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Evaluation of prognostic factors for survival in patients with Hepatocellular carcinoma treated with Transarterial Chemoembolisation

A thesis submitted in fulfillment of the requirements for the degree of

Doctor of Philosophy

Written By

Dr Gauri Kamal Vaseni Mishra

BBiomedSc, MBBS (Hons), FRACP

Faculty of Medicine, Nursing and Health Sciences

Central Clinical School

Monash University, Australia

May 2020

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver with the second highest rate of cancer related mortality and an increasing global incidence,.[1-3] According to the most widely utilized staging systems, Barcelona Liver Cancer Clinic (BCLC), transarterial chemoembolisation (TACE) is the recommended treatment for patients with unresectable or intermediate stage (BCLC stage B) HCC.[4,5] However, the intermediate stage incorporates a wide range of tumour burden and hepatic dysfunction, resulting in significant variation in outcomes with median survival rates ranging from 20-45 months.[6-10] Recently, multiple scoring systems have been developed to improve patient selection including the albumin and bilirubin (ALBI) grade.[11-13]

The clinical utility of the ALBI grade was explored in this thesis through an comprehensive meta-analysis and systematic review in an international cohort of patients undergoing TACE. The analysis demonstrates the ALBI grade has good, albeit variable discriminatory function in stratifying patients and is a useful adjunct to currently available clinical tools for assessment of liver reserve prior to initial and repeat TACE. The applicability of novel prognostic scores, including the ALBI grade, to a local cohort undergoing TACE for HCC was subsequently analysed with data collated from six large Australian tertiary hospitals.

The initial study included an analysis of baseline and treatment related prognostic factors in 431 patients undergoing TACE from 2009 to 2014. The presence of ascites, lower serum albumin, and greater tumour burden prior to treatment was associated with poorer survival outcomes. Conversely, background chronic hepatitis B infection was associated with better overall survival, and may reflect the influence of associated favourable characteristics,

including participation in HCC surveillance programs and lower rates of cirrhosis.

In patients treated with repeat TACE the development of hepatic decompensation following initial TACE was associated with the highest risk of mortality [HR 4.50, (1.86-10-89), p=0.001], along with baseline higher tumour number (p=0.02), higher serum bilirubin (p=0.007) and serum AFP ≥ 200 ng/ml (p=0.001) after the initial TACE. Subgroup analysis demonstrated that serum AFP level following initial treatment in patients undergoing repeat TACE for HCC is a useful clinical prognostic marker for guiding appropriate patient selection in addition to factors associated with tumour stage and underlying hepatic dysfunction.

These two baseline studies formed the basis of a performance appraisal of novel emerging prognostic models in comparison to currently utilized staging tools. The prognostic performance of the HAP (Hepatoma arterial-embolisation prognostic) score and the traditional Child Pugh Score (CPS) were superior to the ALBI (albumin, bilirubin) and PALBI (platelets, albumin, bilirubin) grade.[11-13] In contrast the widely adopted BCLC stage had the poorest discriminatory power, reflecting the limitations of each model beyond their original derivation population with regards to TACE therapy.[10]

The four studies outlined in this thesis highlight the challenges of treating a widely heterogenous cohort within the framework of evolving guidelines and variable TACE technique. Improving TACE outcomes in patients with HCC requires a careful assessment of factors including severity of underlying hepatic dysfunction and tumour burden. This thesis aims to provide insights into current clinical practice with regards to TACE utilization and outcomes by evaluating factors associated with prognosis in a real-world setting to improve patient selection and treatment allocation.

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ACKNOWLEDGEMENTS

The opportunity to undertake and complete this PhD would not have been possible without the support of many individuals who provided their generous assistance. I would like to express my sincere thanks to my supervisors Professor Stuart Roberts and co-supervisor Associate Professor Anouk Dev for providing their guidance, supervision and mentorship throughout this project. I have greatly appreciated their encouragement and gained valuable experience and insight into the complexities and challenges of conducting a large multi-centre project with both national and international collaborators.

I thank Dr. Eldho Paul and Professor Guy Eslick for their assistance with statistical analysis and interpretation. I would also like to take this opportunity to thank all the members of the Liver Cancer multidisciplinary teams across each of the participating hospitals for their support in facilitating access to data and collation. I would also like to thank Monash University Central Clinical School for supporting this research with an Australian Government Research Training Program (RTP) Scholarship.

I would like to express my deep affection and appreciation towards my parents, thank you for providing me with a such a strong foundation to embark on this journey, and for your unconditional love and support. I would also like to thank my close friends for their understanding of extended absences and motivation to persevere.

To my dear husband Vimalesh, thank you for your patience, humour and unwavering support. Your encouragement and perspective have been invaluable in overcoming challenges and achieving this significant milestone.

ABBREVIATIONS

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2D	Two dimensional
3D	Three dimensional
AASLD	American association for the study of liver diseases
ABCR	Alpha-fetoprotein, BCLC, Child-Pugh class, Radiological response (score)
ADR	Adverse drug reaction
AFP	Alpha-fetoprotein
ALBI	Albumin, Bilirubin (grade)
ALT	Alanine transaminase
ART	Assessment for retreatment with TACE
AST	Aspartate transaminase
BCAA	Branch chain amino acids
BCLC	Barcelona clinic liver cancer classification
CI	Confidence interval
CPS	Child Pugh Score
CR	Complete response
CT	Computed tomography
cTACE	Conventional TACE
DEB TACE	Drug Eluting Bead TACE
DC Beads	Drug coated beads
EASL	European association for the study of the liver
ECOG	Eastern Cooperative Oncology Group (performance status)
EHS	Extra hepatic spread
ETOH	Alcohol
GIT	Gastrointestinal tract
GSP	Gelatin sponge particle

HAP score	Hepatoma arterial-embolisation prognostic score
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HGDN	High grade dysplastic nodule
HKLC	Hong Kong Liver Cancer (staging system)
HR	Hazard ratio
IQR	Interquartile range
IU	International unit
JIS	Japan Integrated Staging (score)
LGDN	Low grade dysplastic nodule
MDT	Multidisciplinary team
MELD	Model of end stage liver disease score
mg	Milligram
mHAP	Modified HAP (score)
mRECIST	Modified Response Evaluation Criteria in Solid Tumours
MVI	Macrovascular Invasion
NAFLD	Non-alcoholic fatty liver disease
ng	nanogram
NLR	Neutrophil lymphocyte ratio
NSAID	Non-steroidal anti-inflammatory drugs
OS	Overall survival
PALBI	Platelet, Albumin, Bilirubin (grade)
PD	Progressive disease
PEI	Percutaneous ethanol injection
PES	Post embolisation syndrome
PET	Positron Emission Tomography
PFS	Progression free survival

PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PVA	Polyvinyl alcohol particle
PVT	Portal vein thrombosis
RECIST	Response Evaluation Criteria in Solid Tumours
RCT	Randomised controlled trial
RNA	Ribonucleic acid
SBRT	Stereotactic body radiotherapy
SIRT	Selective internal radiation therapy
SD	Stable disease
TACE	Transarterial chemoembolisation
TAE	Transarterial embolisation
TARE	Transarterial Radioembolisation
TIPS	Transjugular intrahepatic portosystemic shunt
TTTP	Time to TACE progression
UGI	Upper gastrointestinal tract
WHO	World health organisation

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THESIS INCLUDING PUBLISHED WORKS DECLARATION

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Declaration for thesis based or partially based on conjointly published or unpublished work.

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously publish**ed** or written by another person, except where due reference is made in the text of the thesis.

This thesis includes a total of four original papers submitted to peer reviewed journals, of these one is accepted for publication, one conditionally accepted pending review of revisions, and two papers are submitted and currently under peer review. The core theme of the thesis is prognostic factors associated with survival in patients with Hepatocellular carcinoma undergoing treatment with Transarterial chemoembolisation. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Central Clinical School, Monash University, under the supervision of Professor Stuart Roberts and Associate Professor Anouk Dev.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapter 3,4, 5 and 6, my contribution to the work involved the following:

Thesis Chapter	***Publication Title***	***Status*** *(published, in press, accepted or returned for revision, submitted)*	***Nature and % of student contribution***	***Co-author name(s) Nature and % of Co-author's contribution****	***Co-author(s), Monash student Y/N****
3	***Clinical utility of Albumin Bilirubin grade as a prognostic marker in patients with Hepatocellular Carcinoma undergoing Transarterial Chemoembolisation: A systematic review and meta-analysis.***	*Returned for revision, submitted*	*80%, review of existing literature, study design, optimization of protocols, data acquisition, statistical analysis, interpretation of data, drafting and revision of the manuscript and submission.*	*1) Ammar Majeed, data acquisition, review and collation for analysis, input into manuscript.* *2) Anouk Dev, review of manuscript, input into manuscript.* *3) Guy D Eslick, statistical analysis and interpretation of data, review of manuscript, input into manuscript.* *4) David J Pinato, data acquisition and review of manuscript, input into manuscript.* *5) Hirofumi Izumoto, data acquisition and review of manuscript, input into manuscript.* *6) Atsushi Hiraoka, data acquisition and review of manuscript, input into manuscript.* *7) Teh-Ia Huo, data*	*N* *N* *N* *N* *N* *N* *N*

				acquisition and review of manuscript, input into manuscript. *8) Po Hong Liu, data acquisition and review of manuscript, input into manuscript.* *9) Philip J Johnson, data acquisition and review of manuscript, input into manuscript.* *10) Stuart Roberts, study design, interpretation of data, and critical revision of the manuscript for important intellectual content, input into manuscript.*	*N* *N* *N*
4	***Prognosis of patients with Hepatocellular Carcinoma treated with Transarterial Chemoembolisation: An Australian multi-centre cohort study.***	*Submitted*	*80%, review of existing literature, study design, optimization of protocols, data acquisition, statistical analysis, interpretation of data, drafting and revision of the manuscript and submission.*	*1) Anouk Dev, multi-site ethics approval and review of manuscript, input into manuscript.* *2) Eldho Paul, statistical analysis and critical review of manuscript, input into manuscript.* *3) William Kemp, multi-site ethics approval and review of manuscript, input*	*N* *N* *N*

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				4) Ammar Majeed, review of manuscript, input into manuscript.	*N*
				5) John Lubel, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				6) Sally Bell, review of manuscript , input into manuscript.	*N*
				7) Paul Gow, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				8) Amanda Nicoll, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				9) Siddharth Sood, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				10) Alex Thompson, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				11) Marno Ryan, review of manuscript, input into manuscript.	*N*
				12) Stuart Roberts, data acquisition and review of manuscript Study	*N*

				design, interpretation of data, and critical revision of the manuscript for important intellectual content, input into manuscript.	
5	***Predicting Survival in Patients undergoing Transarterial Chemoembolisation for Hepatocellular Carcinoma: Comparison of current and emerging models.***	*Submitted*	*80%, review of existing literature, study design, optimization of protocols, data acquisition, statistical analysis, interpretation of data, drafting and revision of the manuscript and submission.*	*1) Anouk Dev, multi-site ethics approval and review of manuscript, input into manuscript.* *2) Eldho Paul, statistical analysis and critical review of manuscript, input into manuscript.* *3) Wa Cheung, radiological review of imaging and reporting, review of manuscript, input into manuscript.* *4) Jim Koukounaras, radiological review of imaging and reporting, review of manuscript, input into manuscript.* *5) Ashu Jhamb, radiological review of imaging and reporting, review of manuscript, input into manuscript.* *6) Ben Marginson, radiological review of imaging and reporting, review of*	*N* *N* *N* *N* *N* *N*

				manuscript, input into manuscript.	
				7) Beng Ghee Lim, radiological review of imaging and reporting, review of manuscript, input into manuscript.	*N*
				8) Paul Simkin, radiological review of imaging and reporting, review of manuscript ,input into manuscript.	*N*
				9) Adina Borsaru, radiological review of imaging and reporting, review of manuscript, input into manuscript.	*N*
				10) James Burnes, radiological review of imaging and reporting, review of manuscript, input into manuscript.	*N*
				11) Mark Goodwin, radiological review of imaging and reporting, review of manuscript, input into manuscript.	*N*
				12) Vivek Ramachandra, radiological review of imaging and reporting, review of manuscript, input into manuscript.	*N*
				13) Manfred Spanger, radiological review of imaging and	*N*

				reporting, review of manuscript, input into manuscript.	
				14) William Kemp, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				15) Ammar Majeed, review of manuscript, input into manuscript.	*N*
				16) John Lubel, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				17) Sally Bell, review of manuscript, input into manuscript.	*N*
				18) Paul Gow, multi-site ethics approval and review of manuscript, input into manuscript..	*N*
				19) Amanda Nicoll, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				20) Siddharth Sood, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				21) Alex Thompson, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
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				22) Marno Ryan, review of manuscript, input into manuscript. *23) Stuart Roberts, data acquisition and review of manuscript Study design, interpretation of data, and critical revision of the manuscript for important intellectual content, input into manuscript.*	*N*
6	***Prognostic role of Alpha-Fetoprotein in patients with Hepatocellular Carcinoma treated with repeat Transarterial Chemoembolisation.***	*Accepted for publication.*	*80%, review of existing literature, study design, optimization of protocols, data acquisition, statistical analysis, interpretation of data, drafting and revision of the manuscript and submission.*	*1) Anouk Dev, multi-site ethics approval and review of manuscript, input into manuscript.* *2) Eldho Paul, statistical analysis and critical review of manuscript, input into manuscript.* *3) Wa Cheung, radiological review of imaging and reporting, review of manuscript, input into manuscript.* *4) Jim Koukounaras, radiological review of imaging and reporting, review of manuscript, input into manuscript.* *5) Ashu Jhamb, radiological review of imaging and*	*N* *N* *N* *N* *N*

				reporting, review of manuscript, input into manuscript. 6) *Ben Marginson, radiological review of imaging and reporting, review of manuscript, input into manuscript.* 7) *Beng Ghee Lim, radiological review of imaging and reporting, review of manuscript, input into manuscript.* 8) *Paul Simkin, radiological review of imaging and reporting, review of manuscript ,input into manuscript.* 9) *Adina Borsaru, radiological review of imaging and reporting, review of manuscript, input into manuscript.* 10) *James Burnes, radiological review of imaging and reporting, review of manuscript, input into manuscript.* 11) *Mark Goodwin, radiological review of imaging and reporting, review of manuscript, input into manuscript.* 12) *Vivek Ramachandra, radiological review*	*N* *N* *N* *N* *N* *N*

				of imaging and reporting, review of manuscript, input into manuscript.	
				13) Manfred Spanger, radiological review of imaging and reporting, review of manuscript, input into manuscript.	*N*
				14) William Kemp, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				15) Ammar Majeed, review of manuscript, input into manuscript.	*N*
				16) John Lubel, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				17) Sally Bell, review of manuscript, input into manuscript.	*N*
				18) Paul Gow, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				19) Amanda Nicoll, multi-site ethics approval and review of manuscript, input into manuscript.	*N*
				20) Siddharth Sood, multi-site ethics approval and review of manuscript, input	*N*

				into manuscript. *21) Alex Thompson, multi-site ethics approval and review of manuscript, input into manuscript.* *22) Marno Ryan, review of manuscript, input into manuscript.* *23) Stuart Roberts, data acquisition and review of manuscript Study design, interpretation of data, and critical revision of the manuscript for important intellectual content, input into manuscript.*	*N* *N* *N*

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: Dr. Gauri Mishra

Student signature: **Date:** 30/04/2020

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Prof. Stuart Roberts

Main Supervisor signature: **Date:** 30/04/2020

CHAPTER ONE

REVIEW OF THE LITERATURE

1.1 HEPATOCELLULAR CARCINOMA

This chapter provides the background and overview of hepatocellular carcinoma development, presentation, staging and treatment options, in particular focusing on transarterial chemoembolisation. In doing so this chapter aims to construct the framework for the studies presented in subsequent chapters by analysing the evolving role of transarterial chemoembolisation in patients with hepatocellular carcinoma and the ongoing controversies therein.

1.1.1 Pathogenesis

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver[1], arising from hepatocytes, stem cells or progenitor cells, usually on the background of chronic liver disease and cirrhosis.[2,3] The process of carcinogenesis is a complex multistep process involving over forty alterations in functional somatic cancer genes, leading to the development of pre-cancerous dysplastic nodules. [4–6] These can progress from low-grade (LGDNs) to high-grade dysplastic nodules (HGDNs) and transform into early-stage HCC.[7,8]

In addition to contributing to tumour development, chronic inflammation and fibrosis of the liver parenchyma results in varying severity of background hepatic dysfunction.[9] This can present as mild liver function abnormalities to hepatic decompensation, including portal hypertension, ascites and hepatic encephalopathy at the time of HCC development.[10,11] As a result HCC have significant genotypic and phenotypic heterogeneity, between patients and also between tumours arising within the same liver.[12,13]

1.1.2 Epidemiology

HCC is the sixth most common cancer globally and the second highest cause of cancer related mortality worldwide, responsible for nearly 841,000 new cases, and 782,000 deaths in 2018.[14–16] It is two to three times more common in men than women, and has increasing incidence with age.[15] There are geographical variations in the incidence of risk factors associated with HCC development including liver cirrhosis, chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcohol abuse, non-alcoholic fatty liver disease (NAFLD), and food contamination with fungal carcinogen aflatoxin B1.[3,13,15]

Infectious aetiologies of chronic liver disease are the most common in the Asia Pacific region, including HBV, HCV and C. sinensis.[14,15] Whilst the incidence has slightly decreased with implementation of HBV vaccination programs in the past three decades[17,18], HCC is still the second highest cause of cancer mortality in the Asia-Pacific, and accounts for 75% of global cases.[15,19,20] In contrast, developed countries including the USA, Europe and Australia have seen an increase in HCC incidence and mortality since the 1980's, associated with non-alcoholic fatty liver disease, chronic HCV infection, alcohol, smoking and chronic HBV infection.[14,21–25]

As a result, HCC has had the second highest increase in incidence compared to all cancers between 1991-2009 in Australia, with poor five-year survival rates of 19.2% between 2011 to 2015. [16,24,25] The greatest burden of disease and mortality is seen in Aboriginal and Torres Strait Islanders, those born overseas and residents from remote and rural Australia.[16,25]

1.1.3 Natural history of HCC

Early HCC are usually asymptomatic[26–28], and have favourable survival outcomes due to the relatively slow growth rate of tumours that are less than 2 cm, with a median tumour doubling time of 6 months.[12,29,30] However, the prognosis of HCC remains poor globally, with mortality and morbidity closely paralelling incidence.[15,28,31] This is due to the majority of cases, up to 70% in Western cohorts, presenting at an advanced stage, often with large multifocal tumour, and poor hepatic function.[1,32,33] Local invasion is often present with satellite tumour nodules within the liver along with macrovascular invasion (MVI) of the main portal vein.[1,28,34] In addition, extrahepatic metastases can also occur to the abdominal lymph nodes, adrenal glands, lungs and bone.[35,36]

The symptoms of HCC often overlap with those associated with advanced liver disease and hepatic decompensation, including, abdominal pain, weight loss, jaundice and lethargy.[19,28,37] Severity of chronic liver disease is a key factor influencing overall survival in HCC, as unlike other solid tumours, significant dysfunction can preclude patients to curative treatment with higher rates of recurrence and increased risk of adverse effects such as liver failure and death.[22,38] Untreated patients with HCC have a poor median overall survival rates as low as 3.6 months [39], with mortality predominantly due to liver failure (34%), bleeding (30%), and tumour progression (24%).[40,41]

The implementation of surveillance programs utilising six monthly Ultrasound, with or without tumour marker alpha-fetoprotein (AFP) [42,43], has resulted in an increasing number of patients being diagnosed at earlier stage of disease in many countries.[44–47] This has directly improved survival rates with patients diagnosed at a curative stage of HCC, and screening is now recommended by all international HCC guidelines.[46–49]

1.1.4 Diagnosis

Once a hepatic lesion suspicious for HCC is detected on screening ultrasound, diagnosis can be confirmed on cross sectional imaging criteria alone, using computed tomography (CT) or magnetic resonance imaging (MRI), without the need for biopsy unlike most other solid organ tumours .[46,47,50] This is due to the unique dual blood supply of the liver, with normal hepatic parenchyma supplied mainly by the portal vein, up to 75%, and a smaller proportion by the hepatic artery, up to 25%.[18,50,51] Unlike the background liver parenchyma, HCC, especially those greater than 2 cm, derive up to 95% of their blood supply from the hepatic artery and to a much lesser extent from the portal vein. [51–53] The pathological difference in blood supply of the HCC compared to normal hepatic parenchyma highlights tumour tissue against background liver parenchyma on contrast enhanced CT and MRI during the arterial phase, followed by washout of contrast during the portal venous phase of circulation facilitating early detection of HCC. [46,47,53,54]

Cross sectional imaging has good sensitivity, and specificity for diagnosing HCC ≥ 2cm using standardised diagnostic criteria, and is incorporated into international guidelines.[46,47,54–56] In particular, CT and MRI have a sensitivity of 74% and 88% with a specificity of 81% and 95% respectively.[55] In cases where the diagnosis is indeterminate, sequential use of cross-sectional imaging with contrast enhanced CT or MRI is recommended.[46,47,53] This is particularly useful in lesions smaller than 1cm to assess for growth and vascular changes.[55] Lesion with atypical findings on two different modes of imaging require biopsy for histopathological analysis.[46,47,54] Most international guidelines have excluded the routine use of serum tumour biomarker AFP as a screening tool as it has suboptimal sensitivity and specificity.[47,57] In particular AFP is not produced by almost 60% of small HCC < 3cm, and can be falsely elevated in the setting of active viral hepatitis.[58,59]

1.1.5 Management

Once diagnosis is confirmed, accurate HCC staging of tumour burden and hepatic reserve is key to ensuring patients are allocated to treatments that maximise survival outcomes.[18,47]

1.1.5.1 Assessment of Liver function

The Child Turcotte Pugh score (CPS) is one of the most widely utilised scoring systems for assessing severity of liver dysfunction.[11,38,60] Originally developed in 1964 and modified in 1973, it was initially used to predict mortality during surgery in patients with cirrhosis associated variceal bleeding.[11,37,61] The CPS incorporates biochemical parametres of serum albumin, bilirubin and INR in combination with clinical assessment of ascites and hepatic encephalopathy to stratify patients into three categories of A, B and C.[11,37] (Table 1.1)

Table 1.1 Child-Turcotte-Pugh classification of chronic liver disease. Adapted from Bruix et al[11]

Clinical and Lab Criteria	Points*		
	1	**2**	**3**
Encephalopathy[#]	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds prolonged) International normalised ratio	<4 <1.7	4-6 1.7-2.3	>6 >2.3

*Child Pugh Score obtained by adding points for each variable. Class A = 5-6 points, Class B = 7-9 points, Class C = 10-15 points. [#]Encephalopathy grade 1 = confusion, altered mood and behaviour, grade 2 = drowsy, inappropriate behaviour, grade 3 = stuporous but obeys simple commands, slurred speech, marked confusion, grade 4 = unable to be roused, coma.

The subjective nature of assessing the degree of ascites as mild, moderate, severe, and hepatic encephalopathy severity limits the CPS reproducibility, whilst each of the three grades lack discriminatory ability by grouping together a wide range of hepatic dysfunction within each category.[36,62]

Another non-invasive method of assessing hepatic reserve is the model for end-stage liver disease (MELD) score.[63,64] Originally created to predict the survival of patients undergoing trans-jugular intrahepatic portosystemic shunts (TIPS), it is utilised primarily to prioritise patients awaiting liver transplantation and for assessment of liver functional reserve and prognosis in patients with HCC.[63–65] The discriminatory value of the MELD score is variable in patients with HCC, as not all patients with HCC present with advanced stage cirrhosis. Furthermore, cachexia and loss of muscle mass can lead to low serum creatinine reducing accuracy of the MELD score as a measure of renal dysfunction in this cohort of patients.[64,66,67]

Various pitfalls associated with both the CPS and MELD score have led to the development of multiple other non-invasive scoring systems specifically designed for patients with HCC[68–70] with variable diagnostic accuracy and reproducibility and are discussed in subsequent sections of this review.

1.1.5.2 Staging Models

Due to the competing mortality from both underlying liver disease and HCC, all HCC staging models rely on baseline assessment of multiple variables, including, liver function reserve, tumour parametres, and functional status, to stratify patients into various prognostic grades.[31,71] The most commonly utilised model for estimation of liver reserve is CPS, whilst tumour parametres can include, the number of tumour nodules, size of largest tumour, macrovascular

invasion (MVI) and extrahepatic spread (EHS).[46,71–73] There are now over 15 different HCC staging systems internationally, including the Barcelona Clinic Liver Cancer (BCLC) classification, the Hong Kong Liver Cancer (HKLC) system, the Cancer of the Liver Italian Program (CLIP) score, and the Japan Integrated Staging (JIS) score, with various discriminatory and, prognostic stratification ability (Table 1.2).[38,74–77]

Table 1.2. Variables incorporated in various international staging models.

Staging system	Liver function	AFP	PS	Tumour spread
Okuda 1985	Ascites, albumin, bilirubin	No	No	Hepatic spread 50%< *vs* > 50%
CLIP 1998	Child-Pugh score	< 400 *vs* ≥ 400 ng/mL	No	Nodule(s), Hepatic spread 50% ≤ *vs* > 50%, Portal vein thrombosis
BCLC 1999	Child-Pugh score	No	Yes	Nodule(s), size, Portal vein thrombosis
JIS 2003	Child-Pugh score	No	No	TNM
HKLC 2014	Child-Pugh score	No	Yes	Nodule(s), size Portal vein thrombosis

BCLC: Barcelona Clinic Liver Cancer; CLIP: Cancer of the Liver Italian Program; JIS: Japan Integrated Staging; HKLC: Hong Kong Liver Cancer; TIS: Taipei Integrated Scoring System; AFP: Alpha-fetoprotein; PS: Performance Status. Adapted from Liu 2016. [72]

The variety of staging systems available is reflective of the baseline differences in the original patient population from which each staging system was derived (Table 1.2).[78] These include incidence rates of HCC, aetiology of underlying liver disease, severity of hepatic dysfunction, tumour burden, and outcomes to treatment. [46,79–81] An example of this is the BCLC staging system, derived from a Spanish cohort of patients with predominant HCV cirrhosis and

significant hepatic dysfunction at time of HCC diagnosis.[82] The original BCLC cohort of patients had poorer survival associated with Child Pugh B liver disease, greater than 3 tumours more then 3cm in size, and macrovascular invasion (Table 1.3)[82,83], and classifies these patients with poorer prognosis as intermediate to advanced stage, appropriate for palliative therapies as outlined in Table 3.[82,84,85]

Table 1.3. BCLC staging classification of HCC. Adapted from Bruix et al.[11]

Stage	PS	Tumour Number	Tumour size	Liver function
Very early (Stage 0)	0	Single tumour	<2 cm	No portal hypertension
Early (Stage A)	0	Single tumour Less than 3 tumours	Any < 3cm	Child Pugh A-B
Intermediate (Stage B)	0	Multinodular tumour	Any	Child Pugh A-B
Advanced (Stage C)	1-2	Portal vein invasion, or N1, M1	Any	Child Pugh A-B
End Stage (Stage D)	3-4	Any	Any	Child Pugh C

However, the definition of intermediate stage HCC according to the BCLC has limited applicability to certain East Asian populations where HCC is often diagnosed at younger age with relatively preserved liver function on a background of endemic chronic HBV.[38,82,86]

Early cohort studies from Asia demonstrated improved survival outcomes in patients with larger HCC and multifocal HCC who were treated with more aggressive options such as surgery, compared to palliative therapies as per the BCLC recommendations.[87–90] Due to these inherent population differences, many staging systems such as the HKLC[38,86] classify patients with Child Pugh B liver disease, ≤3 tumours measuring ≤2 cm and limited vascular invasion as early stage, and therefore eligible for curative treatments.[86,91]

While there is a lack of universal classification system, the BCLC algorithm is one of the most widely adopted staging systems.[47,87] The unique combination of both staging and treatment recommendations of the BCLC stage has been validated in America, Europe, Taiwan, and Australia.[37,92–94] The variables used by the BCLC to stratify patients into five main stages is outlined in the Table 3 and the treatment allocation for each stage is discussed in the subsequent section.

