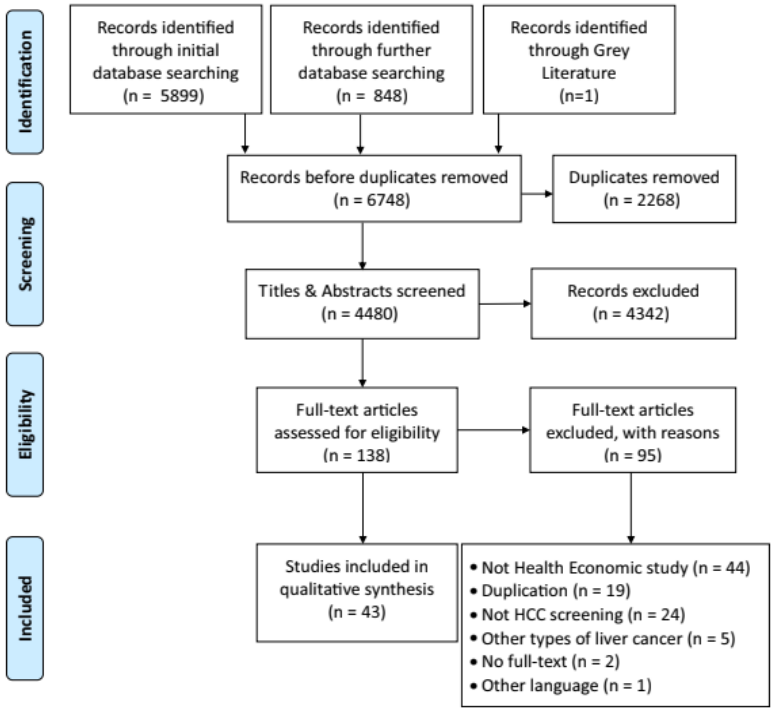
Study Characteristics

Most studies (34.9%, n = 15) were conducted in Asia, 12 (27.9%) in the United States, and 7 (16.3%) in Europe. The majority (65.1%, n = 28) of studies were model-based, of which 22 used Markov model structures and one used both Markov and decision analytical models.[48] For nonmodeling studies describing the populations' demographic characteristics, all studies reported a mean age of >45 years and higher ratios of males to females, with the exception of one study reporting on patients with cirrhosis, which reported 35.4% of the sample were male and 64.6% were female (Table 1).[49]

Twenty-three studies focused on patients with cirrhosis: 6 on HBV carriers,[50-55] and 14 on populations with different liver diseases (cirrhotic or noncirrhotic chronic HBV and HCV, nonalcoholic steatohepatitis, or fibrosis).[48,56-68]

Markov-modeling studies mostly used lifetime horizons,[48,52,53,63,64,69-78] with 4 applying horizons of 10 to 25 years,[62,79-81] 1 of 30 years (for 40-year-old patients),[82] and 1 of between 15 to 50 years for patients of different ages (30, 40, and 50 years old).[66] The horizon was not reported in four modeling studies.[51,54,68,83]

Figure 1. PRISMA flowchart. HCC indicates hepatocellular carcinoma.



Discount rates were reported in all Markov-modeling studies; a single study applied discounting for both costs and outcomes but did not report the rate used.[73] Studies using other modeling approaches did not discount the costs/outcomes, with the exception of a spreadsheet-based study.[50] Discount rates of 3% and 5% were used by 12[50,53,62,63,68,70,71,75-77,82,83] and 5[48,52,64,72,81] studies, respectively for both costs and outcomes, 2 studies discounted the costs at 3% but not the outcomes.[74,79]

All studies considered direct medical costs, with 5 also reporting direct nonmedical costs (food and transportation).[50,53,63,81,84] Three studies adopted a societal perspective, incorporating indirect costs such as productivity losses.[53,63,84] Although 2 other studies also reported adopting a societal perspective, they did not include indirect costs.[79,82]

QALYs were the most frequently used outcome measure (in 15 modeling studies). Other studies used non−preference-based outcomes as effectiveness measures, with LYs gained and HCC cases detected most commonly reported (n = 15).