1.5.3 Treatment

Based on HCC stage, and the severity of underlying liver dysfunction, patients are allocated to various treatments according to local guidelines.[38,95] The timely initiation of stage appropriate treatment is key in optimising survival outcomes as both treatment underuse and delayed treatment are associated with significantly worse OS.[48,49] According to the BCLC staging early HCC can be curatively treated in patients with good liver reserved (CPS A) and functional status, with options including, liver transplantation, surgical resection or local ablation. [46,47,85,96] However, only a minority of patients are eligible for curative options, of approximately 30% in western cohorts, and less than 10% in Asian populations. [15,96]

The majority of patients with HCC present with large, multifocal HCC, and relatively preserved liver function (CPS grade A or B). [84,96,97] The combination of greater tumour burden and advanced hepatic dysfunction makes them unsuitable to invasive surgical options due to significant associated morbidity and mortality risk.[1,32,33] As such, patients with intermediate and advanced stage HCC are treated with palliative treatments such as Transarterial Chemoembolisation (TACE) or Transarterial Radioembolisation (TARE).[33,98]

Recently Stereotactic body radiation therapy (SBRT) and proton beam therapy have shown promising results in achieving local tumour control.[99] Systemic treatment with oral tyrosine kinase inhibitors, such as Sorafenib, Regorafenib and Lenvatinib are reserved for patients with moderate liver disease and advanced HCC associated with extra hepatic spread and limited vascular invasion.[31,100,101] In cases with significant vascular invasion, extra hepatic metastases, poor hepatic reserve and functional status, best supportive care is recommended.[11,31,37]

1.1.5.4 Multidisciplinary Team management

Given the complexity of HCC presentation and staging, current best practice guidelines recommend that all treatment decisions are guided by a local multidisciplinary team (MDT) to further standardize treatment and improve patient care.[50,102–104] Multidisciplinary HCC management teams are composed of specialists relevant to different modalities of treatment including, Gastroenterologists, Interventional Radiologists, Surgeons, Oncologists and HCC nurses to guide treatment decisions.[104–106]

The MDT guided management of HCC facilitates greater standardisation in the approach to diagnosis and staging of HCC at individual treatment centres, allowing clinicians to formulate tailored treatment plans for individual patients based on latest guidelines and local expert

consensus.[106,107] The utilisation of MDT has improved OS at multiple institutions, especially in patients with intermediate stage HC undergoing TACE treatment and is considered the standard of care for management of HCC internationally.[46,47,102,108–110]

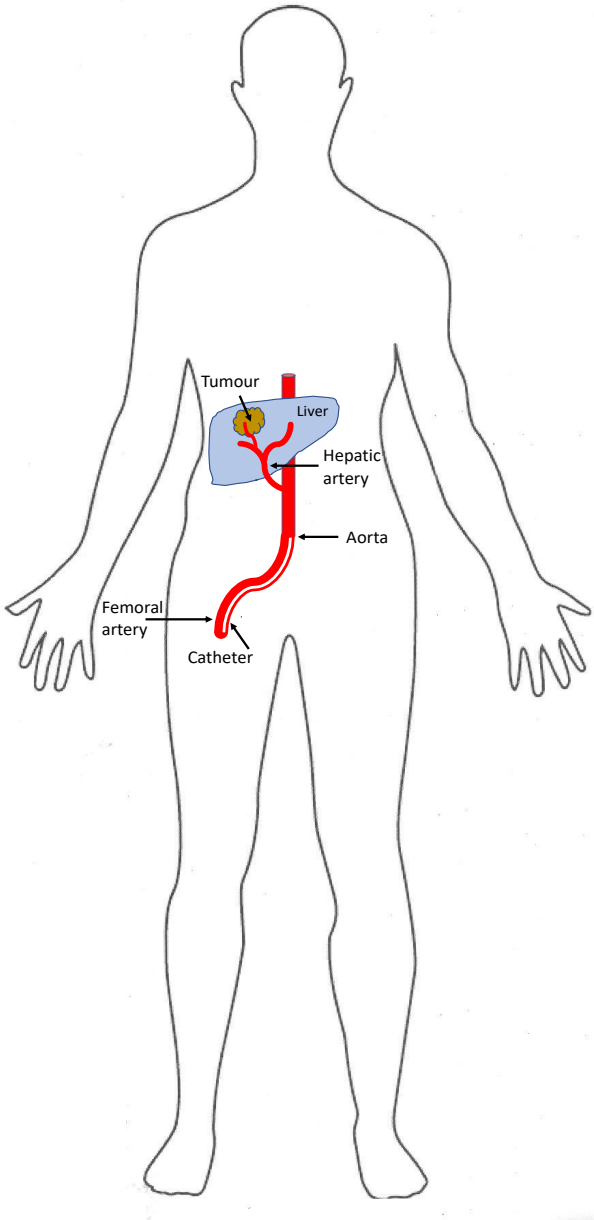
1.2 HISTORY AND DEVELOPMENT OF TACE TECHNIQUE

TACE was first developed in the 1970's, in an era when patients with unresectable HCC were limited to systemic chemotherapy.[111–113] The high doses required to achieve tumour necrosis caused significant systemic and hepatic toxicity with only 12-20% objective tumour remission rates.[113,114] As such a more localised approach to deliver chemotherapy and reduce HCC growth was required.[114] Early angiographic studies of HCC using radiopaque contrast confirmed previous surgical anatomical sections, that branches from the hepatic artery primarily supplied the tumour vascular bed, and were distinct from the branches of the portal vein that supplied the majority of the background liver. [51,115–118]

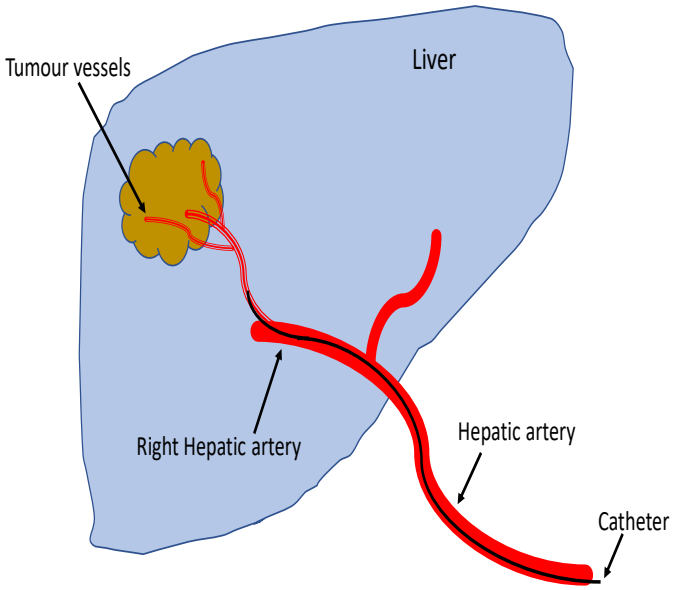
The discovery of the unique dual blood supply of the liver in contrast to HCC is the underlying principle that forms the basis of all transarterial HCC therapies.[115] Interventional Radiologists can access branches of the hepatic artery supplying the tumour for localised therapy by guiding a 4 to 5 French diametre catheter inserted via the peripheral femoral artery in the patient's groin or radial artery in the forearm using the Seldinger technique over a guidewire (figure 1.1a).[119] To reduce patient discomfort with catheterisation local anaesthetic agents and light sedatives are often administered along with small boluses of short acting opioids and sedatives.[111,120,121]

Once inserted the catheter is advanced proximally through the aorta to the origin of the hepatic artery where selective exploratory angiography is performed of the celiac trunk. This allows for further sub selective catheterisation of the hepatic arterial branches supplying the tumour vascular bed and infiltration of the target vessels with embolic materials such as gelatin sponge particles (figure 1.1b).[121,122]

Figure 1.1 a) Femoral artery approach to transarterial catheterisation and angiography. Adapted from Idee et al.[122]



b) Selective catheterisation of hepatic arterial branches. Adapted from Idee et al.[122]



This technique of transarterial embolisation (TAE) results in immediate occlusion of blood supply to the tumour as observed in real time during angiography with lack of radiopaque dye flowing beyond the treated vessel (figure 1.2a, b).[121,122]

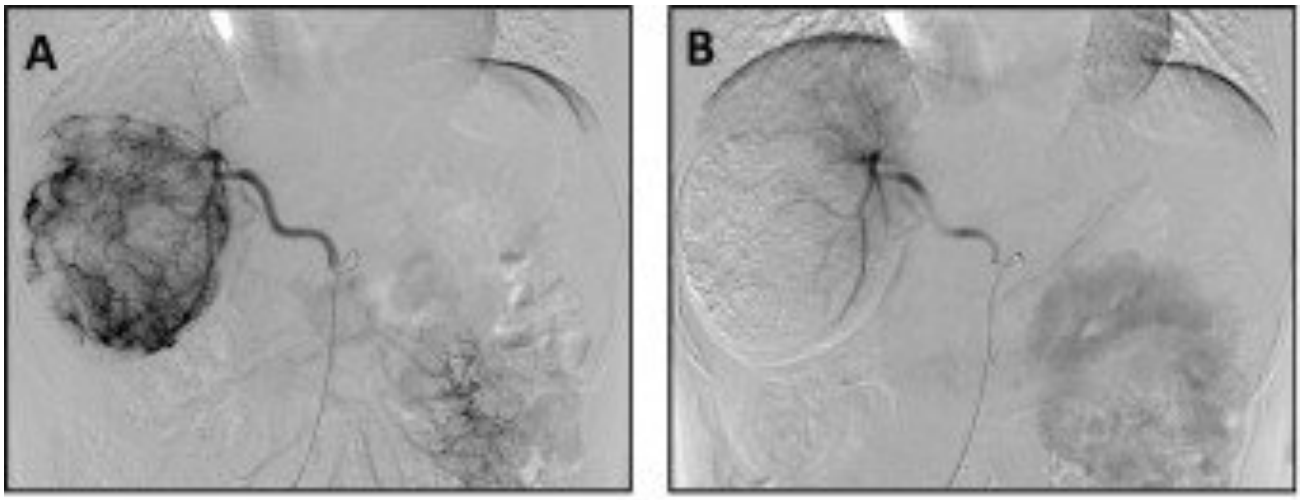


Figure 1.2a-b. Opacification of HCC during angiography prior to TACE showing tumour staining in the right lobe of the. (B) Following chemoembolisation the tumour vasculature disappears with stasis of blood flow beyond the catheter tip. Adapted from Jian W et al.[134]

Due to the unique dual blood supply of the liver and HCC, embolisation induces localised ischaemic necrosis of the tumour vascular bed whilst sparing the surrounding liver parenchyma that supplied mainly by the portal vein.[123,124] Early small case series with TAE demonstrated reduction of tumour burden and improved survival however non-target embolisation and recurrence were also significant.[125–127]

Subsequent investigators combined TAE with cytotoxic drug infiltration of the target artery. Labelled transarterial chemoembolisation (TACE), it was first utilised in HCC in 1977 and reported in 1983 by Yamada et al.[128,129] The addition of chemotherapy followed by embolisation, further enhanced tumour lysis and reduced tumour burden, with cumulative one-year survival rate of 44%, confirmed on follow-up angiography and histology.[130–132]

This form of TACE is also known as conventional TACE (cTACE), and is the most commonly utilised form of TACE. It usually involves instillation of an emulsion of chemotherapeutic drugs with the contrast agent lipiodol, into the target tumour artery till stasis. This is often followed by embolisation with either gelfoam or polyvinyl alcohol (PVA) particles dependent on the calibre of the feeding vessels.[121,133] Each component of cTACE is discussed further in the following section.

1.3.1 Lipiodol

Lipiodol is an iodized poppy seed oil emulsion discovered in 1901, with widespread use as an opacification agent for angiography studies including myelography and cystography since 1921.[122,133,135] It was first utilised in the treatment of HCC in the early 1980's, for its unique properties that allowed both chemotherapy drug delivery and assessment of embolisation of hepatic arterial branches.[133]

Lipiodol stagnates within tumour tissue for weeks to months, due to its higher density, active absorption by tumour tissue, and lack of scavenging Kupffer cells to remove the contrast, unlike the background liver parenchyma.[136,137] The preferential and prolonged deposition of the lipiodol emulsion within the tumour vascular bed, results in transient embolisation, and enhances tumour ischaemia.[121,133,138] In response to ischaemia the tumour tissues upregulate production of vascular endothelial growth factors, thereby increasing vessel permeability and localised cell membrane dysfunction resulting in further stasis of blood flow within the tumour vascular bed.[122,123,139,140] This stasis of vascular flow limits the systemic circulation of the cytotoxic drugs reducing their side effects and maximising their concentration within tumour tissue.[141,142] Lipiodol also diffuses through the perisinusoidal arterioportal anastomoses, resulting in stasis within portal venules that can supply the periphery of the tumour resulting in dual embolisation of the tumour blood supply.[141,143]

Lipiodol based TACE has become the standard of care at most centres based on two early large RCT's demonstrating significant survival benefits.[144,145] Retention of lipiodol within the tumour bed on follow up imaging correlates highly with tumour necrosis and is used as a surrogate measure of embolisation efficacy on follow up imaging.[146–148]

1.3.2 Radiology

Developments in cross sectional imaging have significantly improved TACE delivery and technique. In particular cone beam CT and multi detector array provide higher resolution images in real time during angiography,[52,53,55,56] and along with the C-arm extension, improved Radiologists ability to distinguish multiple overlapping tortuous vessels supplying a single HCC, facilitating the most selective hepatic arterial branch catherization. [53,149–151]

Imaging is also a key modality for assessing response following TACE accurately including quantification of residual tumour, and subsequent treatment planning.[152,153] Estimation of viable tumour is currently based on visual estimation of reduction in the size of the target tumour along with enhancement on contrast enhanced imaging with either CT or MRI.[153,154] Visual estimation can be challenging where intra-tumoural lipiodol and arterial enhancement of residual tumour overlap. [155,156] In such cases comparison with pre-treatment imaging is required to prevent underestimation of residual viable tumour and improve interobserver agreement between reporting Radiologists.[148] Various algorithms to improve standardisation of TACE response on imaging have been developed and are discussed in subsequent sections.

The emergence of functional imaging including Positron emission tomography (PET) [55,157,158], and diffusion weighted MRI, have improved assessment of post TACE tumour necrosis rather than relying on comparison of tumour diameter and 2D enhancement patterns alone.[155,156] Further 3D reconstruction software utilising artificial intelligence has shown promising results with enhanced estimation of response and requires further larger prospective trials.[148,159,160]

1.3.3 Angiography Catheters

The degree of distal hepatic arterial branch cannulation at the time of angiography is described as either non-selective, selective, or super selective.[121,161] Non-selective TACE describes catheter advancement to the proximal right or left hepatic artery, with selective and super-selective treatment catheterisation describing advancement of the catheter tip into the segmental or subsegmental arteries respectively.[161]

Selectivity of treatment is associated with tolerability and efficacy of the TACE procedure by allowing maximal tumour vascular bed infiltration whilst minimising exposure of normal

parenchyma to tissue ischaemia and cytotoxics.[162,163] Early studies utilising embolisation following non-selective TACE were associated with increased adverse events and complications post procedure due to ischaemic necrosis of a larger area of liver including non-tumour tissue.[111,128,164]

Significant improvements in TACE technique were led by development of micro catheters in the 1990's, allowing for superselective TACE delivery to smaller subsegmental hepatic artery branches, and also smaller ectopic tumour vessels, reducing non-target tissue ischaemic necrosis.[119,165–167] As a result, the rates of irreversible liver decompensation have reduced to 3% compared to up to 25% with non-selective procedures, without increase in recurrence rates.[81,121,167,168]

The combination of advances in angiography microcatheters, and CT guided imaging has rapidly improved TACE technique and delivery demonstrated by improvement in 3-year OS from studies in the early 1990's of 67% using segmental TACE to 77% using subsegmental TACE in 2001.[138, 147,168]

1.3.4 Embolisation Material

Embolisation of the target hepatic artery branch is a key component of TACE, and is carried out prior to withdrawal of the catheter in TAE or after instillation of chemotherapeutic drug emulsion in cTACE.[121,123] Embolisation prevents reflux of the cytotoxic agent into the systemic vasculature, prolongs contact between cytotoxic and target tumour tissue, and enhances tumour necrosis through direct ischaemia.[167,169] Effective targeted embolisation (TAE) has been shown to result in the same overall survival and progression free survival as embolisation combine with chemotherapeutic agents (cTACE) in recent matched trials.[170–172]

Typical agents used for embolisation, include biodegradable compounds such as, gelatin foam or sponge particles (GSP), starch microspheres and collagen particles, or synthetic agents including polyvinyl alcohol particles (PVA)[172,173], that are manufactured in various sizes to suit differing calibres of hepatic arterial branches.[174,175]The main benefit of gelfoam particles over PVA is their degradability, ensuring eventual re-canalisation and patency of the tumour feeding artery[173]. This facilitates repeat TACE treatments in the future, in contrast PVA particles can reach smaller calibre distal vessels and a result in a more permanent obstruction.[175,176] However randomised studies and meta-analysis have failed to demonstrate superiority of one embolic agent above another.[171,176,177]

Embolisation increase the risks of post TACE complications in patients with tumours >9cm due to increased area of tissue ischaemia and release of inflammatory vasoactive compounds from the necrotic tissue.[169,178,179] In this setting embolisation with GSP is associated with improved tumour response without a significant increase in severe adverse events[169,180]. Therefore, tailoring embolisation agent and particle size to the target vessel is important to prevent embolisation of non-target tissues and minimise complications.[175,181]

1.3.5 Chemotherapeutic drugs

Cytotoxic chemotherapeutic agents typically utilised in cTACE include doxorubicin, epirubicin, 5-fluorouracil, cisplatin and mitomycin, often infused as a combination with lipiodol of one or two agents.[177] The combination of two cytotoxic agents has demonstrated improved disease control rates and progression free survival, with no significant benefit with combination of three different cytotoxic agents.[177,182,183]

Despite several societal guidelines published on TACE [184,185], there remains significant variation in TACE technique with regards to chemotherapeutic dosage across institutions. [176,186–188] This is primarily due to the dosage of chemotherapeutic emulsion administered being calculated empirically often at the time of procedure, based on number and diameter of lesions, selectivity of hepatic arterial cannulation and the time till stasis in flow of emulsion during instillation.[187,189]

1.3.5.1 Anthracyclines

Anthracyclines are a class of cytotoxic compounds derived from Streptomyces bacteria, utilised in the treatment of various cancers including HCC. One of the earliest anthracyclines used as an emulsion with lipiodol was Doxorubicin, and was associated with a 2-year OS of 83.6%.[177,187,190] This emulsion however has poor stability, requiring rigorous mixing immediately prior to injection to prevent separation of the water-soluble doxorubicin to the oily poppy seed-based carrier, lipiodol.[191,192]

Epirubicin a 4-epimer of doxorubicin, is more lipophilic with a better toxicity profile with less myelosuppression and cumulative dose related cardiotoxicity than doxorubicin.[193,194] As a result, epirubicin is more widely used then Doxorubicin, and often in combination with Mitomycin C, an antineoplastic antibiotic isolated from the culture fluid of *Streptomyces caespitosus* bacteria.[194–196]

More recently, another anthracycline, Idarubicin, has demonstrated more stable lipiodol emulsion and favourable PK and safety profile then doxorubicin.[197,198] Emulsions that are more stable are associated with less myelosuppression, including post procedure anaemia and thrombocytopenia (P=0.013) compared to unstable emulsions, in a single centre double blind

prospective randomised controlled trial.[199] However, there has been no demonstrated difference in Median OS and tumour response. Further larger prospective trials with adequate blinded randomisation are required to fully elucidate the clinical advantage of agents such as idarubicin to traditional doxorubicin-based regimens.[123,177,200,201]

1.3.5.2 Platinum

Cisplatin is the first generation of platinum-based complexes and was developed as an alternative cytotoxic agent for patients with anthracycline resistant HCC after multiple rounds of cTACE.[123,201,202] One of the main advantages of platinum-based chemotherapies is non-hepatic based metabolization, with excretion in the urine, and therefore reduced hepatotoxicity. However, dose adjustment is required in patients with renal insufficiency to reduce systemic absorption.[177,203]

Subsequent generations of platinum based cytotoxic drugs include the lipophilic platinum complex, Miriplatin, that has improved solubility in lipiodol resulting in a more sustained and stable release of its active components at the tumour site.[195,204,205] Initial studies using Miriplatin with gelatin particles have demonstrated excellent tolerability in patients with chronic renal failure and tumour response, however there was no significant advantage in overall survival when compared to epirubicin based TACE in cohort studies and recent meta-analysis.[111,206–208]

1.4 TYPES OF TACE

1.4.1 Drug Eluting Beads (DEB) TACE

Innovation in the field of chemotherapeutic delivery led to the development of synthetic chemotherapeutic coated nano particles or beads (DC Beads or DEB TACE) in 2006 to provide consistent deposition of the cytotoxic drugs whilst limiting systemic toxicity.[209–212] Known variously as DC-beads or DEB TACE, drug-eluting beads are composed of polyvinyl alcohol-based microspheres that carry a static reversible ionic charge that allows for reversible binding with drugs such as doxorubicin.[212,213] Once loaded with chemotherapeutic drugs these microspheres are then injected into the target hepatic artery branch using the same transarterial approach as cTACE.[214,215]

Upon instillation into the target vessel the nano beads lodge into the end arterioles of the tumour vascular bed, resulting in tumour tissue necrosis due to combination of embolisation, and cytotoxic effect of the coated chemotherapeutic agent.[212,214] The main advantage of drug eluting beads to cTACE is the gradual release of chemotherapeutic drug over 7-10 days, with an improved pharmacokinetic profile, lower systematic absorption and less side effects.[212,216,217]

DEB TACE can be tailored to the vascularity and the size of the lesion with differing bead diametre and composition.[214,217] Larger beads release doxorubicin at a slower rate, and vice versa with smaller beads resulting in greater pan-necrosis of the target lesion.[217] The risk of toxicity with larger beads is higher to adjacent liver tissue and also the feeding vessel, thus impairing access for repeat treatment TACE.[217–219]

Both independent and manufacturer sponsored trials of various DEB TACE delivery particles have demonstrated improved tolerability and treatment response in patients undergoing treatment for unresectable HCC. [220–222] This has supported increased utility of DEB TACE despite two to three times higher cost than cTACE. [223,224] Whilst early small cohort studies [225–227] suggested an improvement in survival outcomes following DEB TACE compare to cTACE, subsequent larger studies have failed to replicate these results, with no significant survival benefit compared to cTACE in multiple large RCT and meta-analysis.[216,222,228–231] Explant studies have also demonstrated similar levels of tumour necrosis with DEB TACE compare to cTACE[232], with similar prognostic factors associated with OS including baseline liver dysfunction and tumour burden.[217,231,233]

The main advantages of DEB TACE are better standardization and reproducibility in technique and reduced side effect profile over cTACE.[172,217,234] Some centres have now shifted exclusively to DEB TACE for all transarterial chemoembolisation cases, whilst others endorse selective DEB TACE in patients with declining hepatic function after multiple cycles of cTACE. This is due to improved tolerability, and progression free survival, compared to cTACE despite no survival benefit. [87,172,222]

1.4.2 Conventional TACE (cTACE)

The role of cTACE in HCC has generated controversy since its conception in the 1980's. Initial randomized controlled trials (RCT) and systematic reviews failed to show a statistically significant survival benefit.[71,235] This was likely due to suboptimal study methodology and use of outdated techniques, such as non-selective TACE in advanced stage liver disease, known to be associated with poor outcomes. [27,82,143, 236]

Subsequently two RCT's published in 2002 from both European and Asian cohorts demonstrated significantly improved OS.[144,145] The first group led by Llovet et al studied 112 Spanish patients and found cTACE superior to TAE, with 1- and 2-y survival probability of 75% and 50% for TAE, compared to 82% and 63% for cTACE. Even though the smaller TAE arm was not adequately powered for this trial endpoint.[144] A similar group in Hong Kong[145] randomized 80 patients with newly diagnosed unresectable HCC to cTACE or symptomatic treatment, with cTACE associated with significantly better survival (1 year, 57%; 2 years, 31%; 3 years, 26%) when compared to the control group (1 year, 32%; 2 years, 11%; 3 years, 3%; p = 0.006).

These results were confirmed in a meta-analysis by Llovet et al in 2003, which included 545 patients across RCT studies from 1988 to 2002, that found cTACE treatment in patients with unresectable HCC improved survival by up to 2 years compared to the control group.[84,237] In particular, subgroup analysis showed chemoembolisation with cisplatin or doxorubicin had significant benefit compared to bland embolisation (TAE) alone. [84,237,238] This was replicated in three further recent meta-analysis comparing cTACE to best supportive care, and established cTACE as the standard of care for unresectable HCC.[177,235,239,240]

1.4.3 Transarterial Embolisation (TAE)

Technical advances with innovations in angiographic imaging, microcatheters and embolic materials over time have improved outcomes for both TAE and cTACE.[121,123,195,241] In particular, the improved side effect profile and efficacy of TAE in recent studies, has challenged the benefit of additional chemotherapy (cTACE) in a meta-analysis in 2006 and subsequent Cochrane review in 2011.[177,242] Both reviews incorporated trials published after Llovet's original meta-analysis in 2002, however the conclusions of the Cochrane review were widely refuted by international authors for bias due to inclusion of trials without control arms, and inadequate patient selection criteria.[243–245]

Recent randomized head to head trials and cohort studies utilising the most advanced techniques and refined patient selection criteria, have not been able to demonstrate a clear superiority of TACE over TAE with median OS (20.1 *versus* 23.1 months, respectively; $p = 0.84$).[177,246,247] These results were replicated in a recent RCT that compared TAE using modern small microspheres *vs.* DEB-TACE, with no significant difference found in radiologic response, adverse events, or overall survival. [170]

The question regarding the superiority of cTACE of TAE remains with a paucity of prospective contemporary trials that fully encapsulate recent advances in TACE technique in the past decade.[243,248–251] Despite the lack of standardized trials, the majority of international guidelines[44,46,47,87] recommend TACE as the standard of care for intermediate stage HCC based on studies subsequent to the initial RCT in 2002 in Europe and Asia.[144,145,238,252,253] TAE is still utilised selectively in cases of chemotherapy contraindication, liver metastases from other primary tumours, and achieving haemostasis in ruptured HCC.[241,254]

1.5 COMPLICATIONS OF TACE

In carefully selected patient population TACE is a safe and effective procedures and can be completed as a day procedure with discharge home on the same day or following observation overnight, without any significant increased risk of 30-day readmission.[255,256] Adverse outcomes can occur, requiring prompt recognition and treatment, as delayed treatment of major complications is associated with significant morbidity, and mortality rates of up to 16%. [255]

TACE related adverse outcomes within 30 days. [71,257]:

- Post embolisation syndrome
- Gastrointestinal bleeding
- Puncture site haematoma
- Portal vein thrombosis
- Hepatic Decompensation
- Liver abscess
- Biliary injury
- Renal failure
- Pancreatitis
- Ischaemic colitis
- Pneumonia, Pulmonary embolism

1.5.1 Local Complications

TACE involves the cannulation and insertion of a vascular catheter from a peripheral arterial site usually from the femoral or radial artery. The radial artery approach has greater patient preference and less operator exposure to radiation in comparison to the femoral approach, with no difference in the incidence of adverse events or procedure time.[258]

Local complications such as bleeding and puncture site haematoma are increased in patients with chronic liver disease due to impaired coagulation and thrombocytopaenia.[257] The use of mechanical and suture-based puncture site closure devices has significantly reduced this risk.[121,259] Puncture site closure devices have subsequently become standard of care as they achieve early haemostasis, allowing patients to ambulate earlier and discharge safely following TACE, improving patient experience and reducing healthcare costs.[260–262]

1.5.2. Intravascular complications

The flexible TACE catheter can inadvertently cause complications during its insertion, including spasm of the hepatic artery from mechanical stimulation, preventing further infusion of emulsion. This can be treated with local lignocaine or nitroglycerin infusion.[263] Significant and complete occlusion of the treating vessel can occur if the TACE catheter punctures or dissects the hepatic vessels resulting in the formation of haematoma and false aneurysm. This is more likely in patients with poor liver function and with high dose cytotoxic infusions.[164]

Damage to adjacent biliary tract during the intrahepatic course of the catheterisation can also occur, causing the formation of a biloma or bile leak. Less commonly tumour rupture and significant intra-abdominal bleeding can result in cases of large tumours close to the liver capsule.[263]

Patients with significant portal hypertension are at increased risk of non-target ischaemia due to arteriovenous or porto-venous vascular shunts, [264–266] that can allow embolisation material to travel to the lungs resulting in pulmonary embolisation, or chemical pneumonitis which can be fatal.[267,268]

Furthermore, as almost half the general population have some form variation of their hepatic blood supply, subsequent catheterisation of aberrant vessels supplying the tumour from branches of phrenic, adrenal gastric arterial branches can result in extra-hepatic embolisation with complications such as pleuritis, ischaemic colitis, empyema, gastric ulceration, cholecystitis and pancreatitis. This has been minimised with higher resolution angiography for treatment planning and the use of microcatheters during TACE. [219,255,267]

1.5.3 Post Embolisation Syndrome

Post embolisation syndrome (PES) is one of the most common complications following TACE, occurring in >50% of patients in some of the earlier case studies. It is associated with extended hospital admission and in some cases, increased mortality.[269–272]

PES comprises of nausea and vomiting along with fever and right upper quadrant pain that often resolves within three days.[272] Fever following TACE is common, and often due to post embolisation syndrome and extensive tumour necrosis rather than infection, with no bacterial growth in culture of all biological fluids in patients with post TACE fever > 38 degrees Celsius.[273] The development of microcatheters, allowing for more targeted TACE therapy and reduced cytotoxic exposure to normal liver tissue and systemic circulation, has reduced the incidence of PES in the reported literature to as low as 6% in recent case series.[121,167,274]

Prophylactic use of non-aspirin NSAID's such as parecoxib have been shown to be effective at relieving fever, reduced postoperative recovery and hospital stay, without any difference in OS. [275–277] Recently dexamethasone has also shown promise in reducing the duration of PES and ameliorating nausea, however larger randomised prospective studies are required.[278,279]

1.5.4 Hepatic Decompensation

Hepatic injury and insufficiency are the most common adverse event following TACE ranging from 22% - 67% and is higher in patients with lower hepatic reserve and larger tumour burden prior to treatment. [263,267] The arterial embolisation component of TACE can result in deterioration in liver function and hepatic decompensation, including the development of ascites, hepatic encephalopathy, hepatorenal syndrome and upper GI bleeding.[267,280]

Careful assessment of hepatic dysfunction and optimisation such as treatment of underlying viral hepatitis, prophylactic variceal banding and treatment of ascites can reduce the risk of post TACE complications, and are discussed in the subsequent sections. Furthermore, the utilisation of super selective arterial catheters for targeted delivery of cytotoxic, and embolisation material to tumour tissue only, can reduce the risk of severe liver injury. [263]

1.5.5 Renal Failure

Renal dysfunction following TACE is often due to contrast agents used during angiography and cytotoxic anticancer drugs.[267,281] Cisplatin based TACE is associated with renal injury, particularly in those with pre-existing co-morbidities including portal hypertension, renal insufficiency, diabetes and hypertension.[282–284]

Prompt investigation and treatment of post TACE renal injury is crucial as it requires inpatient treatment to prevent progression to renal failure. In cases where patients are eligible for repeat TACE, pre-hydration, avoidance of renal toxic chemotherapy with repeat TACE and minimisation of IV contrast during angiography can reduce the risk of recurrence. Peri-procedural haemodialysis may also reduce the risk of adverse outcomes in patients with severe renal impairment.[285,286]

1.5.6 Infection

Whilst the incidence of liver abscess after TACE is low (0.33%), some treatment centres routinely administer pre-procedure IV antibiotics and in small case series also inject concentrated antibiotics directly into the target vessel as a combination with embolic particles.[287,288] However, routine use of prophylactic antibiotics is not included in major society guidelines based on prospective non-randomised trials.[121,289]

A subgroup of patients with biliary abnormalities are at increased risk of liver abscess formation due to an incompetent ampulla of Vater allowing migration of gut bacteria into the biliary tree.[179,290] Rates as high as 26% have been reported following TACE in those with compromised biliary ducts systems due to previous ampullary sphincterotomy or enterobiliary anastomosis.[263,291–293]

Furthermore, impaired immune response due to underlying cirrhosis or diabetes mellitus, increase the risk of both spontaneous infections as well as rapid progression of localised infections.[290,294,295] As bacteraemia can result in further hepatic decompensation and poorer TACE outcomes, certain subgroup of patients with predisposing factors to may benefit from tailored short duration pre-procedure antibiotics.[287,294,296]

1.6 TACE in International Guidelines

TACE is an established treatment option for unresectable HCC in all current International guidelines, and is currently the most cost-effective treatment available for patients with non-curative HCC in comparison to systemic treatments and best supportive care.[11,46,47,224,297] Careful assessment and staging of patients with HCC prior to TACE therapy is pivotal to achieve optimal tumour response and reducing risk of further hepatic decompensation. As a result, multiple guidelines have been developed for patient selection, based on factors associated with poor outcomes in cohort and randomised studies, and are listed below.[235,298]

Absolute Contraindications:

- Decompensated cirrhosis (Child-Pugh class B ≥8) including, jaundice, clinical encephalopathy, refractory ascites, hepatorenal syndrome.
- Extensive tumour with massive replacement of both entire lobes
- Severely reduced portal vein flow (e.g. non-tumoural portal vein occlusion or hepatofugal blood flow)
- Technical contraindications to hepatic intra-arterial treatment, e.g. untreatable arteriovenous fistula
- Renal insufficiency (creatinine ≥2 mg/dl or creatinine clearance <30 ml/min)

Relative contraindications:

- Tumour size ≥10 cm
- Co-morbidities involving compromised organ function, including active cardiovascular disease and active lung disease.
- Untreated varices at high risk of bleeding
- Bile-duct occlusion or incompetent papilla due to stent or surgery

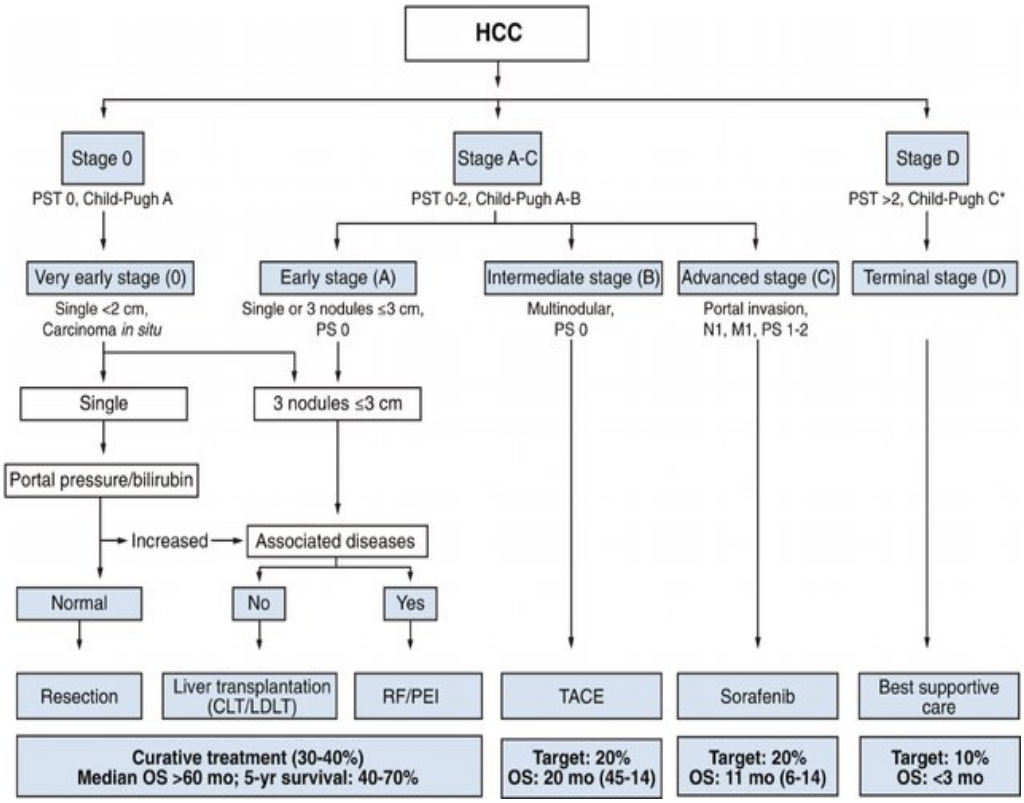
1.6.1 BCLC Staging system

While there are differences in staging of HCC between Asian and Western cohorts, common to all guidelines are factors associated with poor outcomes, including, extrahepatic metastases, main portal vein invasion and moderate to severe liver dysfunction, due to increased risk of adverse effects without significant improvement in OS. [46,80,81,103] The BCLC staging system is one of the most widely utilised treatment algorithms globally and forms the basis of many international HCC guidelines, including Australia, as it incorporates key tumour staging and hepatic function parametres.[47,94]

Developed in 1999, the BCLC staging identifies clinical stages based on many of the factors outlined in the previous section, including tumour stage (tumour size, number of nodules, and presence of portal vein thrombosis), liver function (Child-Pugh score, portal hypertension, bilirubin level), and performance status.[82] Based on these prognostic variables, patients with HCC are divided into four categories, and allocated a prognostic range in comparison to untreated patients in a similar stage derived from control groups in randomized studies.