Reporting Quality Assessment

The overall mean reporting quality score was 67.0% (standard deviation [SD] = 19.0; Table 2). The mean quality score for modeling studies was 73.5% (SD = 14.0) while for nonmodeling studies this was 54.7% (SD = 21.4). For modeling studies, 17 had scores ≥75%, 9 had scores between 50% to 75% and 2 <50%. For nonmodeling studies, 5 were deemed to be of high reporting quality: 3 of moderate and 7 of low quality.

Data Synthesis

All studies used ultrasound ± AFP at annual, biannual, or shorter intervals (3-month in the presence of cirrhosis)[48,62,76] as either screening strategies or comparators. Two of 3 studies with shorter screening intervals were conducted in Taiwan,[48,62] the other in the United States.[76] Three Italian studies evaluated ultrasound + AFP at 6-month intervals.[79,85,86] Studies set in Japan and the United States evaluated a wide range of screening strategies and intervals. Magnetic resonance imaging (MRI) and computed tomography (CT) screening were mostly included in studies from the United States (7 of 10 studies[67,70,73,74,82,87,88]).

Data were synthesized by 3 groups: cirrhotic, chronic HBV, and high-risk populations with different liver diseases. Patients with chronic HCV were not categorized as a subgroup because all HCV-related studies targeted either HCV cirrhotic populations or patients with other liver diseases in addition to HCV. Cost-effectiveness was based on a willingness-to-pay threshold (WTP), which was within 3 time the given country's gross domestic product per capita.[89,90]

Cirrhosis Only

Twenty-three studies (53.5%) focused on patients with cirrhosis, with mixed evidence of cost-effectiveness. Studies reporting cost-effectiveness evaluated different strategies and outcomes. An Egyptian study examining biannual ultrasound and ultrasound + AFP compared with no screening reported incremental cost-effectiveness ratios (ICERs) of EGP7907 and

Table 1. General characteristics of included studies (n = 43).

Characteristics	n	%
Publication year		
2010-2020	24	55.8%
2000-2009	13	30.2%
Before 2000	6	14.0%
Location of study		
United States	12	27.9%
Europe	7	16.3%
Australia	3	7.0%
Asia	15	34.9%
Japan	4	
Korea	4	
Taiwan	3	
Other	4	
Other	6	13.9%
Patient population		
Cirrhosis only	23	53.5%
Chronic HBV only	6	14.0%
High-risk population with different liver disease	14	32.5%
Type of economic evaluation		
Cost-effectiveness analysis	29	67.4%
Cost-benefit analysis	1	2.3%
Partial economic evaluation	13	30.3%
Cost: outcome description	10	
Outcome analysis	1	
Cost analysis	2	
Perspective		
Government (healthcare system)	27	62.8%
Societal	5	11.6%
Healthcare provider	1	2.3%
Not reported	10	23.3%
Study design		
Markov disease-state transition model	22	51.2%
Other model (decision analytic, nomogram, math, spreadsheet, stochastic, microsimulation)	7	16.3%
Nonmodeling studies	15	34.9%
Retrospective clinical review	7	
Prospective clinical trial	1	
Prospective population-based study	2	
Prospective cohort study	3	
RCT	2	

HBV indicates hepatitis B; RCT, randomized controlled trial.

8430/QALY respectively, which was within the country's WTP.[49] One Italian study comparing biannual ultrasound with annual ultrasound + AFP showed biannual screening was more cost-effective in patients with compensated than decompensated cirrhosis, with an ICER of €1997/quality adjusted life month: less than the country's WTP of €3000/ quality adjusted life month.[79] A US-based study concluded 6-month AFP screening was dominated by 6-month ultrasound + AFP, which was cost-effective with an ICER of $26 689/QALY compared with no screening.[70] Contrast-enhanced ultrasound in a Japanese study was cost-effective compared with no screening (ICER: $18 384/QALY).[83]

Although the majority of studies reported screening to be cost-effective, several studies reported opposing evidence. Those studies compared 6-month ultrasound + AFP with no screening, using cases detected[84-86,91,92] and survival time[72,86,91] as outcome measures. This negative result could imply that, despite the gain in survival time (ranging from 1.5-15 months),[72,86,91] the effect was too small compared with the costs. Similarly, an Indian study used annual CT scans in addition to biannual ultrasound + AFP, adding substantial costs to the screening program.[84]

Seven studies evaluated CT or MRI as screening strategies.[70,73,78,81,82,87,88] Generally, CT and MRI were clinically more effective than ultrasound at the same interval. Two US-based studies using CT and MRI resulted in higher QALYs and QALEs gained than ultrasound.[70,73] However, CT and MRI were much more costly than ultrasound.[70,73,81,82,88] A Korean study estimated an ICER of $25 202/QALY for the biannual MRI against biannual ultrasound, higher than the WTP of $20 000.[81] However, biannual ultrasound brought about better clinical outcomes than annual CT.[73,82,87] A US-based RCT showed biannual ultrasound detected more HCC cases than annual CT, with a lower cost/case detected ($12 069 vs $18 768).[87] One US-based modeling study also showed annual CT was dominated by biannual ultrasound.[73] Abbreviated MRI (AMRI) was evaluated in 2 studies and reported to be cost-effective against ultrasound.[78,88] A Canadian study reported an ICER of CAD 39 681/QALY for AMRI, which was within the WTP of 50 000/QALY.[78]

Chronic HBV

Six studies focused exclusively on patients with chronic HBV[50-55] and concluded screening this population was cost-effective. A Thai study concluded biannual ultrasound ± AFP was cost-effective against no screening, with ICERs of 118 796 and 123 451 Baht/QALY, respectively: less than the WTP (160 000 Baht/QALY).[53] CT and MRI were not cost-effective: ICERs of 175 583 and 187 064 Baht/QALY, respectively.

Adding AFP to ultrasound was more cost-effective than ultrasound alone in most studies. A US-based study reported the cost-effectiveness of a staged screening strategy: AFP >10 ng/mL followed by ultrasound compared with biannual ultrasound. Although ultrasound alone detected more early tumors (14 vs 10 cases), its overall cost was more than double that of AFP + ultrasound ($814 000 vs $357 000).[50] A Korean study reported similar results and suggested the accuracy of detecting HCC would be significantly improved if ultrasound screening incorporated HCC risk predictors (age, sex, cirrhosis status, and AFP).[54] A Singaporean study also showed ultrasound + AFP was more cost-effective than ultrasound or AFP separately, and was capable of detecting 90% of cases at early stages.51 However, limitations of this modeling study, including lack of probability distributions and critical parameters (such as transition probabilities from chronic HBV to cirrhosis and HCC) meant these results should be interpreted with caution.

An Australian study assessed biannual ultrasound + AFP screening. Compared with no screening, the ICER was unacceptably high: AUD401 516/QALY. Nevertheless, when pharmacologic treatment of chronic HBV was included, the strategy became cost-effective (ICER: AUD12 956/QALY, well below the WTP of AUD50 000[52]).

High-Risk Populations With Different Liver Diseases

Overall, screening populations with cirrhosis, or no cirrhosis but living with chronic HCV, HBV, nonalcoholic steatohepatitis, or fibrosis appeared to be cost-effective. Two studies concluded ultrasound screening on patients with cirrhosis was more cost-effective than for patients with other liver diseases. A Canadian study reported a lower ICER for screening patients with cirrhosis compared to patients with fibrosis using ultrasound at 12- or 6-month intervals.[64] Additionally, a Taiwanese study assessed annual ultrasound for patients with chronic HBV and 3-month ultrasound for patients with cirrhosis with no screening.