Unlike other staging systems the BCLC staging system also provides a treatment recommendation for each stage based on the best available treatment option.[47,94,299] (Figure 1.3) Patients with intermediate-stage HCC (BCLC B) are characterized by multinodular disease, preserved liver function, and the absence of tumour-related symptoms, vascular invasion and extrahepatic spread. BCLC stage B patients are recommended transarterial chemoembolisation (TACE), based on results from RCTs and one meta-analysis of pooled data that was available at the time of the BCLC algorithm development.[83,237,300,301]

Figure 1.3. Staging and therapeutic algorithm for HCC according to BCLC. Adapted from Dufour 2013.[299]



Incorporation of staging systems such as BCLC in international guidelines has improved standardisation of treatment allocation and increased global utilization of TACE over the past two decades.[50] This has directly improved OS from median OS of 18 months to > 40 months on recent cohort studies during this period without significant change in TACE technique.[145,238,302] This is likely due to guideline driven improvements in patient selection, such as TACE for lower tumour burden (multinodular without vascular invasion) and relatively preserved liver function (Child-Pugh A or B).[81,248,302] Recent studies have demonstrated the median survival post TACE now ranges from 16 to 45 months in the early stage (BCLC A) of disease, 16 to 26 months in the intermediate stage (BCLC B) and 7 to 14 months in the advanced stage (BCLC C) HCC.[163,235,303,304]

1.6.2 Limitation of BCLC

The original BCLC was derived from early studies that included patients with early stage HCC and well compensated Child Pugh A liver disease, limiting the applicability of their results to patients with more advanced Child Pugh B liver disease and greater tumour burden as defined by BCLC stage B.[78,80] However the BCLC stage B classification of intermediate HCC encompasses a wide spectrum of tumour burden and liver dysfunction. As reported by Raul and Bolondi et al, both a patient with well-preserved liver function (Child-Pugh A5) and only two HCC nodules <3 cm and a patient with ascites and jaundice (Child-Pugh B) with multifocal large HCC are classified as having intermediate-stage HCC.[71,253,305]

As a result, studies utilizing the BCLC classification for allocating TACE treatment demonstrate a wide variation in OS ranging from 20-25 months in early RCT's to 40-45 months in more recent prospective cohort studies from Asia and Europe, reflecting the inherent heterogeneity of the patient population classified as unresectable, intermediate stage HCC. [81,145,235,237]

Differences in earlier treatment practices for HCC may have been due to local referral patterns, lack of MDT case review, and TACE at care centres with limited options for other HCC treatments.[102–104] As such the benefit of TACE in patients with more advanced liver dysfunction and tumour burden requires refinement. [96,306] This has been outlined in a proposed sub-classification by Bolondi et al to further subdivide BCLC stage B into four categories, (B1-B4) based on Child Pugh score, tumour extent, and ECOG performance status (Table 1.4).[305]

Table 1.4 - Bolondi sub classification criteria. Adapted from Bolondi 2012.[305]

BCLC Sub stage	**B1**	**B2**	**B3**	**B4**
Child Pugh Score	5-6-7	5-6	7	8-9
Beyond Milan and within up-to-7 criteria	In	Out	Out	Any
Tumour related performance status	0	0	0	0-1
PVT	No	No	No	No
1st Treatment option	TACE	TACE Or TARE		Best supportive care
Alternative	Liver transplant TACE + Ablation	Sorafenib	Research Trial TACE Sorafenib	Liver Transplant

Abbreviations: PVT, portal vein thrombosis; TARE transarterial radioembolisation.

The Bolondi classification stratifies tumour extent using sum of the size of the largest tumour (in cm) and the number of tumours based on two liver transplant criteria; the Milan criteria includes a solitary HCC less than 5 cm, or 2 to 3 nodules all < 3 cm, whilst The up-to–7 criteria includes HCC up to 7 cm with a maximum 7 tumour nodules.[307]

According to this classification system, patients with BCLC B1 and B2 disease are recommended to have TACE, or for B2 transarterial radioembolisation (TARE), while patients with more severe liver dysfunction and/or tumour extent (B3, B4) considered for alternative treatment options and/or best supportive care.[305] Even though the Bolondi system is not specific to patients undergoing TACE, the sub-classification has better prognostic power and has been externally validated in a cohort of HCC patients in both South Korea and Taiwan.[308,309]

1.6.3 TACE beyond BCLC criteria

Whilst both the original BCLC staging and sub classification attempt to defined the ideal patient for TACE, they do not encompass all the aspects that can determine treatment outcomes, including variations in technique, chemotherapy, embolisation agents, frequency of therapy and intervals between treatment sessions, all of which make general statements about efficacy of TACE for HCC according to BCLC difficult. [310,311]

Improvements in TACE technique including microcatheters, new generation CT guided imaging and chemotherapeutics, have made TACE a safer option for patients who may previously have been considered unsuitable.[312] Indeed, studies of real-world practice have demonstrated TACE being increasingly utilised in patients outside of BCLC B criteria and a significant number of patients undergoing TACE are BCLC stage C. [152,313–315]

As many as one third of patients presenting with HCC are being treated outside of current international guidelines due to advanced age, comorbidities and location of the tumour.[316] In a large US cohort study TACE was utilised in less than 40% of patients who met AASLD criteria, the authors note this may reflect the advanced median age of 70 years in the population group.[315]

Suboptimal adherence to BCLC criteria also occurs in Australia, as seen in a single centre MDT audit from 2014 -18 which found HCC is not always managed according to BCLC recommendations, with 22% of BCLC C patients receiving locoregional therapy rather than the recommended systemic therapy.[317,318] Interestingly small cohort studies have demonstrated patients who received TACE outside of the BCLC based criteria had a significant survival advantage suggesting it maybe too restrictive. This theory is supported by prospective studies

in Asian and European populations demonstrating the benefit of TACE in carefully selected BCLC C patients with limited vascular invasion, not involving the main portal vein. [318–320]

However, the value of TACE in more advanced stage HCC has been downgraded in a recent systematic review and meta-analysis of therapeutic options for patients with poor prognostic factors including MVI and EHS. In an analysis of 3 RCT and 11 observational studies Finn et al found there was a lack of high-quality data supporting the use of other treatment modalities such as TACE in patients with more advanced HCC. The observational studies that evaluated locoregional therapies alone or in combination with other treatments were limited by very-low-quality of evidence. Furthermore, they recommended sorafenib as the only treatment that improved OS in cases of advanced HCC and CP A liver function.[321]

The treatment of patients outside of the BCLC guidelines with TACE requires closer analysis with large prospective validation studies to examine the BCLC algorithm and real-world outcomes to provide clinicians with better guidance on treatment allocation.[38,322]

1.7 ASSESSMENT OF RESPONSE

Assessment of tumour response to TACE is assessed on cross sectional imaging, with either CT or MRI, and is typically carried out at 4 weeks following treatment. Minimal technical requirements to ensure optimal image acquisition for analysis include, patient compliance with breath holding to reduce motion artefact, and coordination of intravenous contrast injection with image capture during arterial enhancement and portal venous phase.[121,156, 326] The target lesion is assessed using validated imaging guided response criteria, including pattern and extent of lipiodol deposition as it correlates with extent of necrosis and OS.[323–325,327,328] Response based imaging criteria have evolved significantly over the last three decades (Table 1.5), with standardised nomenclature for treatment response, as either complete, or partial, and no response, described as either stable or progressive disease.

Table 1.5. Assessment of target lesion response by RECIST, WHO, European Association for the Study of Liver (EASL), and modified RECIST (mRECIST) criteria. Adapted from Prajapati et al [329]

Response	RECIST	WHO	EASL	mRECIST
Complete response	Disappearance of all TL's[a]	Disappearance of all TLs	Disappearance of all VL's[b]	Disappearance of all VLs
Partial response (PR)	≥30% ↓ in the sum of the greatest one-dimensional diameters of TLs	≥50% ↓ in the sum of the product of bi-dimensional diameters of TLs	≥50% ↓ in the sum of the product of bi-dimensional diameters of VLs	≥30% ↓ in the sum of the greatest one-dimensional diameters of VLs
Progressive disease (PD)	≥20% ↑ in the sum of the diameters of TLs	≥25% ↑ in the sum of the diameters of TLs	≥25% ↑ in the sum of the diameter of VLs	≥20% ↑ in the sum of the diameters of VLs
Stable disease	Any case that do not qualify for either PR or PD	Any case that do not qualify for either PR or PD	Any case that do not qualify for either PR or PD	Any case that do not qualify for either PR or PD

[a]Target lesions (TLs). [b]Viable lesions (VLs)—enhancing lesion on arterial phase of T_1 post-contrast sequence on dynamic abdominal magnetic resonance imaging study. ↓, decrease; ↑, increase.

1.7.1 WHO Criteria

The initial Response Evaluation Criteria was developed and published by the World Health Organisation (WHO) in 1979 and relies on uni-dimensional measurement of the enhancing portions of target tumours after treatment to evaluate response.[330] However, as the WHO criteria was derived from previous protocols used in post therapeutic monitoring of non-HCC solid cancers after systemic cytotoxic therapy it was unable to capture the non-homogenous shrinkage and necrosis of HCC post TACE and the added complexity of lipiodol enhancement, leading to subsequent modifications.[83,331]

1.7.2 EASL

Developed in the year 2000, as a proposal to improve the WHO guidelines, the EASL guideline accounted for treatment induced tumour necrosis by measuring the product of the longest diameters of the viable portion of the tumour, as recognized by contrast-enhanced radiological imaging.[332,333] However, the EASL guidelines are limited to the evaluation of target lesions only, and unable to account for post treatment progression such as extrahepatic metastases and vascular invasion, both associated with poorer TACE tolerability and reduced survival outcomes.[62,334,335] Furthermore, the definition of partial response as $\geq$ 50% reduction in the diameter of the target lesion has been suboptimal at stratifying patients into separate prognostic groups.[329]

1.7.3 RECIST

The development of the Response Evaluation Criteria in Solid Tumours (RECIST) was a major advancement towards the standardization of response assessment following treatment in HCC as it defines the target lesions, nontarget lesions, and new lesions, and provides overall response classifications for each. In particular the target lesion is measured by unidimensional

measurements and the sum of the longest tumour diameters instead of the bi-dimensional approach of the WHO method including two measurements and the sum of the products.[156,334,335]

One of the main drawbacks with the RECIST criteria is that it measures tumour response in two dimensions only, measuring the anatomical shrinkage of the treated lesion as an overall objective response.[334] This can result in gross under evaluation of complete and partial response as HCC undergo non-homogenous tumour necrosis following TACE with asymmetrical tumour reduction and intra tumoural enhancement. Furthermore, in cases where systemic treatments are given concurrently there can also be an initial increase in size of the target lesion leading to misleading measure of response as progressive disease.[336]

1.7.4 mRECIST

To overcome the limitations of the RECIST criteria further modified RECIST (mRECIST) criteria were proposed in 2008, by measuring tumour enhancement as a surrogate marker for viable tumour and relying on the difference between vascularized and non-vascularized regions of the treated tumor.[332,333,336] This has improved interobserver agreement, with validation in large explant studies correlating mRECIST evaluation with histopathology.[337,338] Furthermore, the mRECIST response significantly correlates with survival, supporting its utilisation as the main response assessment tool in trials involving HCC treatments.[335,339,340]

mRECIST is currently the most widely utilised criteria for post TACE response assessment, however, there are some limitations. These include irregular distribution lipiodol, hindering accurate delineation of viable residual tumour at the TACE site, and inability to capture asymmetrical tumour necrosis and shrinkage following TACE on two-dimensional cross-

sectional imaging.[341,342] As a result, variations in assessment can occur between reporting Radiologists dependent on the image slice being analysed and compared. Lastly, and one of the main limitations, is inability to account for non-target lesion progression, whereby patients develop multifocal recurrence or extra hepatic spread beyond the target lesion, a factor associated with poor overall survival even with TACE therapy. [148,326,335]

Quantitative three-dimensional (3D) computed analysis along with advances in artificial intelligence (AI) and pattern recognition software, has shown promising results with the greatest interobserver agreement of up to 82%.[343] These tools may become increasingly utilised to enhance post TACE assessment of response with future prospective validation studies planned.[159,160,344,345]

1.8 REPEAT TACE

Most patients undergoing TACE require repeat treatment, as complete response does not usually occur after a single session. HCC recurrence or partial response is the common indication for repeat TACE after initial treatment and occurs due to re-vascularisation of residual viable tumour tissue, with recurrence rates at 1, 3 and 5 years of 22%, 64% and 79%, respectively.[346–348] Repeat TACE treatment is associated with improved tumour response and overall survival in appropriately selected patients.[349–351] However, timing of repeat treatment remains controversial as few studies have validated the optimal approach for repeat TACE with most guidelines based on expert consensus and retrospective studies.[181,352]

TACE administered at fixed time intervals is based on recommendations from initial studies on patients with early stage HCC, whereby patients undergo a minimum of two treatments over two months prior to assessing treatment response.[353,354] This approach has shown significant benefit in OS in early stage BCLC stage A HCC, however up to 10% of patients already had complete response after the first TACE and therefore could have avoided the second session.[355,356]

In contrast, the on-demand TACE regimen recommends assessment after each TACE, including repeat imaging, hepatic function and clinical review at 4 weeks. This approach is based on post TACE hepatic dysfunction being the most common complication with variable recovery times. Deterioration in liver reserve can manifest as changes in serum biochemistry, decompensation and diminished performance status through fatigue and pain.[357–359] Functional decline is more common in patients undergoing multiple treatments, especially following three TACE cycles, and is associated with poorer overall survival outcomes.[360–363]

Some authors postulate poorer survival in patients undergoing greater than three TACE sessions is reflective of HCC with more aggressive biology, resulting in earlier and more severe progressive disease. Furthermore, patients undergoing repeat TACE are often older with higher tumour burden and incomplete response following initial therapy.[346,364,365]

Therefore, repeat TACE requires careful balance between the risks of complications and benefits in this group of patients. As a result, the fixed interval regimen has been superseded by the on-demand cTACE approach to repeat treatment based on real world studies demonstrating the benefits of personalised repeat TACE treatment intervals in improving tolerability and survival outcomes.[200,366,367]

1.9 TACE DISCONTINUATION

Most international HCC treatment guidelines lack clear definitions of TACE failure or TACE refractory status, with a significant number of patients undergoing repeat treatment despite being ineligible for TACE according to their local guidelines.[352,368]

Results of a large global studies including patients from USA and Japan demonstrated unnecessary repeat TACE resulted in increased risk of ADR, whereas median OS was better in patients who had timely stage migration and received systemic therapies, such as sorafenib at the time of TACE ineligibility.[369,370]

The results of two early RCT's with repeat TACE have been used to formulate definitions of TACE failure.[84,145,368] They include two incomplete responses to two consecutive TACE, defined by tumour necrosis (<50% deposition of lipiodol) and or disease progression with appearance of new lesions within 4 weeks of treatment, vascular invasion, extra hepatic spread (EHS) or rising AFP.

These findings have been supported by multiple smaller retrospective studies where HCC associated with EHS had significantly poorer prognosis, suggestive of aggressive tumour biology, of which tumour progression is a surrogate marker.[369,370] As a result, the time to TACE progression (TTTP) has increasingly demonstrated correlation with OS in particular patients with TTTP < 5 months may not benefit from repeat TACE procedures reflected in the rapid HCC growth rate and doubling time.[371,372]

The reason for TACE discontinuation also carries prognostic value as studied by Labeur et al. Whilst most patients discontinue TACE due to radiological progression, those that discontinued due to decompensation did not recover to the point of being able to receive second-line treatment.[373]

This study suggests that hepatic decompensation and performance status are a significant marker of worse OS then tumour progression as worsening hepatic reserve has a greater impact on mortality then tumour response to TACE alone.[361,363,373] Based on these studies, some guidelines such as the AASLD support additional criteria in defining TACE failure including performance status, CPS score and BCLC stage post treatment, while Japanese guidelines considers prior response to TACE. [47,362,374]

Further global standardization is needed on the indication and definition of TACE refractoriness or failure to prevent ADR from unnecessary repeat treatment and allow for stage migration or enrolment into clinical trials.[375]

1.10 PREDICTORS OF SURVIVAL IN PATIENTS TREATED WITH TACE

International studies conducted across various population groups have identified key factors that are associated with prognosis in patients undergoing TACE for HCC.[1,27,238] Whilst most of these variables are incorporated in current staging systems and international guidelines, recent cohort studies have also demonstrated additional factors, and are discussed in the following section.

1.10.1 Tumour Characteristics

Tumour biology in HCC varies within patient groups and over the timeline of each patients' treatment pathway.[376] Whilst biopsy for histopathological confirmation is not routinely performed in the diagnosis and staging of HCC, tumour parametres can provide a surrogate measure of poor tumour biology and are associated with overall survival.[1,8,377] These parametres include maximum tumour diameter, number of tumour nodules, portal vein thrombosis and serum alpha-fetoprotein levels even in patients with more advanced HCC with extrahepatic spread.[34,378,379]

Tumour beyond 3 cm have increased risk of micro metastasis and satellite nodules, while HCC > 5cm have reduced tumour response to TACE due to limited permeability of the tumour vascular bed by cytotoxic agents.[1,2,301] This also applies to patients with large tumour burden such as bilobar disease as it is associated with worse prognosis in comparison to unilobar disease.[235,365,380] As a result, larger HCC often requiring repeat cycles of TACE and also have higher rates of post embolisation complications including decompensation, with many guidelines defining 10 cm as the upper limit for TACE.[186,381] Small case series however, have recently suggested stepwise cTACE in patients with single HCC > 10cm is safe and effective with bile duction complications in 8% of patients.[228,382,383]

In addition to tumour size, the number of nodules is a pre-treatment prognostic factor prior to initial TACE, and remains significant following subsequent treatment TACE cycles, associated with both higher recurrence and poorer survival outcomes.[381,384,385] The location of the tumour also plays a prognostic role with studies demonstrating poorer complete response rates in HCC located at hepatic watershed zones, due to multiple branches of the hepatic artery supplying the same tumour.[386,387] Similarly, tumours with ectopic vessels derived from non-hepatic arteries such as the phrenic and gastric artery branches are more technically difficult to target angiographically during TACE, often requiring additional sessions, with increased risk of incomplete response, and adverse events with ischaemic necrosis of non-target tissues.[388–390]

1.10.1.1 Alpha-Fetoprotein

Various HCC biomarkers including serum alpha-fetoprotein (AFP), *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3), and des-gamma-carboxy prothrombin (DCP) have been shown to predict micro metastases, vascular invasion and overall survival.[57,391] In particular high serum AFP > 200ng/ml has significant prognostic value and has been utilised as part of TACE scoring systems to aid clinicians with prognostication both pre and post treatment.[57,392] However, AFP has not been adopted by many HCC staging systems due to the variation in AFP secondary to inflammation, heterogeneity of AFP cut off levels used in various studies and high false negative rates, in up to 50% of HCC that do not secrete AFP.[393–396] Recent molecular genomics studies have demonstrated a relationship between serum levels of tumour micro RNA with TACE response, and may provide clinicians with a more refined tumour biomarker than AFP to predict patients that are at increased risk of poor outcomes.[396–398]

1.10.1.2 Portal Vein Thrombosis

Historically patients with tumours obstructing the main portal vein, classified as BCLC stage C, are excluded from TACE therapy due to the increased risk of hepatic infarction and decompensation, and are assigned to systemic treatments, such as sorafenib.[60,100,399] However, BCLC stage C patients are a heterogeneous group, with varying degrees of extrahepatic spread (EHS), macrovascular invasion (MVI), Child-Pugh scores (A5-B9), and performance status (PS 0-2).[400–402]

The recommendation against cTACE in patients with PVT are based on early studies that included patients with main portal vein thrombus and utilized techniques that are now obsolete. Recent cohort studies have expanded the utility of TACE and DEB TACE in a subgroup of patients with low burden of PVT.[76,403–405] Two recent systematic review and meta-analyses of TACE in the treatment of HCC with PVT found TACE is a safe treatment for a highly selected population of HCC patients with PVT limited to portal vein branches.[406,407] In particular, peripheral rather than central PVT is associated with better survival outcomes, compared to main portal vein thrombosis ($p<0.001$) and therefore contraindicated for TACE therapy.[298,403,406,407]

1.10.2 Aetiology of Liver disease

Both viral hepatitis B and C are associated with high risk of HCC development globally, and also influence treatment outcomes.[15,16,408] Complete suppression of HBV viral load with treatment has been shown to improve median overall survival, median progression-free survival and lower risk of post TACE decompensation in patients with HBV related HCC.[409–411]

Similarly, in patients with HCV, achieving sustained complete response either with pegylated interferon-based regimen or direct acting antivirals is associated with improved survival and reduced tumour recurrence in intermediate stage HCC.[411–413]

More recently NAFLD has emerged as an increasing cause of advanced liver disease and HCC. NAFLD associated metabolic syndrome, in particular diabetes mellitus has been associated as a significant risk factor for poor prognosis following TACE with earlier median time to progression and poorer overall survival likely due to a combination of associated risk factors such as cardiovascular disease, obesity, immune dysregulation and renal dysfunction.[282,414–416]

1.10.3 Severity of Chronic Liver disease

The severity of chronic liver disease can be assessed by the presence of decompensation that becomes increasingly evident as it progresses from early Child Pugh A to Child Pugh C disease. Many of these factors are inter-related such as portal hypertension and ascites and are associated with poor TACE outcomes.[253,305]

1.10.3.1 Portal Hypertension

Significant portal hypertension is a marker of diminished hepatic reserve due to advanced cirrhosis, and has been associated with poorer TACE treatment outcomes, including overall survival and progression free survival.[417,418] In a study of 147 patients who underwent cTACE a first-line treatment for a single HCC, Choi et al found clinically relevant portal hypertension was significantly associated with local tumour progression. This finding may not be applicable to DEB TACE, as unlike lipiodol emulsion, drug-eluting microspheres cannot embolize the peritumoral portal vein. Therefore, the influence of portal hypertension on outcomes may differ substantially.[231,418]

Significant portal hypertension can present as upper GIT variceal bleeding and carries significant increased risk of hepatic decompensation and increased mortality. Various factors have been associated with post TACE UGI bleeding including older age, alcoholism, smoking history, ascites, and MELD score higher than 10.[285,419] In a study of 271 patients with intermediate stage HCC undergoing TACE, previous history of ascites prior to TACE was an independent predictor for GI bleeding following treatment (HR: 2.48, P=0.002).[420]

Therefore, Gastroscopy surveillance with appropriate banding ligation of varices is recommended prior to TACE, especially in those with evidence of clinically significant portal hypertension such as splenomegaly and ascites. Reduction of portal pressures with non-specific Beta Blocking medications such as propranolol, have demonstrated adjuvant effect with TACE (p =0.0007), mediated by their direct effect in reducing splanchnic blood pressure and therefore portal hypertension.[411]

1.10.3.2 Ascites

TACE for HCC in patients with ascites and advanced tumour stage has shown limited advantage over best supportive care, and as such these patients are categorised within the BCLCL stage C or D category.[82,298,419] This association reflects the presence of significant ascites as a marker of deteriorating hepatic reserve and portal hypertension. Patients with ascites are at an increased risk of renal failure and significantly increased overall risk of 30-day readmission following TACE.[256]

The degree of ascites however can vary from mild, moderate to severe as per the Child Pugh Classification and can be modulated by factors such as paracentesis, diuretic therapy and transjugular intrahepatic portosystemic shunt (TIPS) placement. Ascites that is refractory to

medical treatment is associated with the greatest risk of post TACE deterioration and is incompletely measured by the Child Pugh Score as it only measures the severity of ascites and not the status of treatment.[405] Furthermore, the presence of hepatic encephalopathy with ascites has been associated with the highest risk of post TACE decompensation and poorer survival outcomes.[256,405]

1.10.3.3 Liver Biochemistry

Deterioration in liver function is one of the most frequently seen side effects following TACE treatment, occurring in up to 53% of patients undergoing treatment, particularly in patients with advanced stage BCLC C disease.[280,313,401] The degree of deterioration prior and post treatment has a direct impact on OS, and can prevent repeat treatment of an HCC that would otherwise be amenable to TACE.[280] As such poor liver function is also a prognostic marker of survival in patients undergoing repeat TACE therapy.[421]

Each components of liver function tested on serum, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, and bilirubin have demonstrated independent prognostic value in various cohort studies.[169,280,422,423] Various combinations of serum liver function tests with other serum markers have shown promising correlation with OS and PFS, including ALT-to-haemoglobin, albumin-to-ALP ratio in patients with inoperable HCC receiving transarterial therapy.[169,424] Most of these studies have been limited by their retrospective analysis of a small sample size in a population groups with differing baseline incidence of chronic liver disease severity and aetiologies. Further larger prospective studies are required to validate the clinical utility of each marker in international cohorts to determine the optimum cut off values.

1.10.3.4 Nutrition

Nutritional status is a key prognostic marker in patients with cancer and particularly in those with HCC.[68,238] Serum albumin is often used as a surrogate marker of nutritional status as well liver synthetic function, indeed trials into supplemental branched-chain amino acid (BCAA) to improve nutritional status in patients undergoing TACE have been encouraging, with prospective studies planned to validate these findings.[425]

Nutritional status has also been measured with imaging guided analysis of pre-treatment CT scans of HCC with excellent validation in association with body composition including visceral fat density and sarcopenia. Patients with higher visceral fat density were significantly more likely to experience hepatic decompensation after TACE ($p < 0.001$) and poorer 1-year survival rates.[426]

Malnutrition as measured by sarcopenia in patients with intermediate stage undergoing TACE also carries prognostic significance. By measuring dynamic change of skeletal muscle index (SMI) on CT during the initial two consecutive sessions of TACE, Nimanong et al found that >10% decline in SMI after second TACE was independently associated with mortality (HR, 2.34, $p = 0.002$). Patients with progressive sarcopenia during TACE had significantly poorer radiologic response and higher risk of decompensation after TACE.[427–429] In contrast studies utilising in-hospital exercise programs in patients undergoing TACE with base line sarcopenia have demonstrated improvements in skeletal muscle index (HR 2.13; 95% CI 1.22-3.85; $P = 0.0085$) and maybe a useful intervention in preventing sarcopenia in HCC patients who undergo TACE.[430]

1.10.3.5 Renal Function

Hepatorenal syndrome is also a marker of hepatic decompensation and can occur post TACE therapy due to various factors including hepatic injury, direct nephrotoxicity of the contrast agent and cytotoxic drugs such as platinum-based chemotherapy.[283] Patients undergoing TACE for HCC are at particular risk of renal injury and renal insufficiency as they often have pre-existing impaired renal function due to co-morbidities including, diabetes, HCV and hypertension that can predispose patients to acute kidney injury after TACE.[431,432] The incidence of renal dysfunction post TACE has been reported to be as high as 21.8% in a prospective study, and was significantly higher in patients with low pre-treatment haemoglobin, higher serum bilirubin, AST, age > 55 years and previous history of renal injury following TACE.[281,433]

Poor kidney function (estimated glomerular filtration rate < 60mL/min)) is an independent risk factor for reduced long term survival following TACE and has also been associated with increased risk of post TACE upper GI bleeding.[283,431] Whilst most TACE related renal injury is transient and reversible with supportive management, patients with prolonged reduction in renal function have poorer survival outcomes.[281]

1.10.4 INFLAMMATORY MARKERS

Immune cells play a key role in regulating and responding to inflammation in the liver and the tumour microenvironment. The prognostic value of various ratios of neutrophils, platelets, monocytes and lymphocytes in patients undergoing TACE been explored in multiple studies.[281,434] One of the most widely studied is the Neutrophil/lymphocyte ratio (NLR), a serum biomarker associated with survival for multiple malignancies including HCC treated by

chemoembolisation. However, the optimal NLR to predict outcome of HCC treatment remains to be elucidated, with variable cut off values in recent small retrospective studies.[435–437]

Platelets are also surrogate markers of inflammation, as well as significant portal hypertension in liver cirrhosis. More recently their role in contributing to HCC growth and metastases has been postulated likely a combination of platelet derived growth factors, platelet tumour interactions facilitating tumour survival by promoting tumour cell clusters and epithelial mesenchymal transition of tumour cells allowing hematogenous metastasis.