Table 2. Summary table of included studies.

Author, year	Country	Study design	Screening strategies	Comparators	CE or not	Cheers score
Patients with cirrhosis						
Kim et al, 2019[81]	Korea	Markov, CEA	MRI 6 mo	US 6 mo	Yes	87.50%
Lima et al, 2019[78]	Canada	Markov, CEA	US/CT/MRI/AMRI 6 mo	Next least expensive, non-dominated strategy	Yes for some strategies	83.33%
Goossens et al, 2017[74]	USA	Markov, CEA	US or MRI at different intervals	US 6 mo	Yes for high and intermediate risk	83.33%
Uyei et al, 2019[76]	USA	Markov, CEA	US 3 or 6 or 12 mo	No screening	Yes	83.33%
Pocha et al, 2013[87]	USA	RCT, CEA	US+AFP 6 mo	CT 12 mo + AFP 6 mo	No conclusion, CT dominated by US	81.25%
Arguedas, 2003[70]	USA	Markov, CEA	US/CT/MRI/AFP 6 mo	No screening	Yes, but MRI not CE	79.17%
Bolondi et al, 2001[86]	Italy	Prospective clinical trial, CEA	US+AFP 6 mo	No screening	No	75.00%
Cadier et al, 2017[80]	France	Markov, CEA	US 6 mo	No screening	Yes	75.00%
Cucchetti et al, 2012[79]	Italy	Markov, CEA	US+AFP 6 mo	US+AFP 12 mo	Yes for both strategies	75.00%
Lin et al, 2004[82]	USA	Markov, CEA	US/CT/AFP 6 or 12 mo	No screening	Yes, CT was CE	75.00%
Patel et al, 2005[75]	USA	Markov, CEA	US+AFP 6 mo + different treatments	No screening or treatment	Yes	75.00%
Paul et al, 2008[84]	India	Prospective cohort study, cost analysis	(US+AFP 6 mo) + CT 12 mo	None	Not supported screening	75.00%
Anderssonet al, 2008[73]	USA	Markov, CEA	US±AFP/CT/MRI 6 or 12 mo	No screening	Yes, but CT and MRI not CE	70.83%
Nouso et al, 2008[71]	Japan	Markov, CEA	US 6 mo	No screening	No conclusion	70.83%
Parikh et al, 2020[77]	USA	Markov, CEA	US±AFP 6 mo	No screening	Yes, US+AFP dominated US	70.83%
Thompson Coon et al, 2008[69]	UK	Markov, CEA	US or AFP 6 or 12 mo	No screening	Yes	70.83%
Eltabbakh et al, 2015[49]	Egypt	Prospective cohort study, CEA	US±AFP 6 mo	None	Supported screening	64.71%
Sarasin et al, 1996[72]	Swiss	Markov, CEA	US+AFP 6 mo	No screening	Yes for only few patients with 5-y survival rate of > 80%	60.87%
Violi et al, 2020[88]	USA	State transition microsimulation model, CEA	Different AMRI 6 mo	US 6 mo	Yes	60.87%
Tanaka et al, 2012[83]	Japan	Markov, CEA	US or contrast-enhanced US	No screening	Yes	50.00%
Ben Chaabane et al, 2011[91]	Tunisia	Retrospective clinical review, cost, and outcome description	US+AFP 3 or 6 mo	None	Not supported screening	43.75%
Bolondi et al, 1997[85]	Italy	Prospective cohort study, cost, and outcome description	US+AFP 6 mo	None	Not supported screening	37.50%
Kchaou-Ouakaa et al, 2007[92]	Tunisia	Retrospective clinical review, cost, and outcome description	US+AFP 3 or 6 mo	None	Not supported screening	25.00%

continued on next page

Table 2. Continued

Author, year	Country	Study design	Screening strategies	Comparators	CE or not	Cheers score
Patients with chronic HBV						
Robotin et al, 2009[52]	Australia	Markov, CEA	US+AFP 6 mo ± HBV treatment	No screening	Yes for screening + HBV treatment	95.83%
Sangmala et al, 2014[53]	Thailand	Markov, CEA	US±AFP/CT/MRI at 6 or 12 mo	No screening	Yes, but CT and MRI not CE	83.33%
Gounder et al, 2016[50]	USA	Spreadsheet-based model, CEA	AFP -> US 6 mo	US 6 mo	Yes	78.26%
Chung et al, 2017[54]	South Korea	Nomogram model, efficacy analysis	US + HCC risk predictors (nomogram)	US 6 or 12 mo + blood test	Yes	61.11%
Kang et al, 1992[51]	Singapore	Mathematical based model, Cost analysis	US or AFP	None	Supported screening	41.18%
Lam et al, 2000[55]	Hong Kong	Retrospective clinical review, cost, and outcome description	US or AFP 4 or 6 or 12 mo	None	Supported screening	31.25%
Patients with different liver diseases						
Farhang Zangneh et al, 2018[64]	Canada	Markov, CEA	US 6 or 12 mo	No screening	Yes for cirrhosis, no for fibrosis	91.67%
Lee et al, 2014[66]	Korea	Stochastic model, CEA	US+AFP at different intervals, initial and ending ages	Next least expensive, non-dominated strategy	Yes for some strategies	91.30%
Chang et al, 2011[62]	Taiwan	Markov, CEA	US 3 or 12 mo	No screening	Yes, screening patients with cirrhosis more CE than patients without cirrhosis	82.61%
Kuo et al, 2016[63]	Taiwan	Markov, CEA	Biomarker -> US or mass US 12 mo	No screening	No	82.61%
Chen et al, 2020[67]	USA	RCT, CBA	US 6 mo ± CT and/or MRI	Different outreach strategies	Yes, outreach provided good payoff	81.25%
Kwon et al, 2020[65]	Korea	Retrospective clinical review, cost, and outcome description	US+AFP 6 mo	No screening	No conclusion, but surveillance program improved survival benefits	81.25%
Shih et al, 2010[48]	Taiwan	Markov + decision analysis model, CEA	Biomarker+US 3 or 6 mo	No screening	Yes	75.00%
Saab et al, 2003[68]	USA	Markov, CEA	US±AFP/CT 6 mo	AFP 6 mo	No	65.22%
Frey et al, 2015[57]	Switzerland	Retrospective clinical review, cost, and outcome description	US±AFP 6 mo	None	Supported screening	62.50%
Mary Qian et al, 2010[59]	Australia	Retrospective clinical review, cost, and outcome description	US+AFP 6 mo	None	Supported screening	62.50%
Ruelas-Villavicencio et al, 2004[56]	Mexico	Decision analysis model, CEA	US or AFP 6 or 12 mo	Between strategies	No conclusion	39.13%
Mima et al, 1994[60]	Japan	Prospective population-based study, cost, and outcome description	US+AFP 12 mo	None	Supported screening	37.50%
Larcos et al, 1998[58]	Australia	Retrospective clinical review; cost and outcome description	US+AFP 6 or 12 mo	None	No conclusion, but US was superior to AFP for HCC detection	31.25%
Rimal et al, 1997[61]	Japan	Prospective population-based study, cost, and outcome description	Biomarkers	Mass US screening	Yes	31.25%

AFP indicates alpha fetoprotein; AMRI, abbreviated magnetic resonance imaging; CBA, cost-benefit analysis; CE, cost-effective; CEA, cost-effectiveness analysis; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; CT, computed tomography; HBV, hepatitis B; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial; US, ultrasound.

Table 3. Evolution of models used in studies.