This hypothesis has recently been supported by a large population-based study of 133 371 health care professionals, that found long-term use of antiplatelet agent aspirin was associated with a dose-dependent reduction in HCC risk.[438–440] The possible role of antiplatelet therapy in reducing tumour metastasis and growth has been suggested, with regular use of Aspirin associated with lower bilirubin after TACE and higher median survival (57 vs 23 months, $p = 0.008$). Interestingly Aspirin was not associated with survival differences after locoregional therapy for liver metastases from neuroendocrine or colorectal cancer, suggesting an HCC-specific effect which may reflect modulation of chronic inflammation associated with cirrhosis.[411,441]

1.10.5 DEMOGRAPHIC VARIABLES

1.10.5.1 Gender

Men have a higher incidence of HCC globally with higher risk of HCC development compared to women, this may reflect higher incidence of risk factors associated with chronic liver disease and progression. Women in general present at an older age at time of HCC diagnosis, with no significant difference in disease presentation or survival with regards to TACE therapy. Recent studies have demonstrated a link between androgen and estrogen sex hormones in modulating pathways of HCC carcinogenesis and future studies may provide novel prognostic biomarkers in patients with intermediate stage HCC undergoing TACE.[442–446]

1.10.5.2 Ethnicity

The role of ethnicity is highlighted by the variations in international HCC staging and treatment guidelines as they are derived from populations that have differing baseline epidemiology of liver disease. In particular more aggressive therapies are supported in more advanced stage tumour in cohorts with high incidence of HBV likely due to the relatively preserved hepatic reserve at the time of HCC diagnosis.[15,38] In contrast, indigenous groups remain over represented in global reports of poor HCC treatment outcomes and this may reflect significant social disparities including access to screening and specialised treatment centers.[15,25]

1.10.5.3 Socioeconomic status

Lower socioeconomic status is often associated with poorer adherence to preventative health strategies and attendance to screening and surveillance programs due to various factors associated with access to local specialised health care and limited social supports. In particular

patients with HCC in uninsured and underinsured districts in the USA have poorer median OS compared to studies in larger metropolitan areas with poorer liver function at diagnosis.[21,23,447]

1.10.5.4 Age at HCC diagnosis

In countries such as Australia an increasingly aging population poses unique challenges to the management of HCC. Older patients often present with intermediate stage disease and significant comorbidities that can limit their suitability for more aggressive therapies therapy. As such, elderly patients are more likely to be allocated to locoregional therapies such as TACE.[448,449] While advanced age is not a contra indication for TACE, it has been associated with an increased risk of decompensation and ADR post treatment related to the higher prevalence of pre-treatment conditions that can increase side effects, such as cardiac and renal insufficiency and lower hepatic reserve.[450,451]

Multidisciplinary team guided management is therefore important in this cohort for tailoring patient selection, to overcome the limited applicability of current guidelines in the advanced age groups.[451–454] Recent cohort studies have been promising in patients aged above 65, 75 and 80 in Europe, Japan and China. Based on real world data they demonstrated no significant difference in OS, progression free survival and overall procedure related ADR compared to younger patients undergoing locoregional therapy for similar tumour stage and treatment modality.[449,454–456]

1.11 EMERGING PROGNOSTIC MODELS

The inherent heterogeneity of patients with unresectable HCC and variations in TACE technique have demonstrated the many limitations of the current utilised staging and treatment algorithms. Utilising data sets derived from large retrospective cohort studies multiple scoring systems have been developed based on variables associated with overall survival in patients with HCC undergoing TACE. These scores have varying prognostic capabilities, ranging from improving patient selection to restaging post treatment prior to repeat therapy. Currently there are over 15 different scoring systems proposed in the literature, and the few that have reached clinical utility are discussed further.

1.11.1 Hepatic Arterial Embolisation Prognostic score

The Hepatic Arterial Embolisation Prognostic (HAP) score was developed in an attempt to improve patient selection for TACE therapy.[69] The HAP score was derived from multivariate Cox regression analysis of baseline factors associated with survival in a training set of 114 patients undergoing TACE or transarterial embolisation (TAE) in UK, with validation in an external cohort of 167 patients. It utilises baseline serum albumin, bilirubin, and alfa-fetoprotein levels, and dominant tumour size, to allocate a score of 0, 1, 2, and > 2 points and stratify patients into risk groups A, B, C and D respectively.

Patients in the low risk (HAP A and B) groups had a median survival of 28 and 19 months respectively, while those in the high-risk groups (HAP C and D) had poor survival of 9 and 4 months respectively. In its derivation cohort The HAP score performed better than Child-Pugh, MELD, CLIP and BCLC stage. However, the original study population included a significant proportion (>50%) of patients undergoing bland embolisation (TAE) alone or in combination with cTACE, a practice that is no longer standard of care.[69]

The HAP score has since been validated in multiple small centre studies and more recently in a larger international cohort.[457–459] These studies demonstrated the HAP score retained its discriminative value in identifying four distinct prognostic subgroups with differing survival following TACE therapy. However, the HAP score has some pitfalls, as it does not include patient baseline performance status or other tumour parameters such as tumour number, and portal vein thrombosis.[460]

This has led to the development of a modified HAP score by Pinato's group in a large multi-center validation study of patients with HCC treated with TACE in Europe and Asia.[461] The modified version of the HAP score (mHAP) utilises hypoalbuminaemia, alfa-fetoprotein (AFP) >400 ng/ml, and cut off tumour size >7 cm at diagnosis (P<.01). By excluding serum bilirubin, the mHAP predicted OS with increased accuracy then the original HAP score in the training and validation cohorts. Further modifications of the HAP score by adding other variables such as tumour number have further enhanced the HAP scores prognostic utility, however the overall discriminatory power has been suboptimal (C-Index < 0.70).[462]

Sequential assessment using the original and modified HAP score have demonstrated good discriminative ability for patient selection prior to repeat TACE.[463,464] More recently a large placebo-controlled, double-blinded, phase 3 trial has demonstrated that the HAP score may also be useful in identifying patients who are becoming TACE refractory, and would benefit from stage migration to systemic therapy or enrolment into trials.[465] The median overall survival according to HAP score was around 31 months for patients with a HAP score of A, 21 months for B, 15 months for C, and 6 months for D. These results support previous validation studies with regards to allocation of alternative therapies to TACE for patients with HAP score D, further prospective trials are needed in those patients with HAP score C.[464,465]

1.11.2 Albumin-Bilirubin Grade

Developed by Johnson et al, the Albumin-Bilirubin (ALBI) grade is based on a logarithmic equation of serum Albumin and Bilirubin resulting in a simple and readily available marker of liver reserve and risk stratification of patients undergoing treatment for HCC, including TACE. The score is derived as a linear predictor = (log10 bilirubin mmol/L x 0.66) + (albumin g/L x -0.085).[68] The continuous linear predictor is then further categorised into three different grades for prognostic stratification purposes: grade 1 (less than- 2.60), grade 2 (between-2.60 and-1.39) and grade 3 (above-1.39)

Various early studies have identified both Albumin and Bilirubin as key prognostic factors associated with OS in patients undergoing TACE and DEB TACE, both as individual factors and as components of commonly used scoring systems of CPS and MELD.[298,399,466,467] Subsequent validation studies reproduced, across Asian, European and American cohorts, demonstrated superiority of the ALBI grade in survival prognostication when compared to the current Child Pugh and BCLC staging systems in patients treated with cTACE and DEB TACE.[457,468,469] In a recent study, Yasui et al found ALBI grade was a useful predictor of worsening Child Pugh grade as early as 3 months post treatment, and was a superior prognostic marker compared to Child Pugh grade in patients undergoing repeated cycles of TACE treatment.[470,471]

Earlier detection of a deterioration in hepatic function with repeat TACE results in timely stage migration, enabling clinicians to switch to systemic therapies, such as sorafenib or enrolment into clinical trials. This was demonstrated by Hiraoka et al who observed an improved prognosis in patients that were ALBI grade 1 at the time they were commenced on systemic

therapy with sorafenib after being deemed refractory to further TACE, in comparison to patients that had higher ALBI grades. [471]

The ALBI grade is an objective, discriminatory and evidence-based method of assessing liver dysfunction and correlates well with prognosis in patients with HCC undergoing TACE therapy. However, the ALBI grade does not incorporate HCC staging as it only measures liver function, and does not account for tumour-related parametres such as size or treatment response. To this extent it is not directly comparable to the HAP score which was derived to assess survival after TACE therapies by combining both liver function and tumour-related factors such as serum AFP and size of largest tumour.[69,457,472]

Furthermore, there are potential weakness within the ALBI grading system as it can be influenced by albumin replacement therapy or obstructive jaundice resulting in inaccurate estimation of liver reserve. Recently Royaie et al developed an modified version of the ALBI grade, by incorporating platelet count as a surrogate marker for portal hypertension, the Platelet, Albumin, Bilirubin Index, or PALBI grade.[473]

The PALBI grade has demonstrated superior discriminatory ability to both the ALBI, and CPS in multiple studies, particularly in patients with early compensated liver disease undergoing curative therapies for HCC such as surgical resection and ablation.[472,474] Interestingly smaller studies evaluating prognosis in patients with more advanced liver disease undergoing treatments with TACE have demonstrated equivalent performance of the PALBI compared to the ALBI grade, suggestive of a reduced ability to stratify patients with intermediate stage disease.[475,476]

1.11.3 ABCR Score

Many scores do not retain prognostic value when applied to variables associated with repeat TACE therapy. The ABCR (Alpha-fetoprotein, BCLC stage, Child Pugh score, Radiological response) score scoring system was developed to determine patient suitability for repeat TACE using a multivariate analysis of a population of 133 French patients with alcohol or viral-induced HCC. The score was then validated in 2 other cohorts of 78 and 100 patients also from academic centres in France.[477] The score is based on a combination of two baseline and two treatment-related factors. The baseline BCLC stage and serum AFP levels are known to be associated with overall survival, whilst the remaining two parametres measure the efficacy of TACE as measured by tumour response and tolerability with the Child Pugh Score.

ABCR score components:

Alpha-fetoprotein. ≥200 ng/mL) at baseline 1 point

BCLC (A/ B/ C) at baseline – 0/2/3 points

Child-Pugh score increase ≥2 points – 2 points

Radiological response (EASL)- -3 points

The ABCR score calculated immediately before the second TACE session was able to identify three prognostic groups with progressively worsening survival based on the point cut off values of, -3 to 0, 1-3, and >3. A higher ABCR score was predictive of a poorer prognosis, with the authors recommending cessation of further TACE therapy in patients with a score ≥4. In addition, they demonstrated in a separate study that the ABCR score was better correlated with survival than another scoring system designed for patients undergoing repeat TACE the ART (Assessment for Retreatment with TACE) score that is reviewed in the following section.[71,477]

However, the training and validation cohort of the ABCR score were quite homogenous and there are ambiguities in the definitions used for the poor prognosis group, resulting in variable applicability of the score beyond its derivation cohort. A recent retrospective comparative study by Kloeckner et al of 176 patients undergoing TACE, of which 81% where BCLC B, demonstrated the ABCR had insufficient predictive value to support its utility to aid clinical decisions.[478]

These concerns were echoed by Facciorusso et al and further prospective studies are required for external validation of this score's clinical utility[479]. Furthermore, the criteria used in the original score for assessment of Radiological response was EASL rather than the current and widely adopted mRECIST. There are significant differences between the two response criteria, as the EASL definition of partial response is based on a decrease of more than 50% of the viable area of the tumour compared to ≥ 30% for mRECIST.[96,477] As a result, the original ABCR score has had limited utility in clinical practices that utilise TACE response evaluation criteria beyond the EASL definition.

1.11.4 ART score

The ART score (Assessment for Retreatment with TACE) was developed to predict overall survival in patients undergoing repeat TACE.[238,480] The score integrates radiologic tumour response (present *vs* absent), liver function impairment (presence *vs* absence of increased Child-Pugh score), and serum AST level increase by ≥25% from pre-TACE level after the first TACE. The ART score stratified the original derivation cohort into two distinct patient groups with significantly different prognosis. Those with a score of ≥ 2.5 after the first TACE had a poorer prognosis and therefore should be considered for alternative treatment options. In contrast a score of 0-1.5 points was associated with better prognosis with further TACE.

A follow-up study by the same group has confirmed the ability of the ART score to predict patient outcomes in those having a third and fourth TACE. This has led to the concept of an ART score-guided retreatment strategy being proposed to guide therapeutic decisions in patients undergoing serial TACE therapy, including definitions of TACE refractory status and TACE discontinuation.[95,368,480] However, the ART strategy has yet to be tested in a prospective manner. Moreover, subsequent publications from Europe have led to debate over whether the ART score is the optimal scoring system for assessing the prognosis in patients with un-resectable HCC undergoing serial TACE or DEB TACE therapy.[478,481,482]

Studies in the Asian population have shown mixed results in validating the ART score, with good prognostic ability for initial and repeat TACE on application to populations with predominantly HBV associated HCC.[369,483,484] In contrast, a large Japanese study of 988 patients undergoing TACE found the ART score had insufficient predictive value to determine OS in patients undergoing >2 TACE sessions within 90 days. The authors cited significant heterogeneity in patient selection, TACE technique and subsequent post TACE treatment as possible factors affecting the overall survival analysis.[485]

The shortcomings of the original ART score has led to its modification with various combinations with other variables, such as the Selection for Transarterial chemoembolisation Treatment (STATE) score, and the Japanese-ART (J-ART) score, that have improved the performance of the ART score in predicting outcomes following repeat TACE treatments.[486,487] Global application of the original ART and modified versions have had limited global application pending validation beyond their original derivation cohorts in large prospective studies, particularly in many Australian centres were serum AST is not a routine component of serum liver function test panel, unless specified.

1.12 CONCLUSION

Despite the increased global adoption of TACE in international guidelines as the standard of care for patients with intermediate stage HCC, there remains significant variation in overall survival outcomes. This is reflective of the heterogeneity of the patient population with unresectable HCC, local treatment guidelines and TACE technique. [249,250]

In particular, the majority of international staging systems, including the BCLC stage, lack criteria for repeat TACE and definition of TACE refractory status. The decision for further TACE is currently assessed on a case by case basis at institutional MDT's incorporating Radiological and clinical response post TACE to determine the ideal candidate for repeat treatment versus stage migration towards systemic therapy.

Furthermore, the impact each of these scoring systems and associated prognostic factors varies in a time dependent manner with regards to pre and post treatment parametres. Whilst tumour progression has a significant influence on short term survival, severity of liver cirrhosis and markers of liver function have shown the greatest long-term prognostic value after diagnosis.[488]

As such, the variations in these prognostic factors require further analysis, both pre and post TACE to validate current models and develop scoring systems that are both consistent and accurate prognostic markers at all stages of the TACE treatment timeline.

THESIS HYPOTHESIS AND AIMS

Hypothesis

The central hypothesis of this thesis is to undertake a comprehensive evaluation of the prognostic factors associated with survival in patients with unresectable HCC undergoing treatment with TACE.

Through collaboration with six large Australian tertiary centres and international co-authors the overall aim is to undertake a real-world Australian cohort study that will provide insight into current clinical practice with regards to TACE utilization and facilitate performance appraisal of novel emerging prognostic models in comparison to currently utilized staging tools.

Specific aims:

AIM 1. To undertake a systematic review and meta-analysis evaluating the clinical utility of the Albumin Bilirubin (ALBI) grade in patients with HCC undergoing TACE.

AIM 2. To determine the baseline (Pre-TACE 1) and treatment (Post-TACE 1) associated factors affecting overall survival in patients undergoing TACE

AIM 3. To compare and contrast the predictive value of current and emerging novel prognostic models including the HAP score, ALBI and PALBI grades in predicting overall survival in an Australian cohort of patients treated with TACE

AIM 4. To determine the baseline and/or post-initial TACE treatment-related factors that predict overall survival in patients having a second TACE.

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CHAPTER TWO

METHODOLOGY

2.1 INTRODUCTION

This chapter provides a general overview of the methods relating to studies presented in Chapters 4, 5 and 6. Further more detailed methodology pertaining to each individual study are provided within the relevant chapters including any deviations from protocol.

2.2 STUDY POPULATION

Patients will be eligible for the study if they meet the following criteria:

1. Patients > 18 years old at the time of first TACE

2. Have documented HCC based on biopsy or AASLD[1] criteria that is deemed unresectable and/or unsuitable for liver transplantation

3. Have received at least one conventional TACE, doxorubicin eluting beads TACE (Deb-TACE) or transarterial embolisation (TAE) therapy. For Aim 4, only patients who received a second TACE or TAE within 90 days of the first TACE will be included in the study analysis

4. BCLC stage A HCC not suitable for resection, local ablation or liver transplantation, or BCLC stage B HCC, or BCLC stage C with segmental branch portal vein invasion

5. Child Pugh A or B liver disease

6. Baseline ECOG performance status < 2

Exclusion criteria for the study:

1. Prior liver transplantation

2. Use of TACE as bridge to transplantation or prior to planned liver resection

3. Use of other treatment modalities in association with TACE

4. Child Pugh C liver disease

5. Main branch portal vein invasion

6. Poor performance status prior to TACE (ECOG ≥ 2)

2.3. COLLECTION OF DATA

Ethics approval with concurrent memorandum of understanding across six participating sites was obtained, including Monash Health, Alfred Health, Royal Melbourne Hospital, St. Vincent's Hospital, Eastern Health and Austin Health. The initial data search was carried out through the prospective multidisciplinary meeting databases at each respective site to identify patients who underwent TACE for HCC between the years 2009 to 2014 inclusive. Once potentially eligible patients were identified through the MDT database and radiology database, clinical and biochemical parametres pre and post TACE were obtained from both electronic and paper-based records. The data points recorded included:

Baseline variables (Pre-TACE 1)

1. *Clinical characterization*

- Socio-demographic: age, gender, ethnicity, country of birth
- Biophysical: Weight, height, BMI
- Performance status at Dx: ECOG score
- Date of HCC diagnosis
- Method of HCC diagnosis: Biopsy, Imaging (CT/MRI), resection

2. *Liver disease status*

- Laboratory: Hb, platelets, WBC, Neutrophils, albumin, bilirubin, ALT, AST, GGT, INR, Na+, creatinine
- Liver disease aetiology: HCV, HBV, ETOH, NAFLD, PBC, Other
- Liver disease: Child-Pugh score and class, MELD, MELD-Na+, AST/ALT
- Cirrhosis status: Yes/No
- Portal hypertension: Yes/No, varices
- Previous or current liver decompensation: Yes/No; ascites Yes/No

3. *Tumour characterization at time of first TACE*

- No. of tumour nodules
- Size of largest tumour nodule (cm)
- Extrahepatic disease: Yes/No, site
- Macrovascular invasion: Yes/no, segmental (Right, Left, or main PV) Yes/No
- AFP level and Units at Dx
- BCLC stage
- Treatment of HCC prior to TACE: resection, local ablation, other

Treatment-related variables (Post-TACE 1)

1. *TACE details*

    - Dates of the first TACE and second TACE procedures
    - Type of treatment: TACE / TAE*;* cTACE/DEB-TACE; chemotherapeutic used

2. *Radiological response post first TACE* (See definitions below):

    - Complete response (CR) or partial response (PR)
    - Stable disease (SD) or progressive disease (PD)

3. *Clinical and laboratory characteristics post TACE 1 and prior to TACE 2*:

    - Maximum MELD score and change in MELD score observed
    - Maximum MELD-Na+ score and change in MELD-Na+ observed
    - Maximum Child-Pugh score and change in Child-Pugh score observed
    - Maximum serum AST level and %change in AST level observed
    - Maximum serum ALT level and %change in ALT level observed
    - Maximum serum bilirubin level and %change in bilirubin level observed
    - Maximum serum albumin level and %change in albumin level observed
    - Maximum serum creatinine level %change in creatinine level observed
    - Maximum INR and %change in INR observed
    - Worst ECOG performance status observed
    - Maximum serum AFP level and %change in AFP level observed

4. *Safety*

    - Serious adverse events or death within 4-weeks of TACE 1

2.4 DEFINITIONS

The primary endpoint for this study was overall survival following initial TACE. The date of death was obtained from the HCC database at each hospital or if missing from the Victoria Death and/or Cancer Registry. If the date of death was not available the last date of last follow up was used.

Radiological response was defined according to standard EASL criteria using modified RECIST (mRECIST) criteria[2] as assessed by triphasic CT scan and/or MRI scan and include the following:

a) Complete response (CR): Disappearance of any intratumoural arterial enhancement in all target lesions

b) Partial response (PR): At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target

c) Stable disease (SD): Any cases that do not qualify for either PR or progressive disease (PD)

d) Progressive disease (PD): An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

2.5 STATISTICAL ANALYSIS

Overall survival (OS) was measured from the date of first TACE/TAE to the date of death or last follow up. Survival curves were calculated using the Kaplan-Meier method. Median survival times (OS) and their 95% confidence intervals (CIs) were reported. The log-rank test was used to assess the effects of baseline clinical, liver disease, and tumour variables (pre-TACE 1) as well as tumour response variables (between TACE-1 and TACE-2) on OS.

The effect of continuous variables (e.g., AST, ALT, GGT, bilirubin, creatinine etc.) on OS was assessed for each variable by considering them as both continuous variables, and as binary variables with cut-offs in the Cox models for ease of interpretation. Variables with P $\leq$0.01 in the univariate analysis were entered as candidate variables into a stepwise Cox regression model (conditional backward selection). All reported P-values are two-sided with a significance level of 0.05 applied throughout.

The discriminatory ability of the emerging prognostic models to predict mortality was assessed in the study cohort with the Harrel C index and Hazard Ratios with comparison of the HAP score, ALBI and PALBI grade against the Child-Pugh score, MELD score, and BCLC stage.

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CHAPTER 3

Clinical utility of Albumin Bilirubin grade as a prognostic marker in patients with Hepatocellular Carcinoma undergoing Transarterial Chemoembolisation: A systematic review and meta-analysis.

Preface

Hepatic functional reserve is a key prognostic marker in patients with hepatocellular cancer (HCC) undergoing transarterial chemoembolisation (TACE) with multiple prognostic models incorporating markers of both liver function and tumour burden. In particular lower serum albumin is a marker of neoplasm associated cachexia and impaired hepatic synthetic function, and has been associated with increased risk of hepatic decompensation and lower survival outcomes.[1-6] Similarly, serum Bilirubin is another marker of liver function, that has been associated with significantly increased risk of post TACE complications, including post TACE embolisation syndrome, and hepatic decompensation.[6-8]

A novel prognostic model based on a simple algorithm of serum albumin and bilirubin, the ALBI grade, has recently gained significant clinical interest with its ability to stratify prognosis in patients with HCC that have a wide range of tumour burden and underlying liver disease.[9] However, clinical utility of the ALBI grade in patients with unresectable HCC treated with TACE has been variably explored.

Our meta-analysis and systematic review investigated the applicability of the ALBI grade to the highly heterogenous group of patients with intermediate stage HCC. The analysis demonstrates the ALBI grade has promising prognostic utility in a large international cohort. In particular, it is a useful clinical tool for clinicians to improve patient selection for treatment allocation with TACE or alternatives therapies such as, systemic agents or enrolment into clinical trials.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major and rapidly increasing cause of global premature morbidity and mortality. It is the fifth most common cancer globally and the second leading cause of cancer-related mortality.[1,2] In managing HCC, the Barcelona Clinic Liver Cancer (BCLC) staging system is a widely adopted system used to stage patients and guide therapeutic decisions[3]. According to the BCLC system, subjects with intermediate stage (BCLC B) HCC should undergo transarterial chemoembolisation (TACE).[4,5]

Indeed, TACE is the most commonly prescribed treatment for patients with HCC as the majority of patients present with disease that is not amenable to potentially curative therapies.[6–8] TACE not only improves the overall survival in such patients, but also has an adjunctive role in controlling disease before liver transplantation as well increasing patient eligibility for other treatments such as ablation and surgery.[9,10] However, patient outcomes with TACE are quite heterogeneous with median survival rates varying between 20 and 45 months.[11–14] This is due, in part, to the wide spectrum of liver dysfunction observed in BCLC stage B patients.[15–17]

Patient selection, therefore, plays an important role in treating patients with TACE as severity of pre-treatment liver dysfunction predicts both post-treatment complications and overall survival.[18–20] Several models have been proposed to assess hepatic reserve [19,21-23], however their clinical utility is limited by variation in both objectivity and sensitivity in stratifying stages of hepatic dysfunction.[7,24-26] The ALBI score, derived from both serum albumin and bilirubin levels, was recently proposed by Johnson et al. as an objective measure of liver reserve in patients with HCC[27]. Subsequently, multiple studies have shown it to have significant discriminatory power in patients undergoing TACE. [28–41]

In particular, it has been found to have equivalent or superior prognostic power to the Child-Pugh score that also includes subjective markers such as ascites and hepatic encephalopathy, as well as the model of end stage liver disease (MELD) score. [24,28–30] We, therefore, undertook a systematic review and meta-analysis of published studies to determine the role of ALBI grade as a prognostic determinant in HCC patients undergoing TACE.

METHODS

Literature search strategy

A comprehensive and systematic literature search was carried out in databases including PubMed, Embase, Medline, Web of Science, and Cochrane library (up to June 1, 2019). The following search terms were combined as key words: : (hepatocellular or liver) and (tumor or cancer or carcinoma or malignant) and (chemoembolization or chemoembolisation or embolisation or embolization) and (albumin to bilirubin ratio or albumin/bilirubin or albumin to bilirubin or ALBI or albumin and bilirubin).

Inclusion criteria

The inclusion criteria included: (i) patients with HCC; (ii) prognostic value of ALBI was evaluated on overall survival (OS); (iii) the survival outcomes were measured by hazard ratio (HRs) with 95% confidence interval (CIs), Kaplan–Meier curve, or data for calculating HR with its corresponding 95% CI; and (iv) studies were full text or conference abstract. Studies were excluded based on the following criteria: (i) case reports, reviews, letters, and comments; (ii) inclusion of patients undergoing liver transplantation; (iii) studies without sufficient data to calculate HR with 95% CI; and (iv) studies where we were unable to obtain missing data

after contacting the corresponding author(s). Studies were included or excluded following consensus between two authors (GM and AM).

Data extraction

All the studies were systematically screened and reviewed by two independent researchers (GM, AM). Data extraction included, study ID (first author's name and publication year), country, sample size, cancer stage, treatment method, survival outcome, analysis model, data source, and follow-up period. Any incongruence in data extraction encountered between reviewers was resolved by a third investigator through discussion.

Statistical analysis

The ALBI score was calculated as ($\log_{10}$ bilirubin μmol/L x 0.66) + (albumin g/L x -0.085) and stratified as follows: grade 1: ≤−2.60; grade 2: > −2.60 to ≤ −1.39; and grade 3: >−1.39. Pooled HRs with their corresponding 95% CI were calculated for each ALBI grade to assess the prognostic value of ALBI on OS in patients with HCC treated with TACE. A high ALBI was closely associated with poor survival outcome when the HR was >1.

We tested heterogeneity with Cochran's Q statistic and Higgins I^2 statistics quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity.[41] I^2 values of 25%, 50%, and 75% corresponded to low, moderate and high degrees of heterogeneity, respectively[42]. If there was no heterogeneity (<50%, P>.1), fixed-effect model would be used. Otherwise, the random-effect model was applied. We quantified publication bias using the Egger's regression model.[43] The result was defined as statistically significant if P<.05. All analyses were performed using Comprehensive Meta-analysis, version 3.0, Biostat, Englewood, NJ (2014).

This is a systematic review and meta-analysis, which does not need to be approved by the Institutional review board or Ethics committee.

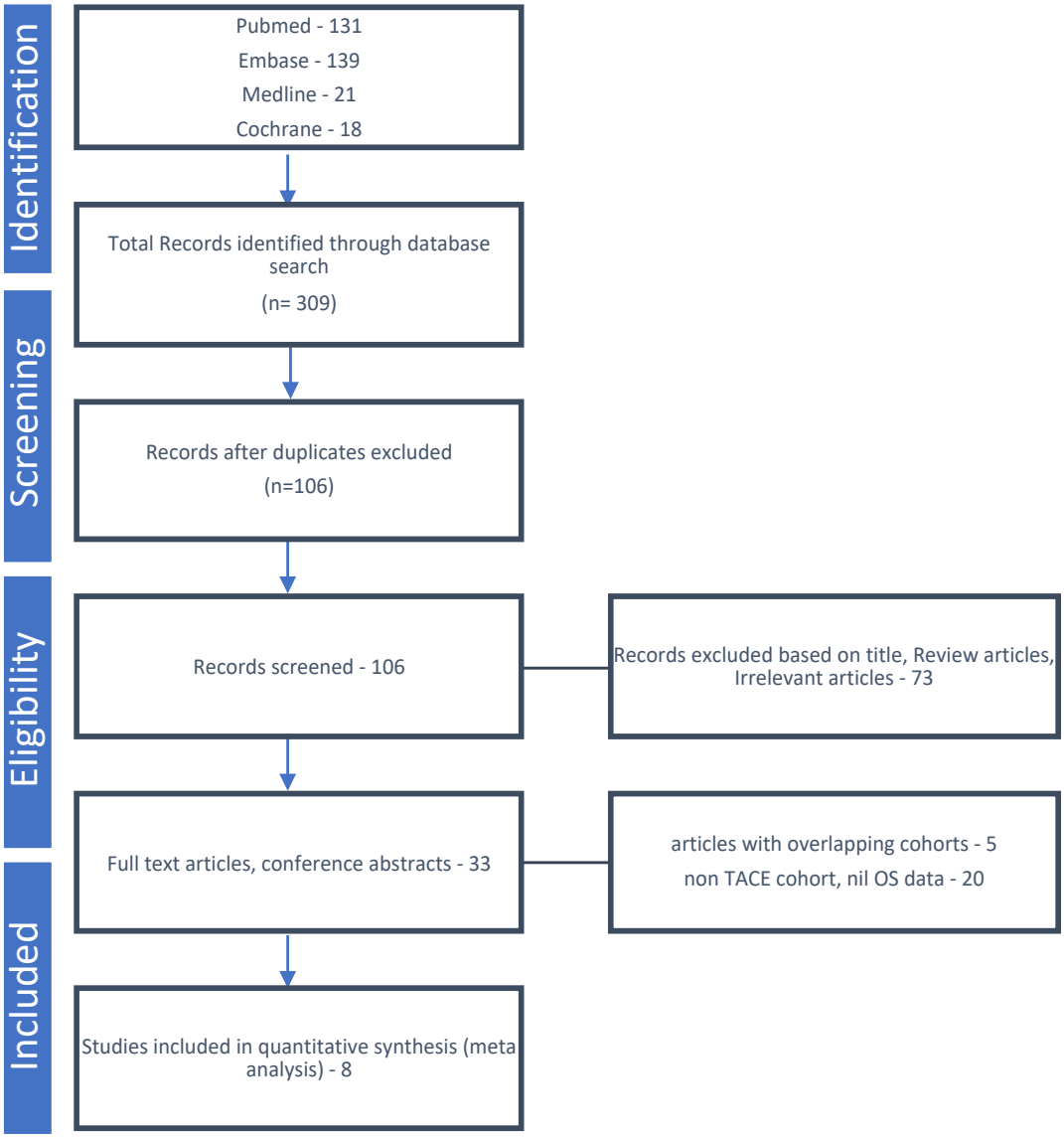
RESULTS

Literature search

Of the 309 articles initially identified related to ALBI grade, 33 studies that included both full text and conference abstracts were eligible for inclusion after exclusion of duplicates (n=106) and review of records and removal of irrelevant articles (n=73). Of these, 12 studies fulfilled all inclusion criteria after removal of those with overlapping cohorts (n=5) and those that did not include TACE as a treatment cohort (n=20) or have OS data available as either HR with 95%CI or Kaplan Meier curves.