	1990-2000	2001-2010	2011-2019
Model type			
Decision tree	0	2	0
Markov model	1	9	12
Nomogram	0	0	1
Mathematical	1	0	0
Spreadsheet	0	0	1
Stochastic	0	0	1
Microsimulation	0	0	1
Deterministic sensitivity analysis	1	10	14
Probabilistic sensitivity analysis	0	3	7

A significantly lower ICER for patients with cirrhosis ($16 719/LY) compared with the HBV cohort ($20 856/LY)[62] was reported; with both ICERs lower than the country's WTP ($33 000/LY).[63]

A Japanese study compared AFP screening for high-risk individuals (elevated AST and zinc sulphate turbidity) and mass, population-wide ultrasound screening. The authors reported AFP screening was more cost-effective than mass ultrasound screening.[61] These results, however, differ to 2 Australian studies evaluating biannual ultrasound + AFP. These studies reported that more liver abnormalities, which were later diagnosed as HCC, were detected by ultrasound than AFP.[58,59]

Evolution of Modeling Studies

The first modeling HCC screening study was published in 1992, using a mathematical model to estimate the cost of screening/HCC case detected.[51] This model included a limited number of parameters without probability distributions. Markov modeling techniques were used by a single study before 2000[72]; subsequently this approach became more frequently used. Most studies published before 2010 performed univariate and multivariate sensitivity analyses[52,56,68-73,75,82]; from 2011 probabilistic sensitivity analysis was increasingly used to address model parameter uncertainties (Table 3).[53,63,64,77,78,80,81]

Key Model Parameters

Incidence

Annual HCC incidence rates were reported in most studies for patients with cirrhosis as one of the most critical parameters affecting cost-effectiveness. Incidence rates ranged between 1.4% to 5%. One US-based study set annual HCC incidence for patients with cirrhosis between 2% to 10%, based on the duration of cirrhosis from 1 to >8 years,[82] and a Taiwanese study used HCC incidence rates of 0.125% and 0.75% for and patients with chronic HBV and cirrhosis, respectively.[62]

Diagnostic performance

The diagnostic performance of screening was also widely considered as an influential parameter. The sensitivity and specificity of ultrasound were reported to range from 45% to 78% and 80-97%, respectively, and for AFP 41% to 60% and 70% to 93%, respectively. The sensitivity and specificity of ultrasound + AFP ranged between 63% to 85% and 80% to 87%, respectively.

Increased HCC incidence or enhanced screening performance improved the cost-effectiveness of screening compared with no screening. The literature sources, from which those key model parameters' values were drawn, also substantially varied among included studies. Some studies extracted these parameters from a single study, while some estimates were based on a wide range of published articles. However, the method of synthesizing results from several published articles into single parameters was only reported in one study.[53]

HSUVs

Most studies using preference-based outcomes reported HSUVs for cirrhosis and stages of HCC. The majority of US-based studies obtained HSUVs from literature published in the United States by Bennett et al,[93] Kim-WR et al,[94] or Younossi et al.[95] Although Bennett et al used the time trade-off method to elicit utilities for different HCV-related states,[93] Younossi et al used the Health Utility Index Mark 2 to measure the utilities of patients with different liver diseases.[95] Kim-WR et al assigned HSUVs for different liver states but did not state how these were collected.[94] Meanwhile, several studies from Asia obtained utilities from studies by Levy et al[96] and Chong et al.[97] Levy et al elicited utilities for different HBV-related states by using the standard gamble technique.[96] Chong et al used the visual analog scale, standard gamble technique, Health Utility Index Mark 3, and EuroQol Index survey to obtain HCV utilities.[97]

Overall, compensated cirrhosis had higher HSUVs (0.66-0.80) than decompensated cirrhosis (0.39-0.67). The lowest HSUVs for both compensated (0.66) and decompensated cirrhosis (0.39) were from the article by Kim-HL et al,[81] who weighted the values from the study by Levy et al.[96] A HSUV for end-stage HCC of 0.07 was used in studies from Taiwan and Egypt[48,49]; however, both studies derived this from the Dutch disability weight of 0.93.[98] Liver transplantation was the most frequently reported curative treatment, with HSUVs ranging between 0.57 to 0.69 ≤1 year after the procedure and 0.67 to 0.85 ≥1 year subsequent. These HSUVs were derived from studies using several multiattribute utility instruments. HSUVs subsequent to surgical resection ranged between 0.70 to 0.80.[64,69,70,75,78] These values were predominantly derived from authors' assumptions or adopted from HSUVs for compensated cirrhosis.