In studies that provided incomplete OS data as either HR with 95% CI or Kaplan Meier curves the corresponding author was contacted for further data including baseline demographic data stratified by ALBI grade. Based on the data available from original studies and further data provided by study author correspondence a total of 8 studies were included for final analysis (Figure 3.1).

Figure 3.1. Study selection flowchart



Clinical studies and cohort characteristics

Characteristics of the eight included studies are presented in Tables 3.1 and 3.2. The studies covered a variety of geographical regions including two large multi-center international studies[28,34] that included populations from USA, Europe, Japan, South Korea and Egypt. The remaining studies included two smaller cohorts [35,36] from the US, one from UK[37], one from Norway[39] one from Japan[38] and one study from Taiwan.[32]

The study cohort size ranged from 49 to 3030. In total, there were 6538 patients with HCC who underwent TACE pooled from the eight eligible studies. The baseline population data derived from these studies are outlined in Table 3.1 and 3.2 with additional demographic data provided by the corresponding authors shown in Table 3.3.

Table 3.1 – Cohort Characteristics, Multicentre studies[28,34]

Author	Pinato D et al,			Waked et al,			
Publication Date	2017			2017			
Population	USA	Europe	Asia*	Europe	Japan	Egypt	Hong Kong
TACE cohort	315	423	723	1232	655	998	145
Date of study	1989-2005	2001-2013	2004-2013				
Female %	76 (24%)	73 (17%)	210 (29%)	209 (17%)	164 (25%)	170 (17%)	22 (15%)
Male%	239(76%)	350 (83%)	512 (71%)	1023 (83%)	491 (75%)	828 (83%)	123 (85%)
Age, (median,	64 (22-93)	69 (33-88)	72 (32-89)	66.5 (59-73)	65 (58-73)	57 (51-62)	65 (56-71)
Aetiology							
HCV	113 (40%),	115 (27%),	454 (70%)	299 (24%)	370 (56.6%)	982 (98.4%)	12 (8.3%)
HBV	81 (28%),		127 (18%)	150 (12%)	121 (18.4%)	11 (1.1%)	116 (79.9%)
HBV/HCV							
ETOH	221 (70%)	160 (38%)					
Other				783 (63.5%)	163 (24.9%)	5 (0.05%)	17 (11.8%)
Child Pugh Stage							
A	220(70%)	307(72%)	542(76%)	868 (74%)	341(52%)	475(48%)	112(77%)
B	95 (30%)	116(28%)	181 (23%)	289(25%)	270(41%)	467(47%)	31(21%)
C				17 (1%)	44(7%)	55(5%)	2(1%)
ALBI grade							
1	41 (13%)	140 (33%)	156 (22%)	384 (32%)	85 (13%)	156 (16%)	34 (25%)
2	209(66%)	253 (60%)	482 (67%)	731 (61%)	462 (71%)	690 (69%)	98 (68%)
3	65(21%)	30 (7%)	85 (11%)	82 (7%)	106 (16%)	152 (15%)	11 (8%)
BCLC stage							
A	43 (14%)	75 (18%)	270 (37%)	N/A	N/A	N/A	N/A
B	272 (86%)	236 (56%)	390 (54%)	N/A	N/A	N/A	N/A
C	0	112 (26%)	63 (9%)	N/A	N/A	N/A	N/A
D							
Tumour nodules							
1-2 nodules	151 (40%)	177(42%)	250 (40%)				
Multifocal	164 (60%)	246 (58%)	473 (60%)	1161 (66%)	654 (69%)	998 (75%)	144 (58%)
Tumour Size (cm) IQR	6 (1-23)	5 (0.9-2)	2 (2-17)	5 (3.4–7.6) n=1180	3.5 (2.2–5.4), n=59	6 (4.0–8.0), n=998	6 (3.8–10.0), n=141
AFP (ng/ml)	73 (2078)	23.6 (234)	28 (200)	46 (6.7–534.5)	45.45 (12.4–510.0)	129.0 (17.0–600.0)	92.0 (10.0–1365.0)
MVI	0	40 (9%)	59 (8%)	1225 (10.61%)	654 (30.28%)	998 (10.32%)	145 (11.03%)
Overall Survival							
ALBI Grade 1	15.4 (11–20)	39 (33-44)	51.8 (45-57)	26.12 (22.9-28.1)	38.91 (27.3-51.4)	30 (20-)	30.2 (16.8-47.2)
ALBI Grade 2	11 (8.3 -14)	18 (14.3-21.6)	34 (30-39)	14.61 (13.4-15.9)	22.43 (19.6-25.4)	18 (17-20)	18.65 (12.6-25.6)
ALBI Grade 3	4.5 (3-6)	18 (14.8-21.1)	21 (14-28)	9.7 (5.8-14.0)	15.33 (9.3-20.5)	13 (9-14)	6.05 (1.2-14.2)

*Includes patient cohorts from Japan and South Korea.

Table 3.2 – Cohort Characteristics – Single Centre studies [35–40]

Author	Aravind P et al	Hansmann et al	Liu et al	Hickey et al	Carling et al	Hiraoka A et al
Publication Date	2017	2017	2017	2016	2019	2017
Population	UK	USA	Taiwan	USA	Norway	Japan
TACE cohort	431	180	881	337	49	212
Date of study	2006-2012	2007-2015	2002-2013	2005-2014	2009-2015	2000-2016
Female %	N/A	38 (21%)	208 (24%)	84 (25%)	11 (22%)	49 (23%)
Male%	N/A	142 (79%)	673 (76%)	253 (75%)	38 (78%)	163 (77%)
Median Age	62	mean 59 ± 9 SD	68 (55-75)	<65yrs,n=212, >65yrs, n=125	66 (40-89)	72 (64-77)
Aetiology						
HCV	N/A	N/A	241 (27%)	N/A	*	162 (76%)
HBV	N/A	N/A	311 (35%)	N/A	*	6 (3%)
HBV/HCV	N/A	N/A	35 (4%)	N/A	*	2 (1%)
ETOH	N/A	N/A	162 (19%)	N/A	*	
Other	N/A	N/A	226 (26%)	N/A	*	42 (20%)
Child Pugh Stage						
A	365 (85%)	44 (24%)	698 (79%)	186 (55%)	49 (100%)	212 (100%)
B	63 (15%)	105 (58%)	167 (19%)	146 (43%)		
C	2(0.005%)	31 (18%)	20 (2%)	5 (1%)		
ALBI grade						
1	208 (48%)	N/A	297 (34%)	19 (5%)	21	88 (42%)
2	196 (45.4%)	79 (44%)	540 (61%)	241 (72%)	27	124 (58%)
3	27(6.3%)	101 (56%)	44 (0.05%)	77 (23%)	1	N/A
BCLC stage						
A	N/A	68 (38%)	N/A	160 (47%)	3	
B	N/A	53 (29%)	N/A	127 (38%)	26	212 (100%)
C	N/A	27 (15%)	N/A	50 (9%)	20	
D		32(18%)	N/A		0	
Tumour nodules						
1-2 nodules	N/A	N/A	619 (70%)	133 (40%)	25 (51%)	N/A
Multifocal	N/A	N/A	262 (30%)	204 (61%)		N/A
Tumour Size (cm) IQR	N/A	N/A	<2 cm/2-5/>5cm, n= 121(14%),329 (37%),431(49%)	3.6 (1.8–20.2)	6 (1.1-18.4)	ALB 1 (1.8 (1.2-3.4) ALBI 2 (2.2 (1.2-4.0)
AFP (ng/ml)	N/A	N/A	13515.0 (98741.3)	N/A	35 (1-81)	N/A
MVI	N/A	16 (9%)	157 (18%)	16 (5%)	6 (12%)	0
Overall Survival						
ALBI Grade 1	26.1 (19.5-32.6)	N/A	38.1(N/A)	N/A	17.7 (3.6-62)	44.1(35.1-49.9)
ALBI Grade 2	18.6 (14.9-21.5)	20.3 (10.5-N/A)	21.3 (N/A)	19.2 (16.1-22.2)	12.8 (1.7-37.7)	16.2 (21.8-32.8)
ALBI Grade 3	11.7(6.1-17.3)	10.7 (3.5-21.6)	11.3 (N/A)	11.3 (8.4-14.1)	N/A	N/A

*Aetiology of liver disease are grouped in original data as, Viral hepatitis / ETOH / or both (n=20 (41%)), NAFLD / other (n=17 (35%)), and cryptogenic (n=12 (24%).

Table 3.3. Demographic and baseline tumour parameters stratified by ALBI grade[28,34,38]

ALBI grade	Study	N	OS (months, 95% CI)	Age (median, SD/IQR)	Sex (M/F)	HBV/HCV/ETOH/Othe	BCLC stage (0/A/B/C)	CPS A/B/C	MVI	HCC size, cm (median, range)
1	Waked et al	663	27.6 (25.5, 29.9)	65 (58-72)	551 / 112	92/271/103/144	N/A	630/22/0	76	5.5 (0.3-18.8)
	Pinato et al USA	41	15.4 (11.1-19.7)	60 (23)	25/16	7/5/28	0/0/ 41/0	41/0/0	0	6.2 (1-20)
	Pinato et al Europe	140	39 (33.3-44.6)	70 (12)	117/23	22/32/42/34	0/18/85/37	136/3/0	15	4.8 (1.2-16.7)
	Pinato et al Asia	156	51.8 (45.8-57.7)	73 (11)	120/36	26/92/33/0	7/46/91/12	155/0/0	8	2.0 (1.0-16.0)
	Hiraoaka et al	88	44.1 (35.1-49.9)	72 (64-77)	72/16	58/4/7/17	0/0/88/0	88/0/0	0	1.8 (1.2-3.4)
2	Waked et al	1983	17.8 (16.9-18.6)	62 (55-70)	1615 /368	250/1125/223/308	N/A	1147/ 770/43	284	5.0 (0.8, 26.2)
	Pinato et al USA	209	10.9 (8.29-13.6)	64 (17)	161/49	53/73/106	0/0/209/0	177/32/0	0	5.5 (1-22)
	Pinato et al Europe	253	18 (14.3-21.6)	68 (16)	207/46	22/80/100/35	0/44/139/70	167/84/0	24	4 (0.9-20)
	Pinato et al Asia	482	34.5 (29.6-39.3)	72 (13)	345/136	84/309/84/3	17/162/262/	377/101/0	41	2 (1-25)
	Hiraoaka et al	124	16.2 (21.8-32.8)	72 (64-77)	91/33	104/2/7/11	0/0/124/0	124/0/0	0	2.2 (1.2-4.0)
3	Waked et al	353	12.4 (9.6- 14.2)	60 (53-66)	278 / 75	40/237/25/46	N/A	12/261/75	85	5.0 (0.5-22.0)
	Pinato et al USA	65	4.57 (2.9-6.1)	58 (18)	53/11	22/34/35	0/0/65/0	2/62/0	0	3.9 (1-22)
	Pinato et al Europe	30	18 (14.9-21.1)	64 (14)	26 / 4	3/3/18/3	0/7/11/12	2/28/0	1	4.5 (1.5-12.8)
	Pinato et al Asia	85	21.5 (17.7-28.2)	69 (12)	47/38	17/53/17/1	6/32/37/10	10/74/0	10	2 (0.9-14)

The majority of patients were male (74%) with median age ranging from 55 to 75 years. The majority of patients had Child-Pugh A (n=4410) 66% or B (n=1839) 30% liver disease. Pinato's multicenter study[28] and Hiraoka et al [38] had mainly Child-Pugh A and B patients, while the smaller study from Norway[39] had exclusively Child Pugh A patients. Child-Pugh C patients were seen in the other studies but their overall numbers were small, n=176 (3%).

BCLC staging data was not available on patients from three studies.[34,37,40] Based on the data available from the remaining studies (N= 2209), 24% were BCLC A, 61% were BCLC B and 13% BCLC C. A relatively smaller cohort were BCLC D 1%, all being derived from a single population in Hansmann's study.[35] The aetiology of liver disease data was available in 86% (n=5590) of the entire cohort, and was not available in three studies [35-37] and multiple aetiologies were grouped together in one study[39]. The most common cause of liver disease was HCV (n=2717), found in 42% of the entire cohort, whilst both HBV, and ETOH had similar incidence at 15%. Other aetiologies including HBV/HCV co-infection occurred in 10% of the total cohort.

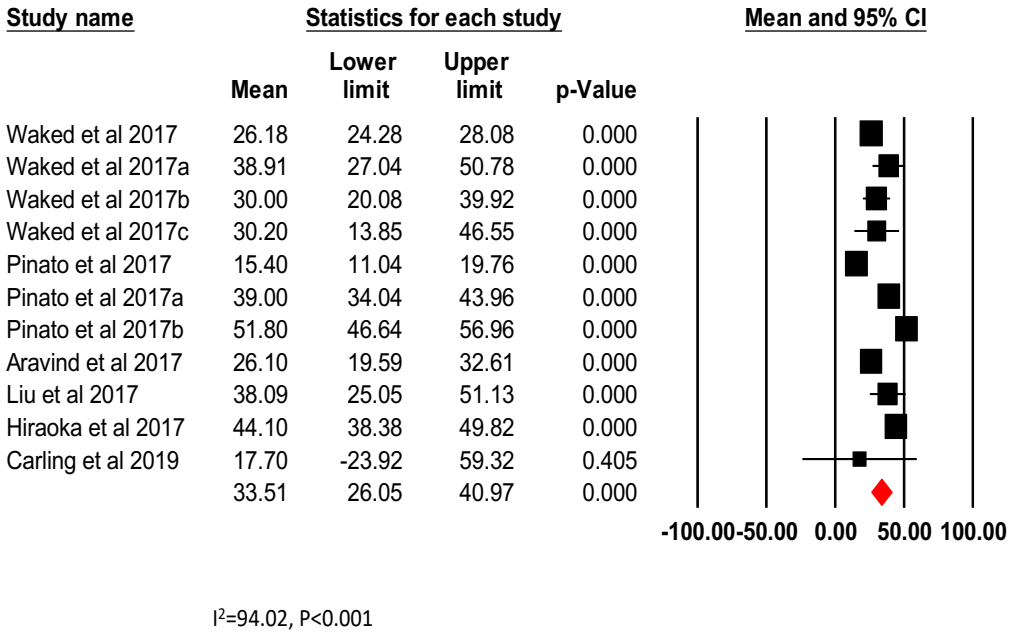
The median tumour size was 4.25 cm and varied widely from a median of 1cm to 19.4cm especially in the two large multicentre studies.[28,34] Macrovascular invasion (MVI) data were available in all cohorts except for one study[37], with MVI present in 11% of the overall cohort with the highest rate of 30% in the Japanese cohort of Waked's multicenter study.[34] Extrahepatic spread (EHS) was present in 38 cases, (1%) of overall cases and derived mainly from the Japanese and South Korean cohort of Pinato's multicenter study[28] and the small Norwegian cohort study.[39]

Effect of ALBI grade on overall survival

A random effects model was used to analyse the aggregated data, to account for significant heterogeneity in the studies included. ALBI grade was able to stratify patients in to distinct overall survival groups with 33.5 months, (95% CI[26.1-41.0], P < 0.001) in ALBI grade 1, compared to 19.1 months (95% CI[16.3-21.9], P < 0.001) in ALBI grade 2, and 12.01 months (95% CI[8.71-15.3], P < 0.001) in ALBI grade 3 (Fig. 3.2 and 3.3).

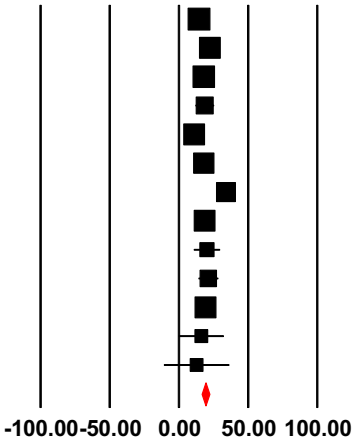
Figure 3.2. Forest plot evaluating effect of ALBI grade 1 (A), grade 2 (B) and grade 3 (C) on overall survival.

(A)



(B)

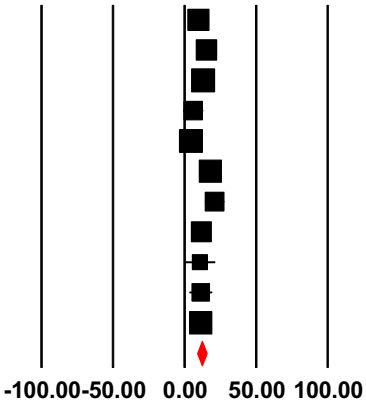
Study name	Mean	Lower limit	Upper limit	p-Value
Waked et al 2017	14.61	13.35	15.87	0.000
Waked et al 2017a	22.43	19.55	25.31	0.000
Waked et al 2017b	18.00	16.00	20.00	0.000
Waked et al 2017c	18.65	11.80	25.50	0.000
Pinato et al 2017	11.00	8.02	13.98	0.000
Pinato et al 2017a	18.00	14.37	21.63	0.000
Pinato et al 2017b	34.00	29.01	38.99	0.000
Aravind et al 2017	18.60	15.72	21.48	0.000
Hansman et al 2017	20.30	10.65	29.95	0.000
Liu et al 2017	21.28	14.02	28.54	0.000
Hickey et al 2016	19.20	16.17	22.23	0.000
Hiraoka et al 2017	16.20	-0.24	32.64	0.053
Carling et al 2019	12.80	-10.94	36.54	0.291
	19.13	16.33	21.93	0.000



I^2=87.25, P<0.001

(C)

Study name	Mean	Lower limit	Upper limit	p-Value
Waked et al 2017	9.70	5.45	13.95	0.000
Waked et al 2017a	15.33	10.26	20.40	0.000
Waked et al 2017b	13.00	12.01	13.99	0.000
Waked et al 2017c	6.05	-1.10	13.20	0.097
Pinato et al 2017	4.50	3.03	5.97	0.000
Pinato et al 2017a	18.00	14.98	21.02	0.000
Pinato et al 2017b	21.00	14.10	27.90	0.000
Aravind et al 2017	11.70	6.13	17.27	0.000
Hansman et al 2017	10.70	-0.07	21.47	0.051
Liu et al 2017	11.32	3.23	19.41	0.006
Hickey et al 2016	11.30	8.50	14.10	0.000
	12.01	8.71	15.31	0.000



I^2=94.02, P<0.001

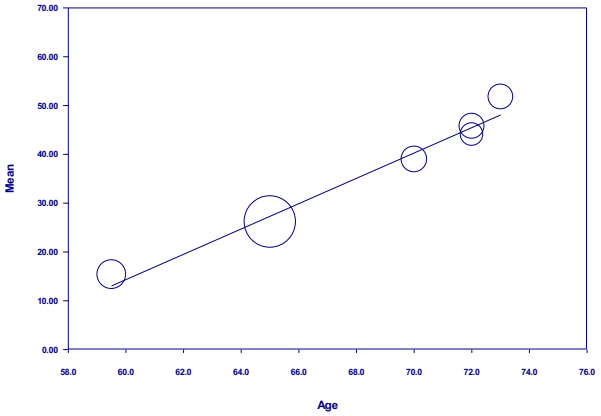
Figure 3.3. ALBI grade 1,2, and 3 association with overall survival in the study cohort.

Subgroup analysis

Stratification into subgroups (Table 3.3), found heterogeneity in the ALBI grade 1 and 2 groups was significantly associated with age and tumour size (P<0.001), while BCLC stage B (p<0.001) was an additional factor in the ALBI grade 1 group (Fig 3.4A-E). In contrast, age and alcohol-related liver disease were associated with heterogeneity in the ALBI grade 3 group (p<0.001) (Fig. 3.4F-G).

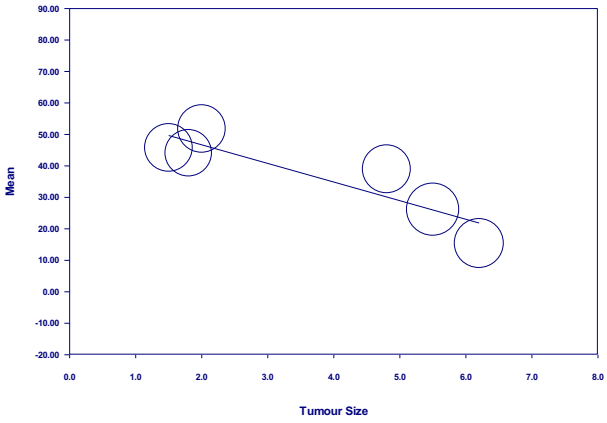
Figure 3.4. Variables associated with heterogeneity within each ALBI grade; ALBI grade 1 (A-C), ALBI grade 2 (D-E), ALBI grade 3 (F, G)

A)



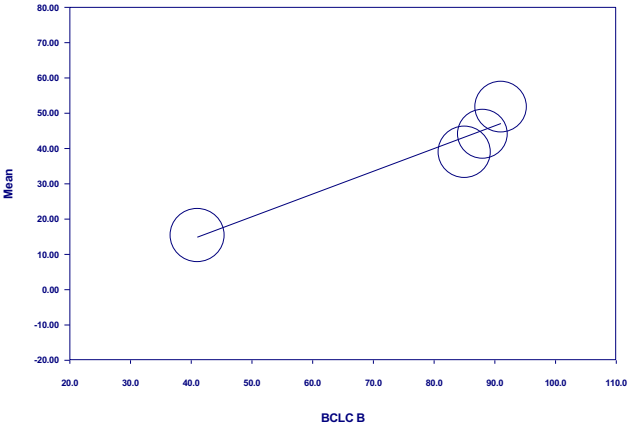
p=<0.001

B)



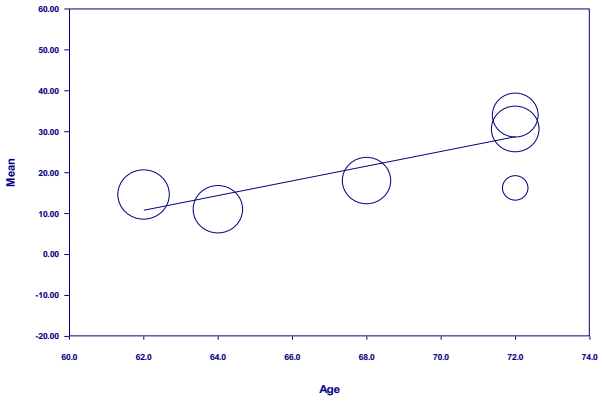
C)

P<0.001



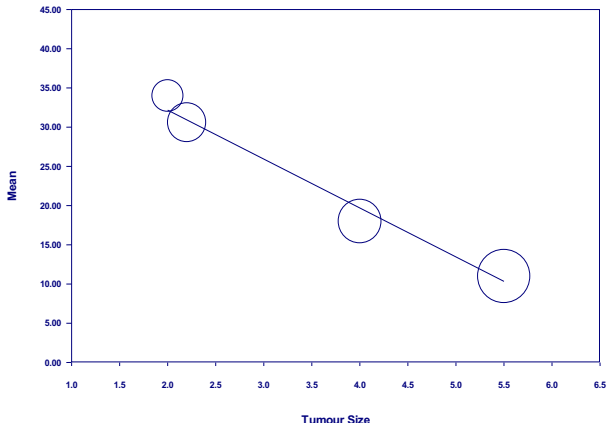
P<0.001

D)



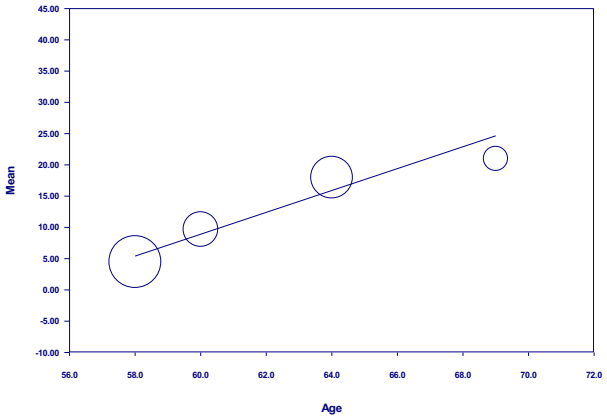
p=<0.001

E)



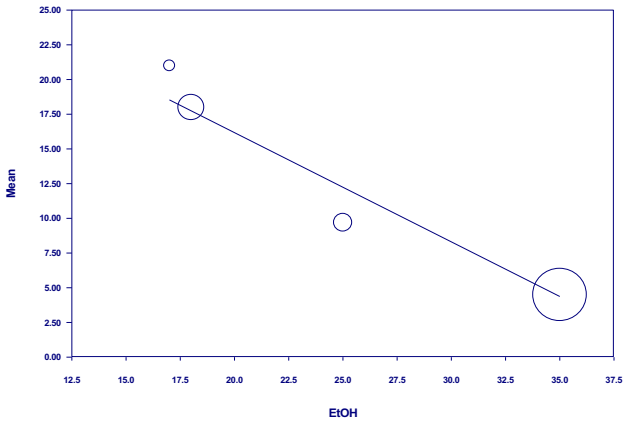
P<0.001

F)



p=<0.001

G)



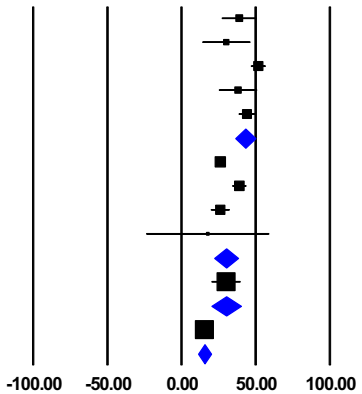
P<0.001

The distribution of the ALBI grade on subgroup analysis also varied between Europe and Asia across all ALBI grades, with the overall heterogeneity decreasing in patients classified as ALBI 3 compared to ALBI 1 and ALBI 2 (Figure 3.5).

Figure 3.5. Forest plots evaluating effect of geographical variations in ALBI grade 1 (A), grade 2 (B) and grade 3 (C) on overall survival.