In general, most studies included sufficient HSUVs for relevant health states. However, several studies obtained HSUVs from assumptions, clinical experts, or unclear sources, which made it difficult to assess the HSUVs' quality. Furthermore, because utilities are best measured with the population of interest, HSUVs obtained from other countries might not accurately reflect the targeted population's utilities.

Screening utilization

The utilization (or adherence or uptake) rate, measuring the percentage of people who follow the recommended screening interval, was considered in only 4 studies in our review (United States[74,76,77]; Canada[78]). One US-based study incorporated a utilization rate for biannual ultrasound of 15%, based on a meta-analysis.[99] This approach was dominated by the no-screening comparator, as it produced lower QALE gains (6.39 vs 6.40) and higher costs ($44 078 vs $42 961).[74] When the utilization rate was set at 100%, biannual ultrasound resulted in higher QALE gains (6.51 vs 6.40) together with higher costs ($51 761 vs $42 961) in comparison with no screening.[74] Another study from the United States showed biannual ultrasound was cost-effective when 20% of the patients adhered to screening and HCC treatment was suboptimal. If the adherence rate was 100% and HCC treatment became optimal, annual ultrasound would be more cost-effective.[76]

Discussion

Our systematic review evaluated the cost-effectiveness evidence of HCC screening by describing the costs and outcomes of screening on different patient groups. Overall, the vast majority of studies reported screening to be cost-effective. However, due to the limitations of these studies, care must be taken when interpreting the results.

In general, most of the included studies reported improvements in health outcomes from screening. Evidence of the clinical effectiveness of screening in improving health outcomes and survival has become clearer in recent years. Findings from a 2014 meta-analysis showed HCC screening markedly improved survival as it increased the probability of early tumor detection and patients receiving treatment.[100] A systematic review also showed screened patients were detected with HCC at earlier stages and had improved survival compared with nonscreened patients.[101] However, these conclusions were based upon low-strength evidence due to limitations of the included studies.[101] Another recent systematic review focusing on screening for patients with cirrhosis concluded that despite the low proportion of HCC cases detected, screening facilitated earlier detection of HCC. This resulted in patients being more likely to receive curative treatment options which, in turn, increased life expectancy.[102] An Australian study also reported improved survival among patients who participated in regular surveillance.[32]

Internationally, Japan implemented effective nationwide screening strategies in the 1980s[103] and Korea in 2003,[65] consisting of ultrasound + AFP for individuals with HBV or cirrhosis, that showed evidence of clinical effectiveness. The 5-year survival rate of patients with HCC in Japan was 43% in 2005, much higher than for the United States (11%-15%) in 2010[104] or Australia (18%) in 2015.[105] The proportion of HCC being diagnosed at early stages in Japan (62%) was twice as high as in Western countries (30%).[104] Korea also experienced a substantial increase in 5-year survival rates for HCC, from 10.7% in 1993 to 26.7% in 2010.[106] It is important to acknowledge that some of these gains may also be partly explained by the population's longer life expectancy and healthcare technology advances.

In our review, biannual ultrasound + AFP stood out as the most cost-effective strategy, which was in line with recommendations from Asia-Pacific and Australia professional bodies[40,41] for patients with cirrhosis and chronic HBV. Our findings support the approach of screening with ultrasound + AFP. Not only did the combination improve the screening sensitivity (despite the trade-off regarding decreased specificity),[107] it was also more cost-effective than ultrasound alone in most included studies.