(A)

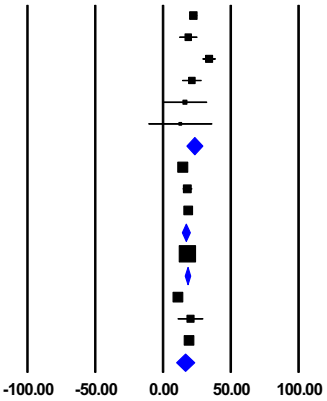
Group by Region	Study name	Mean	Lower limit	Upper limit	p-Value
Asia	Waked et al 2017a	38.91	27.04	50.78	0.000
Asia	Waked et al 2017c	30.20	13.85	46.55	0.000
Asia	Pinato et al 2017b	51.80	46.64	56.96	0.000
Asia	Liu et al 2017	38.09	25.05	51.13	0.000
Asia	Hiraoka et al 2017	44.10	38.38	49.82	0.000
Asia		42.91	36.07	49.74	0.000
Europe	Waked et al 2017	26.18	24.28	28.08	0.000
Europe	Pinato et al 2017a	39.00	34.04	43.96	0.000
Europe	Aravind et al 2017	26.10	19.59	32.61	0.000
Europe	Carling et al 2019	17.70	-23.92	59.32	0.405
Europe		29.95	21.90	38.01	0.000
Middle East	Waked et al 2017b	30.00	20.08	39.92	0.000
Middle East		30.00	20.08	39.92	0.000
North America	Pinato et al 2017	15.40	11.04	19.76	0.000
North America		15.40	11.04	19.76	0.000



Asia I^2=65.67, P=0.02
Europe I^2=86.88, P<0.001
ME I^2=0.00, P=1.00
NA I^2=0.00, P=1.00

(B)

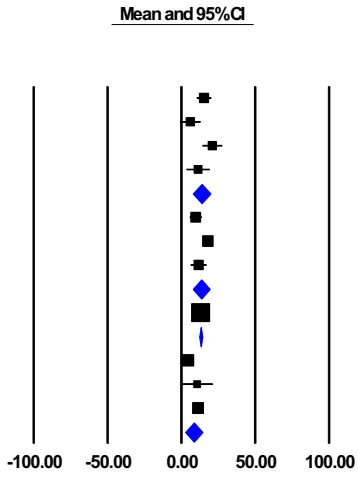
Group by Region	Study name	Mean	Lower limit	Upper limit	p-Value
Asia	Waked et al 2017a	22.43	19.55	25.31	0.000
Asia	Waked et al 2017c	18.65	11.80	25.50	0.000
Asia	Pinato et al 2017b	34.00	29.01	38.99	0.000
Asia	Liu et al 2017	21.28	14.02	28.54	0.000
Asia	Hiraoka et al 2017	16.20	-0.24	32.64	0.053
Asia	Carling et al 2019	12.80	-10.94	36.54	0.291
Asia		23.04	17.14	28.94	0.000
Europe	Waked et al 2017	14.61	13.35	15.87	0.000
Europe	Pinato et al 2017a	18.00	14.37	21.63	0.000
Europe	Aravind et al 2017	18.60	15.72	21.48	0.000
Europe		16.78	13.83	19.72	0.000
Middle East	Waked et al 2017b	18.00	16.00	20.00	0.000
Middle East		18.00	16.00	20.00	0.000
North America	Pinato et al 2017	11.00	8.02	13.98	0.000
North America	Hansman et al 2017	20.30	10.65	29.95	0.000
North America	Hickey et al 2016	19.20	16.17	22.23	0.000
North America		16.26	9.58	22.95	0.000



Asia I^2=76.40, P=0.001
Europe I^2=75.52, P=0.02
ME I^2=0.00, P=1.00
NA I^2=86.98, P<0.001

(C)

Group by Region	Study name	Mean	Lower limit	Upper limit	p-Value
Asia	Waked et al 2017a	15.33	10.26	20.40	0.000
Asia	Waked et al 2017c	6.05	-1.10	13.20	0.097
Asia	Pinato et al 2017b	21.00	14.10	27.90	0.000
Asia	Liu et al 2017	11.32	3.23	19.41	0.006
Asia		13.61	7.69	19.54	0.000
Europe	Waked et al 2017	9.70	5.45	13.95	0.000
Europe	Pinato et al 2017a	18.00	14.98	21.02	0.000
Europe	Aravind et al 2017	11.70	6.13	17.27	0.000
Europe		13.36	7.68	19.03	0.000
Middle East	Waked et al 2017b	13.00	12.01	13.99	0.000
Middle East		13.00	12.01	13.99	0.000
North America	Pinato et al 2017	4.50	3.03	5.97	0.000
North America	Hansman et al 2017	10.70	-0.07	21.47	0.051
North America	Hickey et al 2016	11.30	8.50	14.10	0.000
North America		8.29	2.48	14.11	0.005



Asia I^2=68.04, P=0.02
Europe I^2=81.87, P=0.004
ME I^2=0.00, P=1.00
NA I^2=89.15, P<0.001

Comparative subgroup analysis of ALBI grade with current prognostic tools

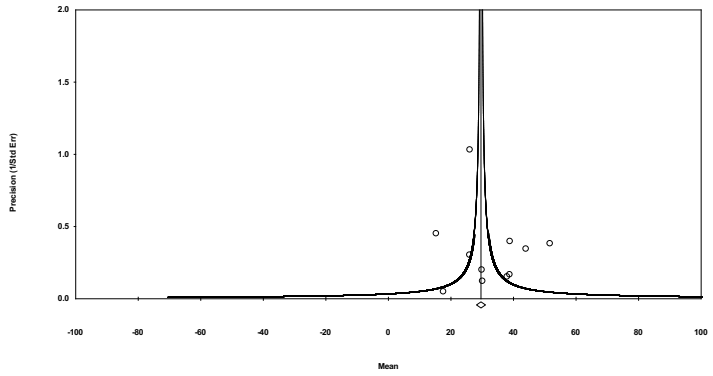
The ALBI grade had superior prognostic ability to the Child Pugh class in the large multinational study by Waked et al, when applied to the cohort from Europe and China (C-index 0.5749 vs 0.5446) and (C-index 0.5898 vs 0.5684) respectively (supplementary Table 3.1 A-H). Similarly, Hickey et al showed that the ALBI grade had superior discriminatory ability to the Child Pugh class (C-index 0.584 vs. 0.524). In addition, further sub-stratification with ALBI grade significantly improved the prognostic ability of the Child Pugh class and BCLC stage in both small single centre and large multinational studies included in our meta-analysis. In particular, Huo et al demonstrated improvement in patients with BCLC stage B and Child Pugh A disease at baseline. Similarly, Hansman et al demonstrated the BCLC stage B had highest discriminatory ability with the application of ALBI grade (C-index 0.917), in addition to BCLC stage A (C-index 0.867) and Child Pugh B (C-index 0.892). Complete comparative data with the MELD score was only available in one study by Huo et al, and demonstrated the ALBI grade (C-index 0.544) had a better discriminatory index compared to the CPC (C-index 0.527) and MELD (C-index 0.497). The BCLC stage had the highest discriminatory index in this cohort (C-index 0.575), likely reflecting the influence of key tumour burden parameters that are incorporated in the BCLC staging system.

Publication Bias

The Eggers regression analysis was not significant for publication bias for the studies included for analysis in each ALBI grade (ALBI 1 p=0.33; ALBI 2 p=0.16; ALBI 3 p=0.75) (Figure 3.6).

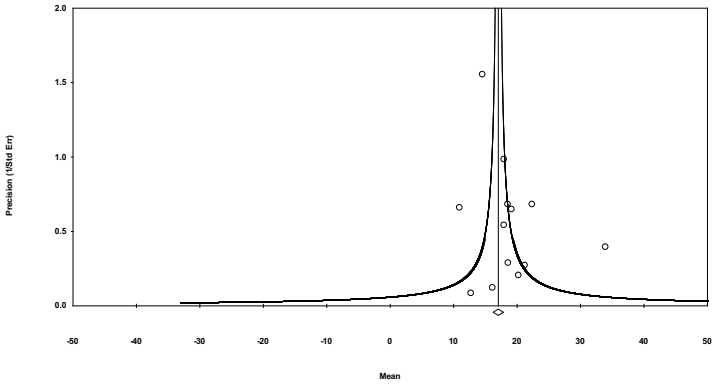
Figure 3.6. Funnel plot of publications included for analysis in each ALBI grade; ALBI grade 1 (A), (ALBI grade 2 (B), ALBI grade 3 (C).

(A)



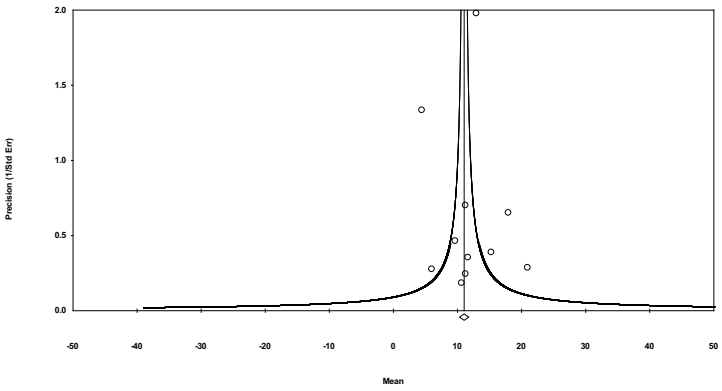
P=0.33

(B)



P=0.16

(C)



P=0.75

DISCUSSION

Accurate staging of HCC is an essential step towards improving patient survival for this cancer[2] that has a very high mortality[44]. The two main staging factors that contribute to HCC mortality, namely the underlying severity of liver dysfunction and tumour burden, make HCC unique in its category and are critical determinants upon which treatment decisions are based.[6,7,21,22,45] In this context, the ALBI score has emerged as a key grading system to facilitate prognostication and survival of patients with this inherently heterogenous disease[15,27,46]. Notably, the ALBI score overcomes many of the inherent differences in patient populations at a global level by using objective markers of liver function rather than other traditional markers such as the Child-Pugh score which are influenced by subjective clinician assessment.[24,46,47] Comparative studies between Child-Pugh and MELD scores in patients undergoing TACE for HCC have found Child-Pugh score correlated better with OS, particularly the albumin component.[26,48–52]

Multiple international cohort studies have demonstrated the ALBI score has good discriminatory power and good prognostic function often equivalent and at times superior to current prognostic scoring systems that have variable performance when applied to populations beyond their original derivation cohort.[53–55] The main findings of our meta-analysis of these cohort studies is the demonstration that ALBI grade is a robust prognostic marker in HCC patients undergoing TACE with high pre-treatment ALBI grade associated with a poor prognosis. Importantly, we found that the ALBI score performed well across major global populations with ALBI grades 1, 2, and 3, identifying three populations with significantly different overall survivals of 33.5, 19 and 12 months respectively.

Moreover, the characteristics of the overall cohort in our study are consistent with previous studies of patients with HCC undergoing TACE.[6,18,23] The significant majority (74%) of patients were male with a median age ranging from 55 to 75 years old, with 66% having Child-Pugh A and 30% Child-Pugh B liver disease. However, while over half (n=1358) of the patients with available data (n=2209) had BCLC B stage HCC, they consisted of only 21% of the entire cohort of 6538 patients due to the relatively low 34% rate of reporting of BCLC stage across studies. Thus, accurate and robust conclusions regarding the impact of BCLC stage characteristics are difficult to make. In contrast, there was a high 87% reporting of data on the aetiology of liver disease of patients and a wide range covered in the median tumour size (1-19.4cm), while rates of reporting of MVI and EHS varied across the different cohorts.

The significant heterogeneity in our overall cohort resulting from the differences in baseline demographic features within each study population likely reflect in part the variations in HCC classification and treatment guidelines between Eastern and Western populations.[16,53–56] The main factors accounting for heterogeneity among the different ALBI grade groups included age, which was present for all ALBI grade groups, and tumour size for ALBI grade 1 and 2 groups. BCLC B stage and alcohol related liver disease were additional factors associated with heterogeneity in the ALBI grade 1 and ALBI grade 3 groups respectively. These factors may reflect the baseline demographics and tumour stage of each population group at the time of TACE therapy with patients in the Asian cohorts presenting at an older age, with higher rates of underlying HBV related HCC and lower tumour burden as defined by both BCLC stage and smaller median HCC diameter.

Heterogeneity is also seen within the included cohorts from Asia with key differences noted in baseline cohort characteristics. For example, the frequency of MVI was 18% in the study by Lui et al[40], and as high as 30% in the Japanese cohort in Waked's study[34], while another study from a single centre Japanese cohort[38] included only patients with intermediate stage BCLC B disease without MVI or EHS. In addition, HCV related liver disease was more common in both the Japanese and Western cohorts, however patients from the Western cohorts were younger and also had a greater proportion of alcohol related liver disease particularly from Europe and the USA.

Interestingly, patients within the European cohort also underwent TACE at a more advanced stage compared to the North American cohort. Further subgroup analysis is limited however due to the significant number studies with missing variables such as BCLC staging data as noted above. There is, however, evidence that patients from the Liu et al. study[40] had more advanced HCC stage as almost 50% presented with HCC > 5cm, and mean AFP levels and rates of macrovascular invasion were high.

Recently, Xu et al.[57] published a meta-analysis of the prognostic value of pre-treatment ALBI in patients with HCC who underwent various treatments including TACE. The final 32 studies included in their meta-analysis were mainly derived from Asia (n=22) with significant heterogeneity (I^2=83.7%, P=.000) in their overall cohort. Utilising the random effects model in their analysis they found high concordance between high ALBI grade and poor OS (HR = 1.577, 95% CI (1.46–1.69), P = .000) on multivariate analysis, with liver failure associated with mortality in 63.1% of cases.

With regards to TACE, Xu et al.[57] performed treatment stratified analysis that included one TACE specific study, although many of the 32 studies included in their MA had subgroups with TACE treatment reflecting limitations of available data for analysis. The authors acknowledged these difficulties with many studies providing HRs with 95%CI from univariate analysis or as Kaplan Meier curves requiring extraction of data using the Engauge Digitizer software to convert graphs into numerical data, further increasing the heterogeneity of their overall cohort. Univariate analysis of the TACE specific data found significant correlation between ALBI grade and post TACE overall survival (HR =1.59, 95% CI(1.39–1.78), P=.000), however further subgroup analysis is limited due to the small sample size.

Our study also included a subgroup analysis of the performance of the ALBI grade in comparison to currently used prognostic tools including the Child Pugh class (CPC) and the BCLC stage (supplementary table 3.1a-h). Notably, the ALBI grade had superior prognostic ability to the CPC in some but not all studies.[34-36, 40] Whilst these results are encouraging it is important to consider the variation in sample size in each the cohorts, and in particular the small number of patients with each cohort included in the sub stratification of the CP class and BCLC stage according to ALBI grade (Supplementary Table 1). In addition, heterogeneity existed among studies with Pinato et al finding that the discriminatory ability of the ALBI grade, BCLC stage, and CPC were similar.[28] Still, the results of the comparative analysis are limited in their interpretability in most studies due to the small number of patients within certain subgroups. In particular, there were very few patients in the groups reflective of advanced liver disease and tumour burden, classified as ALBI grade 3, BCLC stage C and CPC-C across all included studies.

The ALBI grade also had a variable performance in improving the discriminatory function of the BCLC and CP class, ranging from significant (C-index 0.917), [35] to below adequate cut off for clinical use (C-index 0.65). [28] These results suggest that incorporation of parameters reflective of tumour burden including, tumour size, macrovascular invasion, extrahepatic spread and tumour markers such as AFP remain important prognostic factors as has been demonstrated in several multi-variate analyses. [28, 34, 36,38,39]

Overall, the ALBI grade is an adjunct tool in the assessment of prognosis in patients with HCC having TACE as post TACE hepatic dysfunction is one of the most common complications and a significant competing cause of mortality along with tumour burden. [10,18] In a comparative group of patients treated with repeat TACE prior to sorafenib commencement, Hiraoka et al demonstrated the ALBI grade was a more sensitive marker of worsening hepatic function compared to the CPC, and patients that were ALBI 1 grade prior to commencing Sorafenib had significantly better outcomes compared to patients that were ALBI grade 2, OS 10.9 vs. 10.04 months respectively ($p = 0.001$).[38] These results were also demonstrated in the multinational study by Pinato et al, and supports the utility ALBI grade as an objective tool for clinicians when assessing liver reserve in patients undergoing repeat TACE and facilitating timely stage migration to systemic therapies or enrollment into clinical trials. [28,38] Further large prospective studies analysing the role of the ALBI grade with repeat TACE therapy are required to determine the prognostic role of the ALBI score and the impact of the degree of ALBI score change on OS in comparison to currently used clinical tools.

The strengths of our study include a comprehensive search strategy, which involved searching four electronic databases and availability of a large pooled population derived from several geographical regions and variably sized cohorts for meta-analysis.

Moreover, there was no evidence of publication bias associated with the studies included in the meta-analysis. In addition, comprehensive subgroup analysis was performed according to geographic region, and several other factors known to influence patients survival including age, tumour burden, HCC stage, and aetiology of liver disease. This enabled us to delineate the strengths and weaknesses of the ALBI scores prognostic value in patients having TACE with regards to several patient and tumour factors akin to what has been done in those undergoing potentially curative treatments. Our results are in concordance with the conclusion of Xu et al.'s meta-analysis[57] and further confirm the performance of ALBI grade in patients undergoing TACE across a larger cohort of TACE patients derived from a greater number of additional studies.

There were several limitations of our study that warrant more detailed discussion. Firstly, when assessing the correlation between factors such as HCC staging and grade of liver dysfunction with each ALBI grade and OS outcomes, we noted several examples of where data were variably reported and/or unable to be correctly separated. For example, in the study of Hansmann et al.[35], BCLC 0 and A were categorised together while data regarding underlying aetiology of liver disease, serum AFP levels and tumour nodule number and size were missing or variably reported. Secondly, while duplicates were removed during the screening process, we noted overlap in cohorts used in multiple publications, although this proved to be advantageous in some cases where missing data could be procured from the second publication.[40,58]

However, the subgroup analysis suggests errors in the reported data such as the breakdown of Child-Pugh categories, with the sum of each grade greater than the original TACE cohort in one particular study.[40,58]

There were also differences due to loss of follow up in each study with slight reductions in sample size used to calculate OS and other baseline factors compared to the overall study population. Furthermore, the lack of overall survival data and cohort demographics was one of the key barriers to incorporation of additional studies relevant to this study.[31,48,59] As a result, these cohorts of patients who underwent TACE and had ALBI scores applied were excluded from our final analysis that may reduce the applicability of the pooled results. Finally, since the initial literature search Lee SK and colleagues published a study comparing the ALBI to PALBI (Platelet, Albumin, Bilirubin) grade in a large cohort of patients with HCC treated with TACE (n = 1715).[49] Additional data were not forthcoming at the time of this publication despite efforts to contact corresponding authors.

CONCLUSION

This meta-analysis incorporating multiple real-world international cohorts demonstrates that the ALBI grade is a useful clinical prognostication tool to aid clinical decisions on treatment allocation. A high pre-treatment ALBI grade was associated with poor prognosis in patients with HCC undergoing TACE therapy. Further prospective studies are required to validate the ALBI grade in patients undergoing repeat TACE therapy and in those receiving TACE in combination with other treatment modalities.

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CHAPTER 4

Prognosis of patients with Hepatocellular Carcinoma treated with Transarterial Chemoembolisation: An Australian multi-centre cohort study.

Preface

Transarterial chemoembolisation (TACE) is recommended therapy for intermediate stage hepatocellular carcinoma (HCC), however, the wide variations in outcomes reflects significant heterogeneity of this patient group, highlighting the importance of patient selection in this cohort. This study evaluates the prognostic factors associated with survival in a real-world setting to identify those at high risk of a poor outcome. We screened a total of 1075 cases treated with TACE across six tertiary institutions in Victoria. Overall 431patients were eligible with unresectable HCC who underwent initial TACE after multidisciplinary team review between 2009 to 2014. Patients were identified via an extensive search of hospital databases, electronic and archived paper medical records, including pathology and radiology. Overall survival (OS) was calculated from the date of initial treatment to date of death or last follow up. All biochemical, tumour and treatment related factors were assessed using univariate and multivariate Cox regression analyses to assess the effects of baseline variables on post TACE survival.

Our study demonstrates that patients with advanced liver disease including presence of ascites and lower serum albumin, as well as those with greater tumour burden have poorer outcomes following TACE treatment. Furthermore, the aetiology of underlying liver disease, in particular chronic hepatitis B infection was associated with better overall survival. This is likely due to association of favourable characteristics in this subgroup, including HCC surveillance programs and lower rates of cirrhosis. Overall our findings are consistent with published data and reflective of current clinical practice including variations in patient selection and TACE technique. As such analysis of the Victorian cohort provides insight into factors that influence the variation in survival after TACE and are useful in improving clinical assessment and MDT guided selection of patients prior to treatment.

INTRODUCTION

Globally, HCC is the second highest cause of cancer death worldwide.[1,2] Severity of chronic liver disease is a key factor influencing overall survival in HCC, as unlike other solid tumours, significant liver dysfunction can preclude patients from treatment because of increased risks of adverse outcomes including liver failure.[3,4] In addition, the stage of liver disease at presentation influences prognosis and treatment options. In this context, the Barcelona Clinic Liver Cancer (BCLC) staging system is one of the most widely utilised treatment algorithms as it incorporates both tumour staging and liver function parameters that influence patient survival.[5–7]

The majority of patients with HCC present with intermediate (BCLC B) stage disease at diagnosis.[8–10] According to the BCLC system, transarterial chemoembolisation (TACE) is the recommended treatment for this group based on robust evidence from a meta-analysis of randomized controlled trials.[11,12] In addition, as we have previously shown, up to 40% of patients with early stage disease may receive TACE as first-line therapy because of unsuitability for resection or ablation.[13]

Notably, patients with intermediate stage disease may have asymptomatic large or multifocal intrahepatic disease in the absence of macrovascular invasion and extrahepatic metastases. In this context, the outcomes of patients having TACE are quite heterogeneous with median survival rates varying from 20-25 months in randomized controlled trials (RCT's) [14,15] to 40-45 months in more recent prospective cohort studies from Asia[16] and Europe.[17]

Such heterogeneity in survival outcomes reported across studies may be due to the wide spectrum of tumour burden and liver dysfunction observed in patients within the BCLC stage B classification. Thus, in order to better understand which patients are likely to benefit from TACE, we performed a multicenter study in a real world setting to identify pre-treatment factors associated with improved survival after TACE.

PATIENTS AND METHODS

Study population

In this multicenter, retrospective real-world study we identified patients undergoing TACE treatment for HCC from six tertiary centers in Melbourne, Australia between January 2009 and December 2014. Patients were included if they were classified as BCLC A, B, or C with relatively well preserved European Co-operative Oncology Group (ECOG) performance status of 0-2. Patients were excluded if they received TACE as bridge to liver transplantation, or if they had TACE for any diagnosis other than HCC. All included cases had undergone review at tertiary hospital multidisciplinary meetings (MDMs) and were recommended to receive TACE.

The diagnosis of HCC was based on imaging criteria or histology according to the current AASLD HCC management guidelines[18], and the presence of cirrhosis based on biochemical and radiological criteria as described previously.[13,19] Each participating institution had prospectively recorded clinical decisions and treatment outcomes on hospital specific databases for all patients with HCC who had undergone TACE. This study was approved by the Institutional Ethics Committees of each participating center. All patient data were de-identified prior to collation and statistical analysis.

TACE treatment

TACE was delivered on demand at each tertiary center according to the local Interventional Radiologist expertise using a combination of two to three chemotherapeutic agents as either an emulsion with or without lipiodol (conventional TACE [cTACE]) or via drug eluting beads with doxorubicin (DEB-TACE) as previously described.[13] Transarterial embolisation (TAE) without chemotherapy was also carried out in some centers. The method of TACE delivery, degree of cannulation of hepatic artery branches and utilization of embolisation agents such as gelfoam or polyvinyl acetate particles was also recorded. Post TACE assessment of therapy response by imaging, based on the mRECIST criteria of the target lesion, was performed by two radiologists at each center without blinding. Laboratory and clinical parameters following TACE were also recorded along with details of complications within four weeks of treatment including death, post TACE syndrome (PTS) and decompensation[12].

Data items and extraction

Data were collected and extracted via direct chart review of each institutional prospectively recorded HCC database, and of electronic and paper records of eligible cases using pre-defined data points and definitions. Demographic data collected included age, gender, and country of birth, in addition to detailed information regarding etiology and severity of underlying liver disease. Tumour specific and related variables recorded included performance status, number of tumours (1,2,3, >3), size of the largest lesions, macrovascular invasion, extrahepatic spread derived directly from pre-treatment and diagnostic imaging, serum alfa-fetoprotein (AFP) levels, and BCLC staging.

Primary endpoint

Overall survival was defined from the date of first TACE/TAE to death or last clinical follow-up up to the 31st January 2019. These data were derived from hospital based electronic records and further cross-referenced with records from the Victorian Births, Deaths and Marriages registry as previously described.[19]

Statistical Analysis

Categorical variables were summarized using counts and percentages. Continuous variables were summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR) according to data type and distribution. The Kaplan-Meier product-limit method was used to plot survival as a function of time after treatment and comparisons between curves were made with the log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazards regression to assess the effects of clinical, liver disease and tumour variables prior to the initial TACE therapy on overall survival, with results reported as hazard ratios (HR) and 95% confidence intervals.

Variables with $p \leq 0.05$ in the univariate analysis or those judged to be clinically important were considered as candidate variables for inclusion in a hierarchical regression model to identify the independent predictors of overall survival. A sub-group analysis was performed on patients with BCLC stage A or B disease who had TACE monotherapy without combination use of other treatment modalities such as radiofrequency ablation or surgical resection (Fig. 1). This subgroup excluded Child Pugh C liver disease, main branch portal vein invasion and poor performance status prior to TACE (ECOG ≥ 2) in order to assess the impact of treatment within current guidelines compared to current practice encapsulated within the overall cohort. All reported p-values are two-sided and a $p < 0.05$ was chosen to indicate statistical significance.

RESULTS

Study population

Between January 2009 to December 2014, 431 patients who underwent TACE for hepatocellular carcinoma across the six participating centers were eligible for inclusion in this study (Table 4.1). Most patients were cirrhotic (92%) and had portal hypertension (86%) at the time of diagnosis. These patients had mostly (61%) compensated Child-Pugh A cirrhosis with a smaller proportion (30%) having Child-Pugh B liver disease. The vast majority had BCLC stage A (59%) and stage B (35%) disease with a small proportion having BCLC stage C (6%) disease. Baseline characteristics including etiology of underlying chronic liver disease and pre-treatment tumour number, size and macrovascular invasion were recorded (Table 4.1). A subset of patients treated within current BCLC guidelines without combination therapies was also selected for subgroup analysis (Figure 4.1).

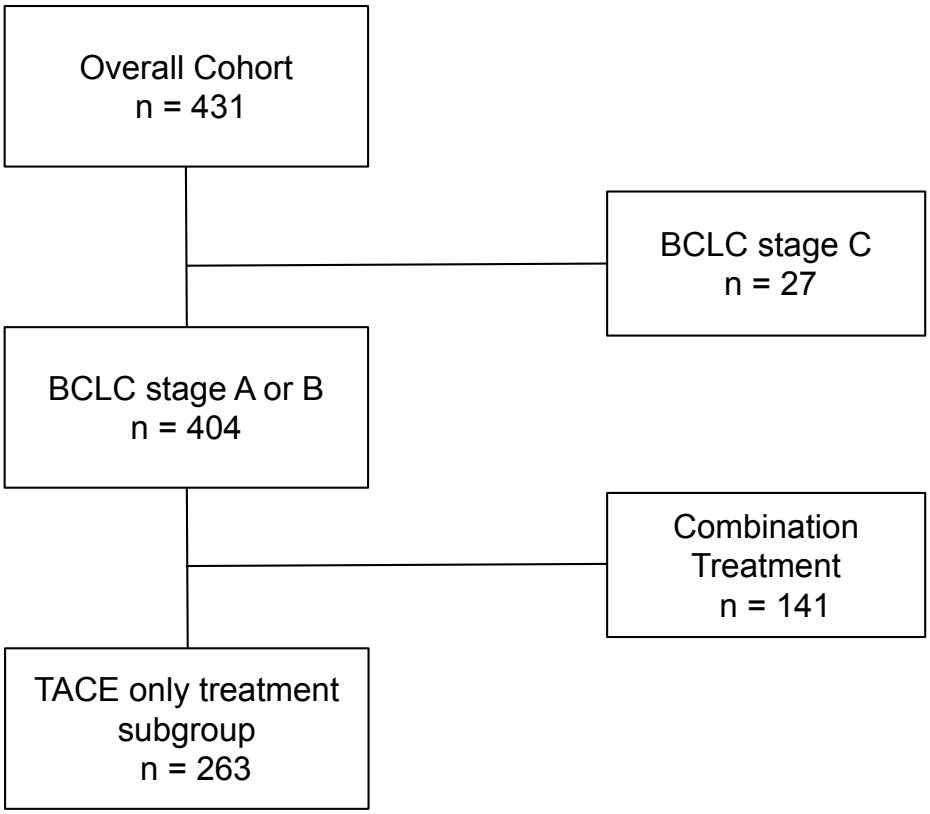
A total of 141 patients had other treatment modalities administered in combination with TACE including surgical resection and local ablation (Table 4.1). Conventional TACE was performed in the majority (81%) of patients with a smaller subset undergoing DEB TACE (19%), while selective catheterization was performed in two thirds of cases. Most patients underwent at least two cycles of TACE with a few (n=12) individuals undergoing greater than five cycles. The refined subgroup comprised 263 patients with BCLC A (61%) and BCLC B (39%) stage HCC who had undergone TACE alone.

Table 4.1. Cohort Characteristics at baseline and post initial TACE therapy in the overall cohort.

Baseline Characteristics	Overall Cohort (n=431)
Age (years), mean (SD)	66 (11)
Male, n (%)	376 (87)
Female, n(%)	55 (13)
Ethnicity, n(%)	
Caucasian	343 (80)
Asian	68 (16)
Other	20 (5)
Aetiology of Liver disease, n(%)	
HCV	167 (39)
HBV	82 (19)
NAFLD	105 (24)
Alcohol	186 (43)
Haemochromatosis	15 (3)
Other	18 (4)
BMI, mean (SD)	27 (5)
Serum markers, median (IQR)	
Haemogloblin, g/L	136(122-147)
Platelets, 10^9/L	119 (81-167)
AFP, ng/mL	17 (5-125)
ALT, U/L	46 (29-76)
Albumin, g/L	35 (31-39)
Bilirubin, µmol/L	17 (12-27)
INR	0.9 (1.0-1.3)
Creatinine, µmol/L	76 (66-90)
Na, mmol/L	139 (137-140)
Liver function, n(%)	
Portal HTN / Ascites / HE	371/62/22 (86/14/5)
Child Pugh grade (A/B)	264/129 (61/30)
MELD score	9 (7-12)
ECOG (0/1/2/3), n(%)	230/163/35 (53/38/8)
Tumour Characteristics	
Tumour Nodules (1/2/3/>3)	196/93/36/106 (45/22/8/25)
Tumour Size, cm (median, IQR)	3.4 (2.1-5.0)
MVI, n(%)	16 (4)
EHS, n(%)	12 (3)
BCLC stage (A/B/C), n(%)	253/151/27 (59/35/6)
Previous treatment, n(%)	
Resection /Ablation/PEI, n(%)	29/42/7 (7/10/2)
TACE treatments (1/2/3/>3), n(%)	138/132/80/81 (32/31/19/ 9)
Type (cTACE / DEB TACE / TAE)	337 / 89 /4 (78/ 21/ 1)
Selectivity	
selective/superselective/non selective	285 / 77/61 (66/18/14)
Post TACE, n(%)	
mRECIST Response	
CR/PR	137/158/ (32/37)
SD†/PD	43/39 (10/9)
Adverse Events	94 (22)
Death	5(1)
PTS/Decompensation	52/16 (12/4)
Renal dysfunction/other	9/24 (2/6)
Post TACE treatment	
Resection /Ablation/ PEI	16/35/12 (4/8/3)
Sorafenib	100 (23)

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional TACE; DEB TACE, drug eluting bead TACE; ECOG, Eastern Cooperative Oncology Group; EHS, extra hepatic spread; HCV, hepatitis C virus; HBV, hepatitis B virus, INR, international normalized ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumours; MVI, macrovascular invasion; N/A, not applicable; NAFLD, non-alcoholic fatty liver disease; OS, overall survival; PD, progressive disease; PEI, percutaneous ethanol injection; Portal HTN, portal hypertension; PR, partial response; PTS, post TACE syndrome; SD, standard deviation; SD†, stable disease; TACE, transarterial chemoembolisation; TAE, transarterial embolisation.

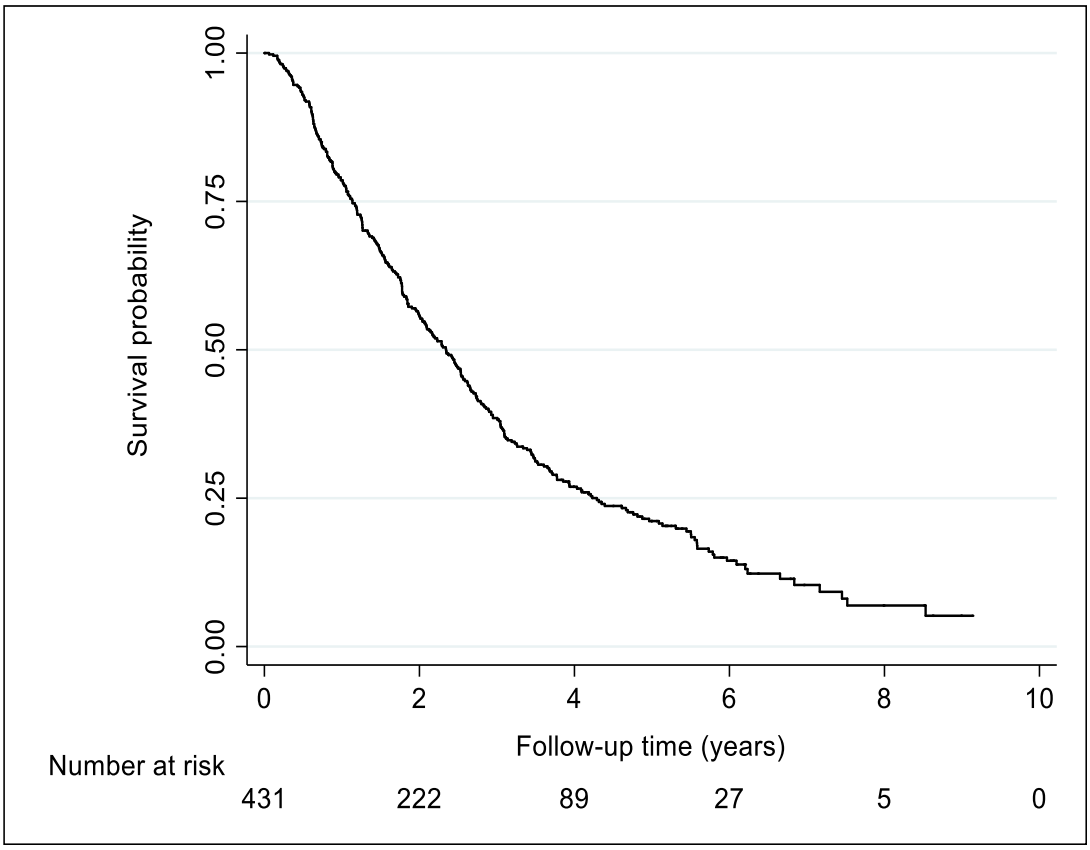
Figure 4.1. Flow chart for patients included in TACE only treatment subgroup.



Overall survival

From January 2009 to January 2019, 333 (77%) of patients had died with the remaining patients follow up censored at the date of last clinical follow up. The median OS of the group was 28 (IQR 14-51) months with a wide range of survival outcomes observed of between 1 day and 110 months (figure 4.2). The median OS of the subgroup with early or intermediate stage (BCLC stage A and B) disease treated with TACE only was 27 months (IQR 13-44) with the range being 1 day to 110 months.

Figure 4.2. Kaplan Meier curves of OS in the overall cohort



Safety

Two patients (0.5%) had severe complications resulting in death within 4 weeks of initial TACE therapy due to mesenteric ischemia, sepsis and hepatic decompensation. Other complications following TACE included liver decompensation in sixteen patients (4%), and renal dysfunction in (2%), whilst post TACE syndrome was the most common at 12% of the overall cohort (Table 4.1).

Univariate analysis of predictors of survival

Overall Cohort: On univariate analysis demographic variables associated with survival included ethnicity, and country of birth with patients of an Asian ethnicity having a better OS than Caucasian patients (p=0.001) (Table 4.2). In addition, tumour burden was associated with

a poor survival, including presence of more than three tumours (p=0.008), size of largest HCC (measured in cm) (p=0.025), and BCLC stage (p<0.0001) (Figure 4.3a). The presence of macrovascular invasion (p=0.13) and extrahepatic spread (p=0.42) were not related to survival in the small number of patients treated with advanced disease. (Table 4.1).

Notably, TACE technique type, selectivity of hepatic artery cannulation and type of embolisation material deployed did not affect survival (Table 4.2a). Combination treatment with TACE either with surgical resection (p<0.001) or ablation (p=0.003) resulted in improved OS (Table 4.2a). Multiple biochemical parameters prior to initial TACE were associated with OS including serum albumin (p<0.0001), bilirubin (p<0.0001), and sodium (p=0.026). Scores that incorporate these variables were also significantly associated with OS including the Child-Pugh grade (figure 4.3b) (p=<0.001) and MELD score (p=0.009) (Table 4.2a).

TACE only treatment subgroup: Several variables were associated with OS on univariate analysis of the refined cohort of 263 patients many of which were similar to that identified in the overall group. These include ethnicity, and pre-treatment serum albumin and bilirubin (p=<0.001) (Table 4.2b). As expected, both Child-Pugh B status and BCLC stage B disease had a negative impact on survival compared to Child-Pugh A and BCLC stage A patients respectively. Of the parameters reflective of tumour burden, only single HCC was significant (p=0.047) (Table 4.2b). TACE technique and selectivity of TACE did not influence OS (Table 4.2b). The complete table of UVA results is detailed in supplementary table 4.1a and 4.1b (Appendix A).

Table 4.2. Univariate analysis of baseline and post treatment variables associated with OS following initial TACE overall cohort (a) and TACE only subgroup (b).

a)

Overall Cohort n= 431				
Variable	**Hazard Ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Demographic				
Asian	0.59	0.43	0.82	0.001
Caucasian	1.55	1.16	2.07	0.003
HBV	0.65	0.49	0.88	0.004
Viral hepatitis treatment	0.47	0.22	1.01	0.048
Tumour characteristics				
size of largest HCC	1.05	1.00	1.09	0.025
single HCC	0.75	0.60	0.94	0.011
> 3 HCC	1.39	1.09	1.77	0.008
Serum Biochemistry				
Albumin, g/L	0.94	0.92	0.96	<0.001
Bilirubin, µmol/L	1.02	1.01	1.03	<0.001
Na, mmol/L	0.96	0.92	1.00	0.026
Severity of Liver disease				
Encephalopathy	1.66	1.06	2.62	0.024
Ascites	2.29	1.71	3.05	<0.001
Child Pugh Score	1.30	1.19	1.42	<0.001
Child Pugh grade A	0.48	0.38	0.60	<0.001
Child Pugh grade B	2.06	1.63	2.60	<0.001
MELD score	1.04	1.01	1.07	0.009
BCLC stage	1.35	1.14	1.60	<0.001
BCLC stage A	0.66	0.53	0.83	<0.001
BCLC stage B	1.44	1.15	1.81	0.001
BCLC stage C	1.33	0.86	2.05	0.191
TACE type				
cTACE	0.78	0.60	1.01	0.056
DEB TACE	1.30	0.99	1.70	0.051
TAE	1.47	0.46	4.71	0.506
TACE technique				
Non selective	1.25	0.91	1.70	0.158
Selective	0.94	0.75	1.19	0.616
Superselective	0.95	0.71	1.26	0.698
mRECIST Response				
CR	0.71	0.56	0.90	0.005
PD	2.04	1.43	2.92	<0.001
Combination therapy				
Post TACE	0.53	0.38	0.74	<0.001
Resection	0.20	0.08	0.50	<0.001
Ablation	0.51	0.32	0.81	0.003

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional TACE; CI, confidence interval; DEB TACE, drug eluting bead TACE; HBV, hepatitis B virus; mRECIST, modified Response Evaluation Criteria in Solid Tumours; OS, overall survival; PD, progressive disease; TACE, transarterial chemoembolisation; TAE, transarterial embolisation.

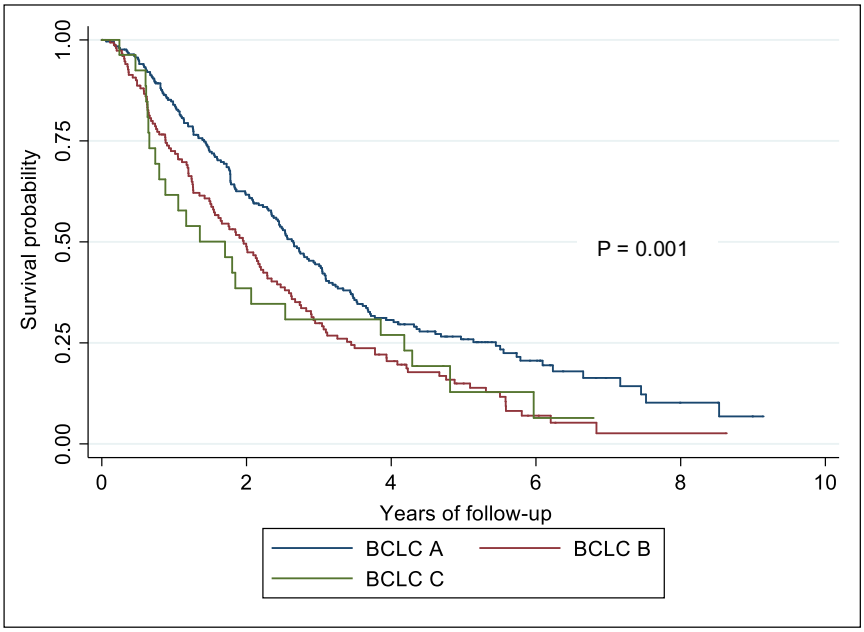
b)

TACE only subgroup n = 263				
Variable	**Hazard Ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Demographic				
Asian	0.58	0.39	0.87	0.008
Caucasian	1.68	1.15	2.45	0.006
HBV	0.80	0.55	1.15	0.216
Viral hepatitis treatment	0.27	0.10	0.74	0.010
Tumour characteristics				
size of largest HCC	1.03	0.98	1.09	0.189
single HCC	0.76	0.57	1.00	0.047
> 3 HCC	1.28	0.94	1.74	0.107
Serum Biochemistry				
Albumin, g/L	0.94	0.92	0.97	<0.001
Bilirubin, µmol/L	1.02	1.01	1.03	0.001
Na, mmol/L	0.98	0.93	1.03	0.354
Severity of Liver disease				
Encephalopathy	1.52	0.90	2.56	0.110
Ascites	1.91	1.35	2.72	<0.001
Child Pugh Score	1.32	1.19	1.47	<0.001
Child Pugh Grade A	0.46	0.34	0.61	<0.001
Child Pugh Grade B	2.14	1.60	2.86	<0.001
MELD score	1.04	1.01	1.08	0.020
BCLC stage	1.50	1.14	1.99	0.004
BCLC stage A	0.66	0.50	0.88	0.004
BCLC stage B	1.50	1.14	1.99	0.004
BCLC stage C	N/A	N/A	N/A	N/A
TACE type				
cTACE	0.85	0.61	1.18	0.320
DEB TACE	1.20	0.86	1.67	0.282
TAE	0.72	0.10	5.37	0.745
TACE technique				
Non selective	1.14	0.77	1.70	0.501
Selective	0.92	0.68	1.23	0.563
Superselective	1.14	0.80	1.64	0.457
mRECIST Response				
CR	0.83	0.61	1.13	0.228
PD	1.83	1.17	2.86	0.007
Combination therapy				
Post TACE	N/A	N/A	N/A	N/A
Resection	N/A	N/A	N/A	N/A
Ablation	N/A	N/A	N/A	N/A

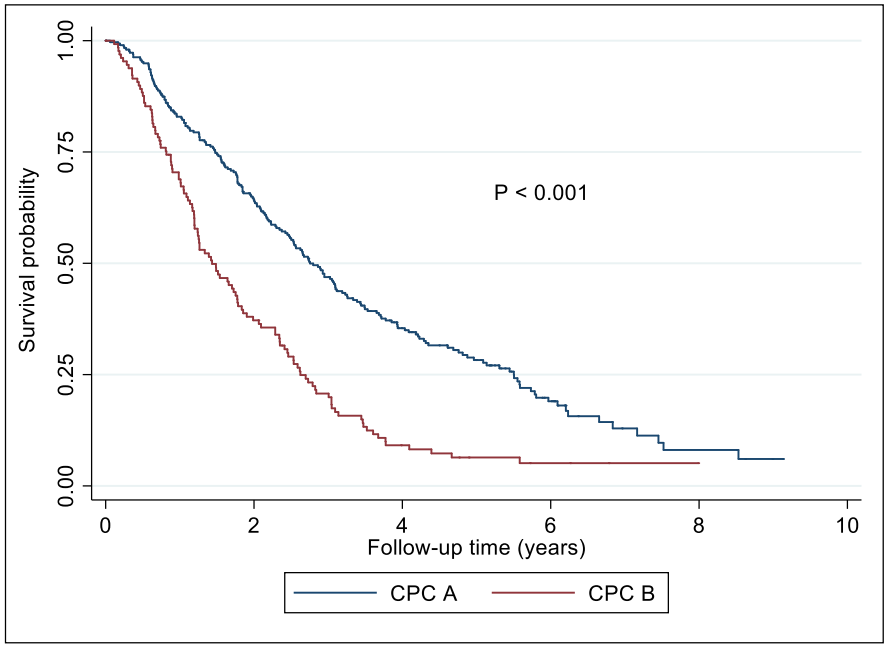
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional TACE; CI, confidence interval; DEB TACE, drug eluting bead TACE; HBV, hepatitis B virus; mRECIST, modified Response Evaluation Criteria in Solid Tumours; N/A, not applicable; OS, overall survival; PD, progressive disease; TACE, transarterial chemoembolisation; TAE, transarterial embolisation.

Figure 4.3. Kaplan Meier curves of BCLC stage (a) and Child Pugh (b) correlation with OS in the overall cohort.

(a)



(b)



Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CPC A, Child Pugh class A; CPC B, Child Pugh class B.

Multivariate analysis

Overall Cohort: On multivariate analysis, ascites pre-TACE, and larger HCC were independent predictors of poor survival whereas HBV infection as the etiology of HCC, higher serum albumin pre-treatment and single HCC were associated with improved survival after TACE (Table 4.3a).

TACE only treatment subgroup: On multivariate analysis of the TACE only subgroup, higher serum albumin ($p<0.001$) was associated with improved OS, whilst pre-treatment ascites ($p=0.008$), greater than 3 tumour nodules prior to TACE ($p=0.024$) and Caucasian ethnicity ($p=0.038$) were significantly associated with worse OS (Table 4.3b).

Table 4.3. Multivariate Analysis - Pre-TACE variables associated with overall survival in the a) overall cohort and b) the TACE only subgroup.

a)

	Overall Cohort n = 431			
Variable	**Hazard Ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Albumin	0.95	0.92	0.97	<0.0001
Ascites	2.33	1.61	3.38	<0.0001
HBV	0.61	0.43	0.86	0.005
Single HCC	0.70	0.54	0.91	0.007
Size of largest HCC	1.06	1.00	1.11	0.036

b)

	TACE only subgroup n = 263			
Variable	**Hazard Ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Albumin	0.94	0.91	0.97	<0.0001
Ascites	1.70	1.15	2.53	0.008
Caucasian ethnicity	1.59	1.03	2.48	0.038
> 3 HCC	1.53	1.06	2.21	0.024

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; OS, overall survival; TACE, transarterial chemoembolisation.

The interrelationship between characteristics associated with ethnicity and viral hepatitis B was explored further in a subgroup analysis and is summarized in supplementary Table 4.2 (Appendix A).

DISCUSSION

TACE is the recommended treatment for intermediate stage HCC: however, significant variation in survival outcomes is observed following treatment despite increased adoption of multidisciplinary based review to improve patient selection. This study is the first large multicenter Australian cohort study to evaluate pre-treatment prognostic factors associated with survival in HCC patients undergoing TACE. Our study identified that markers of hepatic function and tumour burden independently predicted the overall survival of the cohort.

Notably, markers of hepatic function prior to TACE were strongly predictive of survival with a higher serum albumin associated with lower risk of post treatment mortality in both the overall cohort and refined subgroup, whilst pre-treatment ascites carried the greatest risk of a poor outcome. These findings are consistent with previous cohort studies that have found decompensation, particularly ascites, had one of the highest risks of post TACE decompensation and poorer survival. [20,21]

Multivariate analysis also highlighted the role of tumour burden in predicting poorer outcomes following TACE. Tumour size and number were significant in the overall cohort, as patients with single HCC classified as with BCLC stage A disease (p=0.007) had better survival, compared to patients with multifocal and larger HCC stage (i.e. BCLC stage B) disease (p=0.036). Tumour number and size, along with MVI or EHS have been previously described

as surrogate markers of tumour biology and aggressiveness[22-26] and have been linked to increased risk of treatment related complications and poorer survival outcomes.[27,28]

The inherent heterogeneity of patients with unresectable HCC in relation to the variations in tumour burden and underlying hepatic dysfunction significantly influences patient outcomes after TACE. This in part explains the wide range of OS we observed in our cohort, although the median survival of the group of 28 months was considerably higher than the 19-20 months reported in an early meta-analysis of randomized controlled studies[14,15] and recently updated systematic review. [29,30]

The difference in survival outcomes may be due to several factors including the routine involvement of MDT in decision making across all sites, the utilization of aggressive treatment modalities such as surgical resection and ablation in combination with TACE, and inclusion of a significant proportion of BCLC stage A along with a small number of BCLC C stage patients (Table 4.1). Nevertheless, we also observed a respectable 27 months median survival in the subgroup of patients that had similar characteristics of cohort studies that form the basis of current TACE guidelines that being BCLC stage A or B disease patients treated with TACE alone. [16,17,21]

A novel finding of this study was that etiology of liver disease and ethnicity were prognostic markers of survival. Specifically, hepatitis B related liver disease was an independent predictor of lower mortality (p= 0.004) with a median OS of 34 months (IQR:15-72) compared to 26 months in the non-HBV group (IQR:13-45). This finding is consistent with previous studies identifying a prognostic role for HBV in HCC patients [19,31,32] and may relate to associated

factors such as participation in active HCC surveillance programs that have a positive effect on survival primarily in those with earlier stage disease.[19,32-33]

This is reflected in the more favourable clinical characteristics of patients with HBV liver disease in our overall cohort compared to non-HBV subjects including, younger age at diagnosis ($p<0.001$), and better liver reserve with lower rates of cirrhosis, (83% vs 94%), and higher serum albumin ($p=0.004$), and lower INR ($p=0.004$), and bilirubin ($p=0.015$). In addition, patients with HBV liver disease had lower rates of concomitant HCV infection ($p=0.001$) and ETOH abuse ($p=0.001$), however further subgroup analysis by other co-factors including alcohol is limited due to the relatively small number of patients within each variable (Appendix A, Supplementary Table 4.2). Commensurate with this, Caucasian ethnicity was associated with poorer TACE related outcomes on multivariate analysis in the subgroup of patients receiving TACE only treatment, likely due to lower rates of HBV related liver disease ($p<0.0001$) and higher rates of multifocal HCC (27% vs 19%) and poorer hepatic reserve (33% Child Pugh B vs. 13%).

Variables beyond BCLC stage can also determine treatment outcomes, such as variations in TACE administration and combination therapies based on the stage migration principle, whereby due to tumour location or comorbidities the individual patient is unsuitable for recommended first line treatment.[13,17,34,35] In our study, we found that the selectivity and mode of TACE utilized did not impact on overall survival regardless of which cohort was analysed. Moreover, there was no impact on survival on multivariate analysis in patients that underwent post TACE surgical resection or ablation although better outcomes were noted from combination therapies on univariate analysis in the overall cohort (Table 4.2b).

Key strengths of our study include the cohort size and multicenter design, and analysis of real-world data of BCLC stage guided treatment, reflecting current established standards of care globally. In particular the utilization HCC surveillance programs, MDT tumour board meetings, TACE techniques and mRECIST assessment of response across the six participating tertiary centers, increased the homogeneity of criteria used for diagnosis, staging and treatment allocation. Furthermore, the majority of our patients were treated within the guidelines for TACE therapy according to the BCLC staging system[36-40] with the exception of a small number of patients with BCLC stage C HCC, consistent with current real-world international practice.[39-43]

Still, the study was limited by the retrospective collection of data and the reliance on accurate records and subjectively assessed parameters such as ascites and performance status that are incorporated into the Child Pugh grade and BCLC stage respectively. Finally, survival status was known in only around 80% of the cohort, with the remainder of subjects censored at last clinical follow-up. However, there with no clinically significant differences between those in whom survival status was known and not know (data not shown).

CONCLUSION

In this large multi-centered real-world study of HCC patients undergoing TACE, we found that patients with more advanced liver disease associated with ascites and/or greater tumour burden have poorer outcomes following treatment. Such findings provide a better understanding of the variation in survival after TACE and could be potentially useful in the selection and counselling of patients undergoing this therapy.

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CHAPTER 5

Predicting Survival in Patients undergoing Transarterial Chemoembolisation for Hepatocellular Carcinoma: Comparison of current and emerging models.

Preface

Several prognostic models have been developed to improve prognostication in patient undergoing TACE for unresectable HCC. These scores have been variably validated in large international cohorts and very few have been widely adopted in clinical practice, reflecting the limitations of each model beyond their original derivation population. This study evaluates the utility of several of these models in discriminating survival outcomes in HCC patients undergoing TACE in a cohort of patients from six large Australian tertiary centres with extensive experience with TACE for unresectable HCC. We evaluated recently developed scoring models, including the HAP (Hepatoma arterial-embolisation prognostic) score, ALBI (albumin, bilirubin) and PALBI (platelets, albumin, bilirubin) grade.

The emerging TACE scores were compared with prognostic models in current clinical use, including the BCLC stage (Barcelona Clinic Liver Cancer), CPS (Child Pugh score) and MELD score using the Harrell C-index and Kaplan Meier curves. Of all the prognostic models applied to our cohort, the HAP score demonstrated superior discriminatory power in stratifying patients according to survival following initial TACE including CPS, whilst the ALBI and PALBI score had better discriminatory ability compared to the BCLC stage. Overall the widely adopted BCLC stage had the poorest discriminatory power compared to the ALBI and PALBI grades. Our study results support further development and validation of these models in larger prospective cohorts as they may better define the ideal patient population with regards to TACE therapy.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is the second highest cause of cancer related death globally with the majority of patients presenting with non-curative intermediate stage disease[1,2]. Transarterial chemoembolisation (TACE) is the standard treatment recommendation for patients with intermediate stage HCC not amenable to curative treatment options such as surgical resection or ablation.[3,4]

Accurate staging of liver dysfunction and tumour burden is a key component of treatment planning prior to TACE.[5–7] The Barcelona Clinic Liver Cancer staging system (BCLC) is one of the most widely adopted internationally as it integrates tumour stage, hepatic reserve and performance status into an evidence-based treatment algorithm.[2,6] The BCLC staging system has limitations however in its ability to capture the significant heterogeneity within the intermediate stage group with regards liver dysfunction as defined by the Child-Pugh scoring system (CPS), aetiology of liver disease, tumour biomarkers and comorbidities. All of these factors influence TACE treatment outcomes as they impact directly on TACE tolerability and overall survival (OS).[2,5,8]

Consequently, several new models have recently been developed that assess liver reserve with the aim being to improve the clinical assessment of prognosis in patients with HCC as well as appropriate treatment allocation. These models utilize several important pre-treatment markers of liver function and severity and include the HAP (Hepatoma arterial-embolisation prognostic) score, ALBI (albumin, bilirubin) and PALBI (platelets, albumin, bilirubin) grades.

However, these prognostic models have mostly been developed and validated from cohorts recruited from center(s) of excellence with limited data available to determine the validity and/or superiority of the prognostic value of one model over another in the real world setting.[9–11] Thus, we evaluated the compared the discriminatory ability and utility of several current and emerging models to predict overall survival in a multicenter cohort of HCC patients receiving TACE in the real-world setting.

METHODS

Study Population:

We identified patients undergoing TACE treatment for HCC from six separate tertiary centers in Melbourne, Australia from January 2009 to December 2014 inclusive. All patients included in this study had the diagnosis of HCC confirmed on imaging based on AASLD criteria[12] or biopsy and were deemed unresectable and/or unsuitable for liver transplantation after review by the multi-disciplinary team (MDT) at each participating hospital. All patients were recommended to receive TACE by the MDT at each hospital including conventional TACE, doxorubicin eluting beads TACE (DEB-TACE) or transarterial embolisation (TAE) therapy.

Subjects were included if they were BCLC A, B, or C with relatively well preserved European Co-operative Oncology Group (ECOG) performance status of 0-2. Exclusion criteria included prior liver transplantation or use of TACE as bridge to transplantation. Each participating institution had prospectively recorded clinical decisions and treatment outcomes on hospital specific databases of all patients with HCC who had undergone TACE. This study was approved by the Institutional Ethics Committee of each participating center with all patient data de-identified prior to collation and statistical analysis.

Data Collection:

Following approval by the respective Institutional Ethics Committees, data was collected and reviewed at each hospital by a single researcher. Variables relating to diagnosis, treatment and response included: clinical characteristics, tumour characteristics, liver disease status, type of TACE, biochemistry and haematology data, clinical response, and radiological response as defined by the mRECIST criteria[3,4].

Primary Endpoint:

The primary outcome of interest was overall survival (OS) that measured from the date of first TACE/TAE to the date of death or last follow-up. The date of death was obtained from the medical electronic records at each hospital, and if unavailable it was obtained from the Victorian Births Deaths and Marriages Registry. In cases where date of death was not available from the above, the last date of clinical review during follow up was used for censoring data at 1st January 2019.

Statistical analysis:

Categorical variables were summarized using counts and percentages. Continuous variables were summarised using means and standard deviations (SD) or medians and interquartile ranges (IQR) according to data type and distribution. Univariate and multivariate analyses were performed using Cox proportional hazards regression to assess the effects of clinical, liver disease and tumour variables prior to TACE therapy on overall survival, with results reported as hazard ratios (HR) and 95% confidence intervals. All variables with a $p < 0.05$ in the univariate analysis or those deemed clinically relevant were included in a hierarchical regression model to identify the independent predictors of overall survival.

Cox proportional hazards regression models were also used to assess the association between several current and emerging scoring systems used to predict mortality with results reported as hazard ratios (HR) and 95% confidence intervals (95% CI). The Kaplan-Meier product-limit method was used to plot survival as a function of time after treatment and comparisons between curves were made with the log-rank test.

The discriminatory ability of the scores including Child-Pugh score, MELD score, HAP score, ALBI grade, PALBI grade and BCLC stage[9-12] was determined via Harrell C index and the corresponding 95% CI. Further analysis was also performed in the pre-specified sub-group of patients in whom TACE has historically been recommended for as primary therapy being BCLC stage A or B disease patients without Child Pugh C liver disease, main branch portal vein invasion or poor performance status (ECOG ≥ 2). All reported P-values were two-sided with a P value less than 0.05 indicating statistical significance.

RESULTS

Study population

We identified 431 patients who underwent TACE treatment and met the inclusion and exclusion criteria across six participating tertiary centers from 2009-2014 inclusive (Table 5.1). The vast majority of the cohort had BCLC stage A (n= 253, 59%) or B (n=151, 35%) disease with a small proportion being BCLC stage C (n=27, 6%). The TACE only subgroup consisted of 263 patients who had not undergone any other treatments as combination pre- or post-TACE therapy (Table 5.1). This group had early stage BCLC A (61%) or intermediate stage B (39%) HCC mostly associated with well-compensated Child-Pugh cirrhosis A (61%) with a smaller proportion having Child-Pugh B liver disease (30%).

Baseline characteristics including etiology and severity of liver disease and pre-treatment nodule number, size and rates of macrovascular invasion for both the overall and TACE only subgroup shown in Table 5.1. The majority of patients were male with a mean age of 67 years with mainly viral hepatitis C viral infection (38%) and alcohol (46%) related liver disease, and 86% having portal hypertension as a result of cirrhosis. The majority of patients underwent selective cTACE with a smaller number undergoing DEB-TACE.

Overall survival

After a median follow-up of 25 months (range: 1 – 110 months), (334) 77% patients died with an estimated median OS for the whole cohort being 28 (IQR 14-51) months, and survival rates of 93%, 79%, and 67% at 6, 12 and 18 months respectively. The estimated median OS was similar in the TACE only subgroup with median OS 27 (IQR 13-44) months with a median follow up time of 24 months (range: 1 – 110 months), with survival rates at 6, 12 and 18 months of 91%, 77% and 66% respectively.

Table 5.1. Baseline characteristics of the overall cohort.

Baseline Characteristics	Overall Cohort (n=431)
Age (years), mean (SD)	66 (11)
Male / Female n (%)	376 (87) / 55 (13)
Caucasian / Asian / Other	343 (80) / 68 (16) / 20 (5)
Aetiology of Liver disease, n (%)	
HCV / HBV / NAFLD / ETOH	167 (39)/ 82 (19)/ 105 (24)/ 186 (43)
Serum markers, median (IQR)	
Platelets, 10^9/L	119 (81-167)
AFP, mcg/L	17 (5-125)
ALT, U/L	46 (29-76)
Albumin, g/L	35 (31-39)
Bilirubin, µmol/L	17 (12-27)
INR	0.9 (1.0-1.3)
Liver function, n (%)	
Portal HTN / Ascites / HE	371/62/22 (86/14/5)
Child Pugh class (A/B)	264/129 (61/30)
MELD score	9 (7-12)
Tumour Characteristics, n (%)	
Tumour Nodules (1/2/3/>3)	196/93/36/106 (45/22/8/25)
Tumour Size, cm (median, IQR)	3.4 (2.1-5.0)
Macrovascular invasion	16 (4)
Extrahepatic spread	12 (3)
BCLC stage (A/B/C), n (%)	253/151/27 (59/35/6)
TACE treatments (1/2/3/>3), n (%)	138/132/80/81 (32/ 31/ 19/ 19)
Type (cTACE / DEB TACE / TAE)	337 / 89 /4 (78/ 21/ 1)
Selectivity	
selective/superselective/non selective	285 / 77/61 (66/18/14)
Post TACE, n (%)	
mRECIST Response	
CR/PR	137/158/ (32/37)
SD†/PD	43/39 (10/9)

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional TACE; DEB TACE, drug eluting bead TACE; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end stage liver disease; mRECIST, modified Response Evaluation Criteria in Solid Tumours; N/A, not applicable; NAFLD, non alcoholic fatty liver disease; OS, overall survival; PD, progressive disease; PEI, percutaneous ethanol injection; Portal HTN, portal hypertension; PR, partial response; PTS, post TACE syndrome; SD, standard deviation; SD†, stable disease; TACE, transarterial chemoembolisation; TAE, transarterial embolisation.

Predictors of overall survival

Baseline variables significantly associated with a poor prognosis in the overall cohort on multivariate analysis included lower serum albumin (p <0.0001), presence of ascites (p<0.0001), and larger HCC (p=0.036), while presence of HBV as the etiology of HCC (p=0.005) and single HCC (p=0.007) was associated with a better survival (Table 5.2a). Multivariate analysis of the TACE only subgroup demonstrated significantly poorer survival in patients that had, lower serum albumin (p<0.001), presence of ascites (p=0.008), greater than 3 HCC (p=0.024) and Caucasian ethnicity(p =0.038) (Table 5.2b).