CT and MRI have been used for screening, especially in the United States, due to their superior sensitivity to ultrasound and AFP.[107,108] CT was deemed cost-effective in 2 studies[70,82] and in a third study when screening utilization was set at 100%.[78] MRI was cost-effective compared with ultrasound when being conducted on high-risk patients with cirrhosis[74] or carried out with fewer sequences (AMRI).[78,88] Nevertheless, the risks associated with CT-based screening, including radiation exposure and contrast-induced renal toxicity,[107] and the time required for MRI investigations, means the risk-benefit needs to be carefully considered.

The most critical parameters affecting the cost-effectiveness of screening were annual HCC incidence rates and diagnostic performance of screening. As the incidence rate has been increasing in many countries,[5,109,110] this could have a substantial impact on the cost-effectiveness of screening.

Of note, no study considered patients' characteristics in the context of the screening strategies' performance. Morbid obesity can significantly limit the detection of HCC using ultrasound,[111,112] while the accuracy of AFP to detect HCC may be limited in the presence of HCV.[113] These factors are of critical importance when evaluating the cost-effectiveness of screening; as such, future studies should incorporate them.

Screening utilization rate was another important factor affecting screening effectiveness that was largely ignored in earlier studies but has become more common in studies published in recent years. As most studies modeled patients over a lifetime horizon, the cost-effectiveness may not be accurately measured if this was ignored.

The heterogeneity was substantial among influential parameters. HCC incidence rates varied amongst different target group and ranged between 0.125% to 10%, while diagnostic performance of investigations had a broad range of 45% to 97%. Furthermore, HSUVs for a variety of disease states were based on published literature, assumptions, expert opinion, and other sources.

It is essential for future modeling studies to apply these parameters from robust sources to strengthen the cost-effectiveness evidence of screening. Studies should also include the impact of central adiposity on the precision of ultrasound as it could substantially limit detection of HCC. Without including this, particularly in light of increasing global prevalence of overweight and obesity, the cost-effectiveness of ultrasound is not known. Real-world utilization rates should also be incorporated instead of assuming it to be 100%, as well as projections of increased HCC incidence. Additionally, there should be more primary studies evaluating the economic evidence of contrast-enhanced ultrasound on HCC detection due to its high sensitivity and specificity (85% and 91%, respectively).[114]

Strengths and limitations

Due to heterogeneity of included studies, a meta-analysis and publication bias assessment were not conducted. We overcame this by conducting a detailed narrative synthesis for reporting the cost-effectiveness evidence of screening programs. Furthermore, the study was not limited to English language as it also included articles in French and Italian.

Conclusions

Considering many economic evaluations on HCC screening have been published, this article contributes to the existing literature by describing the published data. Although many studies suggest HCC screening is cost-effective, substantial limitations of these studies mean the results should be interpreted with caution. Future robust studies need to consider all key parameters, including central adiposity, real-world utilization rates, and projections of increasing incidence over time.

Supplemental Materials

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Author Affiliations: Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia (A. Nguyen, H. Nguyen, Palmer,

Blizzard); School of Medicine, University of Tasmania, Hobart, Tasmania, Australia (Yee); Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia (Palmer).

Correspondence: Barbara de Graaff, PhD, Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool Street, Hobart, Tasmania 7000, Australia. Email: barbara.degraaff@utas.edu.au

Author Contributions: *Concept and design*: Nguyen A, Yee, Palmer, Blizzard, de Graaff
Acquisition of data: Nguyen A, Nguyen H
Analysis and interpretation of data: Nguyen A, Nguyen H, Yee, Palmer, Blizzard, de Graaff
Drafting of the manuscript: Nguyen A, Palmer, Blizzard, de Graaff
Critical revision of the paper for important intellectual content: Nguyen A, Yee, Palmer, Blizzard, de Graaff
Provision of study materials or patients: Nguyen A, Nguyen H
Obtaining funding: Yee, de Graaff
Supervision: Yee, Palmer, Blizzard, de Graaff

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