Table 5.2. Univariate analysis and multivariate analysis of variables associated with OS following initial TACE in the overall cohort (a) and TACE only subgroup (b).

a)

Overall cohort n= 431	**Univariate analysis**			**Multivariate analysis**		
Variable	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Baseline Characteristics						
Asian	0.59	0.43-0.82	0.001			
Caucasian	1.55	1.16-2.07	0.003			
HBV	0.65	0.49-0.88	0.004	0.61	0.43-0.86	0.005
Viral hepatitis treatment	0.47	0.22-1.01	0.048			
Tumour characteristics						
size of largest HCC	1.05	1.00-1.09	0.025	1.06	1.00-1.11	0.036
single HCC	0.75	0.60-0.94	0.011	0.70	0.54-0.91	0.007
> 3 HCC	1.39	1.09-1.77	0.008			
Serum Biochemistry						
Albumin, g/L	0.94	0.92-0.96	<0.001	0.95	0.92-0.97	<0.0001
Bilirubin, µmol/L	1.02	1.01-1.03	<0.001			
Na, mmol/L	0.96	0.92-1.00	0.026			
Severity of Liver disease						
Encephalopathy	1.66	1.06-2.62	0.024			
Ascites	2.29	1.71-3.05	<0.001	2.33	1.61-3.38	<0.0001
mRECIST Response						
CR	0.71	0.56-0.90	0.005			
PD	2.04	1.43-2.92	<0.001			

b)

TACE only subgroup n= 263	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Baseline Characteristics						
Asian	0.58	0.39-0.87	0.008			
Caucasian	1.68	1.15-2.45	0.006	1.59	1.03-2.48	0.038
HBV	0.80	0.55-1.15	0.216			
Viral hepatitis treatment	0.27	0.10-0.74	0.010			
Tumour characteristics						
size of largest HCC	1.03	0.98-1.09	0.189			
single HCC	0.76	0.57-1.00	0.047			
> 3 HCC	1.28	0.94-1.74	0.107	1.53	1.06-2.21	0.024
Serum Biochemistry						
Albumin, g/L	0.94	0.92-0.97	<0.001	0.94	0.91-0.97	<0.0001
Bilirubin, µmol/L	1.02	1.01-1.03	0.001			
Na, mmol/L	0.98	0.93-1.03	0.354			
Severity of Liver disease						
Encephalopathy	1.52	0.90-2.56	0.110			
Ascites	1.91	1.35-2.72	<0.001	1.70	1.15-2.53	0.008
mRECIST Response						
CR	0.83	0.61-1.13	0.228			
PD	1.83	1.17-2.86	0.007			

Abbreviations: CI, confidence interval; CR, complete response; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazards ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumours; OS, overall survival; PD, progressive disease; TACE, transarterial chemoembolisation;

Discriminatory ability of scoring systems to predict survival

Application of novel scores including the PALBI, ALBI and HAP scores showed significant association with OS along with the traditionally used CP score, MELD and BCLC in both overall cohort and TACE only subgroup on univariate analysis (Table 5.3). In particular, the incremental increase in the linear values associated with the logarithmic equations for the ALBI and PALBI scores had greater sensitivity, compared to the stratified grades.

Table 5.3. Univariate analysis for each scoring model with OS in the overall cohort (a) and the TACE only subgroup (b).

(a)

Overall cohort n= 431					
VARIABLE	***P* value**	**HR**	**95% CI**	**C-Index**	**95% CI**
Child Pugh Score	<0.001	1.30	1.19-1.42	0.598	0.565-0.630
Child Pugh Grade A	<0.001	0.48	0.38-0.60		
Child Pugh Grade B	<0.001	2.06	1.63-2.60		
MELD score	0.009	1.04	1.01-1.07	0.571	0.535-0.607
BCLC stage	<0.001	1.35	1.14-1.60	0.558	0.528-0.588
BCLC stage A	<0.001	0.66	0.53-0.83		
BCLC stage B	0.001	1.44	1.15-1.81		
BCLC stage C	0.191	1.33	0.86-2.05		
ALBI score	<0.001	1.88	1.55-2.28		
ALBI grade	<0.001	1.74	1.42-2.13	0.585	0.554-0.615
ALBI grade 1	<0.001	0.47	0.35-0.64		
ALBI grade 2	0.001	1.50	1.17-1.93		
ALBI grade 3	0.003	1.70	1.19-2.43		
PALBI score	<0.001	2.47	1.82-3.37		
PALBI grade	<0.001	1.52	1.30-1.78	0.594	0.560-0.628
PALBI grade 1	<0.001	0.58	0.44-0.76		
PALBI grade 2	0.815	0.97	0.77-1.22		
PALBI grade 3	<0.001	1.83	1.43-2.33		
HAP Score	<0.001	1.49	1.31-1.70	0.609	0.577-0.641
HAP grade A	0.008	0.70	0.53-0.92		
HAP grade B	0.001	0.68	0.54-0.86		
HAP grade C	<0.001	1.52	1.21-1.91		
HAP grade D	<0.001	2.73	1.89-3.94		

(b)

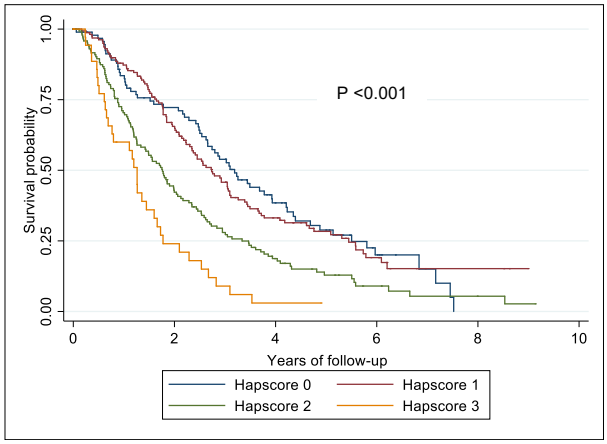
TACE only subgroup n= 263					
VARIABLE	***P* value**	**HR**	**95% CI**	**C-Index**	**95% CI**
Child Pugh Score	<0.001	1.79	1.41-2.27	0.601	0.561-0.641
Child Pugh Grade A	<0.001	0.46	0.34-0.61		
Child Pugh Grade B	<0.001	2.14	1.60-2.86		
MELD score	0.020	1.04	1.01-1.08	0.586	0.540-0.633
BCLC stage	0.004	1.50	1.14-1.99	0.549	0.513-0.586
BCLC stage A	0.004	0.66	0.50-0.88		
BCLC stage B	0.004	1.50	1.14-1.99		
BCLC stage C	N/A	N/A	N/A		
ALBI score	<0.001	1.79	1.41-2.27		
ALBI grade	<0.001	1.70	1.32-2.18	0.586	0.548-0.624
ALBI grade 1	<0.001	0.44	0.29-0.66		
ALBI grade 2	0.005	1.57	1.14-2.17		
ALBI grade 3	0.061	1.50	0.97-2.33		
PALBI score	<0.001	2.14	1.46-3.14		
PALBI grade	<0.001	1.52	1.25-1.85	0.592	0.550-0.635
PALBI grade 1	0.003	0.58	0.41-0.83		
PALBI grade 2	0.480	0.90	0.67-1.21		
PALBI grade 3	<0.001	1.82	1.35-2.46		
HAP Score	<0.001	1.44	1.21-1.70	0.598	0.558-0.638
HAP grade A	0.120	0.75	0.52-1.09		
HAP grade B	0.007	0.68	0.51-0.90		
HAP grade C	0.011	1.44	1.08-1.91		
HAP grade D	<0.001	2.34	1.48-3.70		

Abbreviations: ALBI, albumin, bilirubin ; BCLC, Barcelona Clinic Liver Cancer ; CI, confidence interval; HAP, Hepatoma arterial-embolisation prognostic ; HR, Hazard ratio; MELD, model for endstage liver disease; PALBI, platelets, albumin, bilirubin.

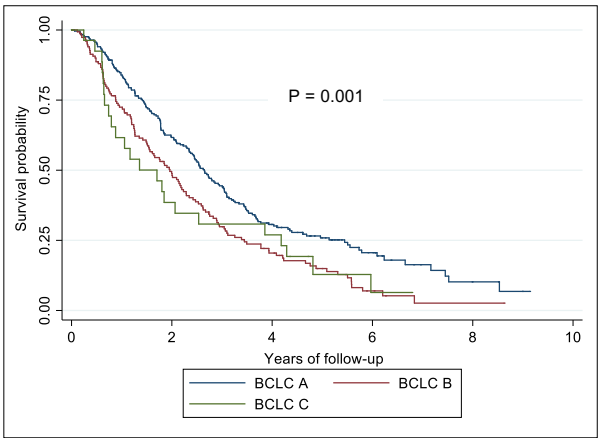
All scores were significantly correlated with OS, however their discriminatory power as measured by the Harrell C index were variable in both the real world and TACE only subgroup (Table 5.3). In the overall cohort, the HAP score had the highest discriminatory power in predicting prognosis following TACE (C-index 0.609), and was able to stratify the TACE cohort into four distinct groups as seen on Kaplan Meier curve (Fig 5.1), followed by the CPS (0.598) and PALBI grade (C-Index 0.594). In comparison, the CPS retained the highest discriminatory power in the TACE only subgroup (C-index 0.601), with the HAP score and PALBI grade also demonstrating similar ability in stratifying this group of patients with C-index of 0.598 and 0.592 respectively (Fig 5.2).

Figure 5.1. Kaplan Meier curves HAP score (a), BCLC stage (b), ALBI grade (c), PALBI grade (d), CPS category (e), and MELD score (f), correlation with OS in the overall cohort (n=431).

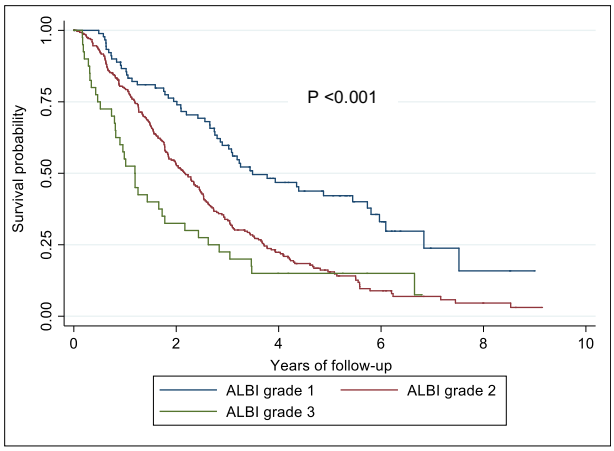
(a)



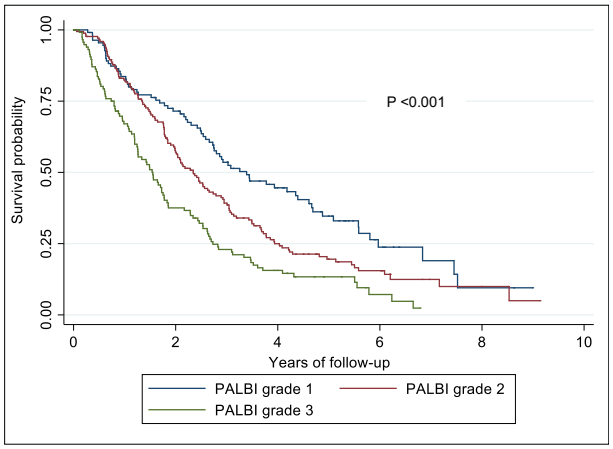
(b)



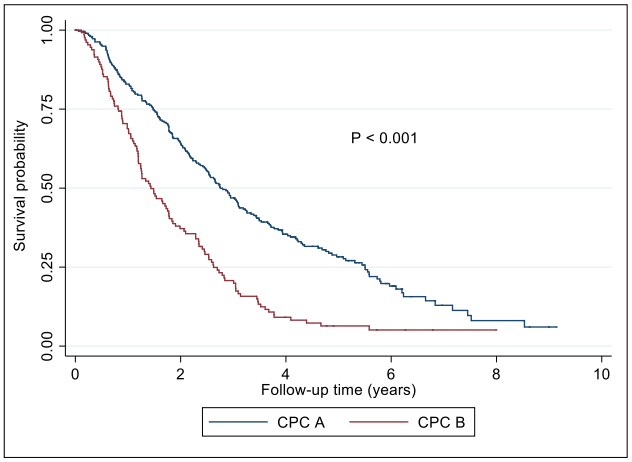
(c)



(d)



(e)



(f)

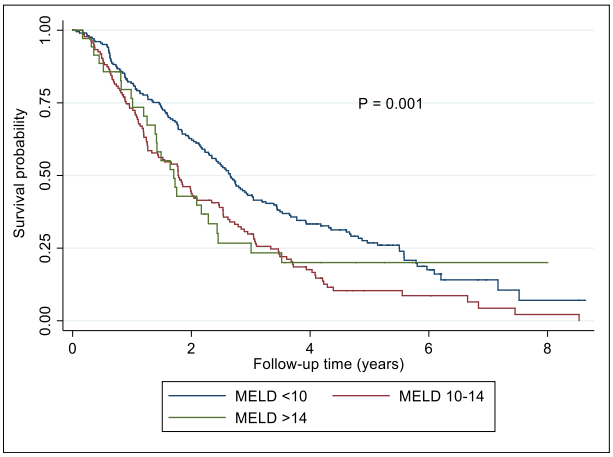
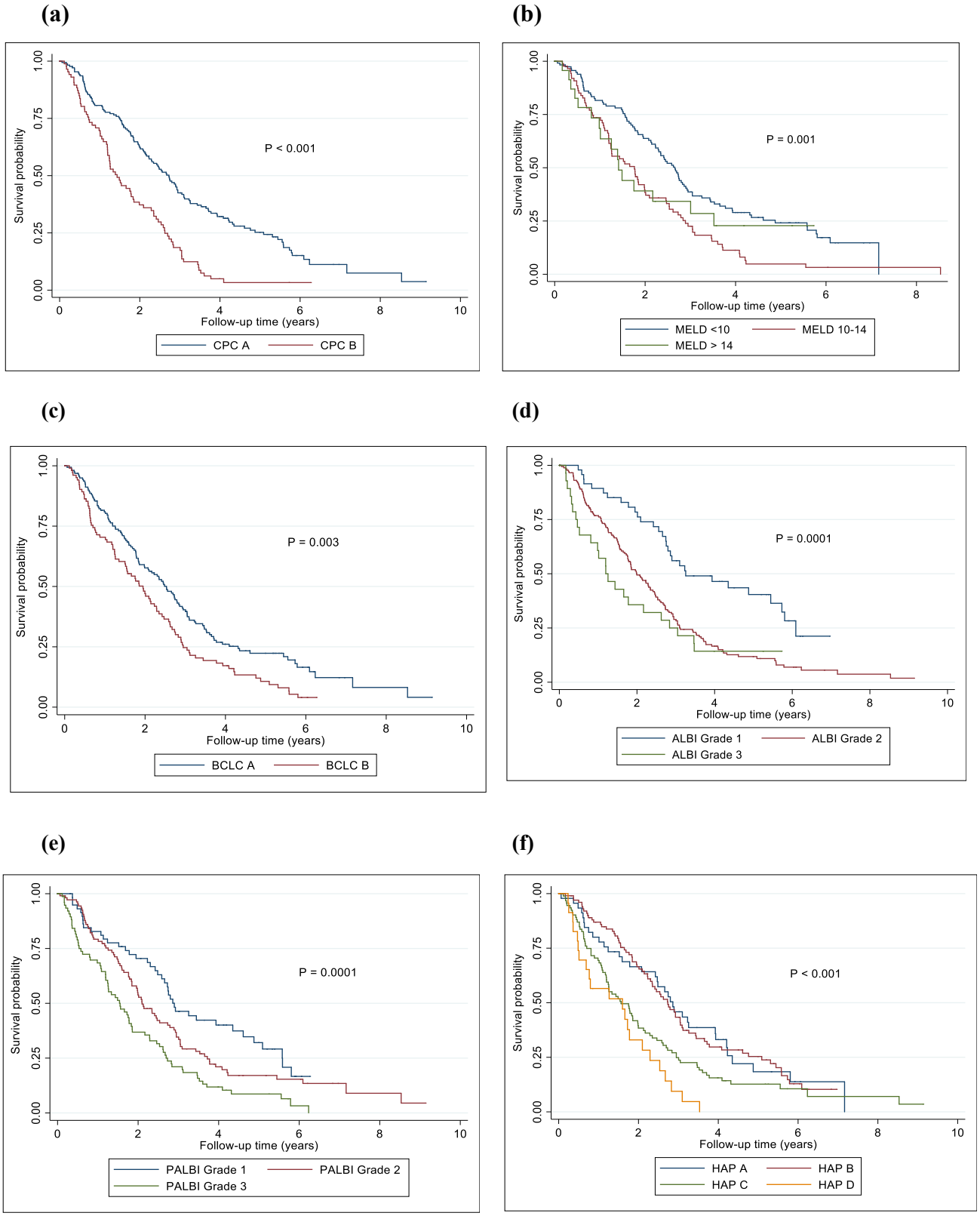


Figure 5.2. Kaplan Meier curves CPS category (a), MELD score (b), BCLC stage (c) ALBI grade (d), PALBI grade (e), HAP score (f), correlation with OS in the TACE only subgroup (n=263).



DISCUSSION

Improvements in TACE technique and patient selection have led to significant gains in median survival of HCC patients, with endorsement of its use in international guidelines. [2,13–15] However, the definition of the ideal TACE candidate differs depending on the model used for assessing liver reserve and tumour stage.[12,16–22] Moreover, most current staging systems are relatively limited in their ability to capture the heterogeneity in intermediate stage HCC. [23–25] As such multiple novel scoring systems have been developed including HAP, ALBI and PALBI to further improve the prognostic ability for clinicians when evaluating patients prior to TACE.

In this large multicentre study we evaluated and compared the prognostic performance of these and traditional scoring systems in a real-world cohort of HCC patients receiving TACE. All the models we evaluated were significantly associated with overall survival. However, the discriminatory ability of all models in stratifying patients according to prognosis was suboptimal with no scoring model achieving a C-index of >0.70 in our cohort, [14,26–28] and did not improve significantly when applied to a subgroup of patient that is typically treated with TACE alone. [5,29,33]

Notably, of all the model systems we studied for assessing hepatic reserve and tumour burden, the BCLC staging system had the lowest discriminatory power in stratifying patients according to survival.[34-37] This may reflect the limitations of a wide definition of intermediate stage disease and the influence of variables outside of the BCLC classification such as tumour markers and aetiology of liver disease.[38-40] The BCLC stage incorporates the CPS as a marker for liver reserve that also has inherent limitations secondary to subjectively measured

components such as ascites and encephalopathy, with suboptimal sensitivity in detecting variations in liver function within each grades.[2,5,34,41]

Despite these limitations the CPS had the second highest discriminatory ability of all the models, when applied to the overall cohort (0.598) and the highest C-index in the TACE only subgroup (0.60) (Table 5.3). This is likely due to the incorporation of markers of synthetic liver function in the CPS that were also significant on multivariate analysis, including serum albumin and presence of ascites. In contrast, the MELD score while overlapping with the CPS, in its components, had the second lowest C-index in both cohorts. Selection bias may influence this result as CPS is more widely utilized clinically for assessing hepatic reserve, both as a bedside marker and as part of the BCLC staging and treatment algorithm.[23,42,43] Further studies analysing the impact of a change in MELD score pre and post TACE procedure may provide greater prognostic value.[2,43,44]

Recent studies have compared the performance of various novel prognostic model's in their cohort and demonstrated the limitations of each prognostic score beyond their derivation cohort.[45-53] For example, the HAP score was modelled on a small population of 114 patients from two UK centres that comprised BCLC A (35%), BCLC B (31%), BCLC C (31%), and BCLC stage D (4%) patients.[9] In our study the HAP score had the highest discriminatory ability in the overall cohort and second highest in the TACE only subgroup as measured by the C-index (Table 5.3). The differences in the HAP scores performance may reflect differing burden of disease in the overall cohort, with inclusion of BCLC C subjects, as tumour size (a component of the HAP score) was significantly associated with survival on multivariate analysis in addition to tumour number.

Despite its superior performance in the overall cohort, the HAP score failed to reach a significant C-index of at least 0.70 when applied to our study population. While this value is consistent with that obtained in larger external validation studies[46,47], it is lower than that obtained in the derivation cohort. [9] This likely reflects the differences in TACE technique of the original HAP study, with almost half of the original cohort treated with TAE compared to 1% in our cohort. Furthermore, our cohort had higher rates of BCLC stage B disease (35% overall, 39% TACE only subgroup) and included additional adverse prognostic factors such as macrovascular invasion and extrahepatic spread, all of which may limit the HAP scores discriminatory performance in our study.[46,47]

In comparison the ALBI score was derived from a large multinational cohort[11] and included populations with varying incidence of HCC and etiologies of liver disease and included patients undergoing curative treatments including liver transplantation. Johnson et al demonstrated the ALBI grade was able to stratify patients with HCC, within the CPS A grade, into three prognostic groups, however BCLC staging information was not defined in the derivation cohort.[11] Subsequent studies have demonstrated the utility of ALBI grade to further refine the CPS. [48-51]

In our cohort the ALBI grade had inferior discriminatory power to the HAP and CPS score in both the overall and TACE only subgroup. This may be due to the lower significance of bilirubin in our cohort as a marker of liver function compared to albumin as demonstrated on the multivariate analysis, in addition to greater heterogeneity in our cohort compared to the original derivation cohort analysed by Johnson et al.[11]

The PALBI grade[10] was developed to enhance the ALBI scores discriminatory power by incorporating serum platelet count as a surrogate marker for portal hypertension severity. Our results are consistent with previous studies in demonstrating that the PALBI grade has superior performance to the ALBI grade in stratifying patients into three distinct prognostic groups in both the overall (0.594 vs 0.585) and TACE only subgroup (0.592 vs 0.586) respectively.[48,52,53] However, while earlier studies have shown that the PALBI model has superior discriminatory power compared to the traditional MELD and CPS scores for assessing liver reserve we found that the PALBI score had inferior discriminatory function overall in comparison to the CPS based on the C-index.[20,52] The suboptimal performance of the PALBI grade may reflect differences to the original derivation cohort of 3,992 patients that had better hepatic reserve (79% CPS A) and underwent curative therapies only.[10]

An important strength of our study is that it was conducted over a period in which utilization of HCC surveillance programs and MDT tumour board meetings were standard of care across all participating sites, increasing the homogeneity of criteria used for diagnosis, staging and treatment allocation. Furthermore, TACE treatment protocols were well developed within each participating centres interventional radiology department as well as utilization of mRECIST criteria for post TACE treatment response assessment. Still, there were several limitations of this study particularly relating to the retrospective analysis of data and good but incomplete collection of survival data. However, the outcomes and analysis are an accurate reflection current real-world practice as data points are prospectively recorded into MDT database at each participating hospital. Furthermore, our results are reflective of the wide ethnic diaspora of our patients and the various stages of hepatic dysfunction and tumour burden at presentation, prior to undergoing TACE treatment. [16,23,29,54,55]

CONCLUSION

Our results highlight the importance of careful patient selection prior to TACE in order to achieve optimal survival outcomes, as well as the need to define the areas of improvement within currently used clinical tools. In particular the HAP score and CPS demonstrated superior discriminatory power in stratifying patients according to survival following TACE, however their overall performance was suboptimal. Development and validation of scoring models that can define the ideal patient population with regards to TACE therapy requires further larger prospective studies that must build into their study design comparison with current models across various cohorts to ensure wide scale applicability.

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CHAPTER 6

Prognostic role of Alpha-Fetoprotein in patients with Hepatocellular Carcinoma treated with repeat Transarterial Chemoembolisation.

Preface

Patients with unresectable hepatocellular carcinoma often require repeat Transarterial chemoembolisation (TACE) therapy to achieve disease control. Several criteria have been proposed to identify patients most suitable for repeat TACE with significant variation in current international guidelines. Hence further analysis is required to identify the key prognostic factors associated with patient survival following repeat TACE to facilitate patient selection.

Derived from the original cohort we analysed patients that had undergone at least two cycles of treatment with TACE. Variables including clinical, tumour, treatment type and response factors were recorded and assessed against the primary outcome of overall survival from time of first TACE. Univariate analysis and multivariate Cox regression modelling were used to identify factors pre- and post-TACE therapy that were significantly associated with survival. The median overall survival (OS) following initial TACE was 30 months (IQR 15.2 - 50.2). On univariate analysis several variables related to baseline and post-TACE hepatic function and tumour burden were significantly associated with OS.

On multivariate analysis, hepatic decompensation following repeat TACE was associated with the highest risk of mortality following repeat TACE [HR 4.50, (1.86-10-89), p=0.001], along with baseline higher tumour number (p=0.02), higher serum bilirubin (p=0.007) and serum AFP $\geq$ 200 ng/ml (p=0.001) after the initial TACE. Our study demonstrates that serum AFP level following initial treatment in patients undergoing repeat TACE for HCC is a useful clinical prognostic marker for guiding appropriate patient selection in addition to factors associated with tumour stage and underlying hepatic dysfunction.

INTRODUCTION

The majority of patients with unresectable HCC (uHCC) will undergo repeat transarterial chemoembolisation (TACE) therapy to optimize treatment response, however a significant proportion are at risk for an adverse outcome after repeat cycles due to either tumour progression or decline in hepatic reserve.[1–4] Whilst most international guidelines provide inclusion criteria for initial TACE, clinical criteria for eligibility for repeat TACE and factors predictive of poor outcomes are inadequately defined.[5,6] In this context, several scoring systems have been developed to facilitate guidance in this area such as ART (Assessment for Retreatment with TACE)[7,8] and ABCR (Alpha-fetoprotein, BCLC stage, Child-Pugh class, and radiological response)[9] score. However, their clinical utility has been limited in part due to their complexity and/or lack of applicability to the real world setting where *on demand* TACE is commonly employed and radiological response assessment has become more refined.[10–13]

Therefore, further studies are required to identify key simple prognostic factors associated with overall survival (OS) following repeat TACE so as to improve patient selection and safety via the avoidance of unnecessary repeat procedures and unwanted side effects.[6,14] Such prognostic data will facilitate clinician decision making and potentially improve patient survival as patients undergo timely stage migration to the next treatment option such as systemic therapy.[15,16] In this study we analysed the prognostic factors associated with overall survival in patients undergoing repeat TACE and in particular the impact of the tumour marker alpha-fetoprotein (AFP). AFP is an established prognostic marker of both poorer HCC phenotype and more aggressive tumour biology.[17–22] While the optimum cut off value varies significantly in published literature on patients with HCC treated with TACE, it has been suggested that higher pre-treatment AFP is associated with earlier recurrence and poorer overall survival.[23–25]

METHODS

Study Population

We retrospectively identified patients with HCC who had undergone TACE therapy from six tertiary centers in Melbourne, Australia between January 2009 and December 2014 using established HCC databases at each hospital and review of electronic medical records. All patients had the diagnosis of HCC confirmed on biopsy or established radiological criteria[26] and were deemed suitable for TACE after review by the multi-disciplinary team at the relevant hospital. Patients were included if they were classified as BCLC stage A, B, or C with relatively well preserved European Co-operative Oncology Group (ECOG) performance status of 0-2. Subjects who had undergone at least two cycles of TACE were included, with the exception of those who were administered TACE as a bridge to liver transplantation.

Pre- and post-TACE clinical, radiological and laboratory characteristics were recorded, including presence of cirrhosis based on biochemical and radiological criteria as previously described.[16,27] Adverse events within 4 weeks of therapy were also recorded including hepatic decompensation as defined by the development of ascites, hepatic encephalopathy, hepatorenal syndrome or upper GI bleeding.[28,29] Following approval of a low-risk application to the respective Institutional Ethics Committees, data regarding patient and tumour characteristics were collected for analysis, including clinical and radiological response, as defined by the mRECIST criteria.[30,31] All patient data were de-identified prior to collation and statistical analysis.

Primary outcome

Overall survival was calculated from the date of first TACE treatment to either date of death or last clinical follow-up, with censoring at 31st January 2019. The date of death was obtained from either the patient hospital records and MDT databases at each hospital or if missing from the Victorian Death and/or Cancer Registry.

Statistical analysis

Continuous data were summarised using mean (standard deviation) or median (interquartile range) depending on the underlying distribution of the data. Categorical data were summarised using frequency tables, presenting the subject counts and percentages. Comparisons between groups (AFP < 200 versus ≥ 200 ng/ml) were made using the Student's t-test for normally distributed continuous variables, Wilcoxon rank-sum test for non-normally distributed continuous variables and chi-square or Fisher's exact test as appropriate for categorical variables.

The Kaplan-Meier product-limit method was used to plot survival as a function of time after treatment and to determine the median survival times. Comparisons between survival curves were made using the log-rank test. Univariate and multivariate analyses were performed via Cox proportional hazards regression to assess the effects of baseline clinical, liver disease, and tumour variables (pre-TACE 2) as well as tumour response variables (between TACE-1 and TACE-2) on overall survival.

Multivariate models were developed using a stepwise selection procedure and a backward elimination procedure before undergoing assessment for clinical and biological plausibility. Results from the Cox regression models were reported as hazard ratios (HR) and the

corresponding 95% confidence intervals (95% CI). All reported P-values were two-sided with a $P < 0.05$ indicating statistical significance. Analyses were performed with the SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

A total of 431 patients received TACE for HCC from 2009-2014 inclusive, of these 292 received at least two TACE treatments and were included in this study (Table 6.1). This cohort comprised mainly of BCLC stage A (57%) and B (39%) disease (Table 6.1). The majority of patients were male (87%), of Caucasian background (78%) and had predominantly alcohol (42%) or HCV (41%) related chronic liver disease. At baseline most had well compensated Child Pugh A (61%) cirrhosis with a smaller proportion having Child Pugh B disease (30%). Most patients had conventional TACE (cTACE) (79%) with the remainder receiving drug eluting beads TACE (DEB-TACE) (19%) or bland embolisation (TAE) (1%).

Incomplete radiological response of the target lesion following initial TACE was common, as defined by mRECIST with majority having partial (43%), stable (9%) or progressive (8%) disease. Repeat TACE was provided on demand in all patients at a median interval of 2.5 months (IQR 1.4-7.7) following initial TACE, with a few individuals undergoing > 6 cycles. The most common complication of TACE observed was post-TACE syndrome (13%) with liver decompensation occurring in 1% of patients.

Table 6.1. Baseline characteristics of the cohort undergoing repeat TACE therapy.

Baseline Characteristics	Overall cohort n=292
Age (years), mean, (SD)	66 (10)
Male, n (%)	254 (87)
Female, n(%)	38 (13)
Ethnicity, n(%)	
Caucasian	229 (78)
Asian	51 (17)
Other	12 (4)
Aetiology of Liver disease, n(%)	
HCV / HBV / ETOH	120/58/122 (41/20/42)
NAFLD / Haemochromatosis/ other	67/12/14 (23/4/5)
BMI, mean (SD)	26 (24-30)
Serum markers, median (IQR)	
AFP, ng/ml	19 (5-175)
ALT, U/L	49 (32-78)
Albumin, g/L	34 (31-39)
Bilirubin, µmol/L	18 (12-27)
INR	1.1 (1.0 -1.3)
Creatinine, µmol/L	75 (65-87)
Na, mmol/L	139 (137-140)
Liver function, n(%)	
Portal HTN / Ascites / HE	253/39/16 (87/13/5)
Child Pugh Score (A/B)	178/88/(61/30)
MELD score	9 (7-11)
ECOG (0/1), n(%)	127/165 (43/57)
Tumour Characteristics	
Tumour Nodules (1/2/3/>3)	127/65/20/80 (43/22/7/27)
Tumour Size, cm (median, IQR)	3.3 (2.0-5.0)
Macrovascular invasion, n(%)	9 (3)
Extrahepatic spread, n(%)	5 (2)
BCLC stage (A/B/C), n(%)	166/113/13 (57/39/4)
TACE treatments (2/3/>3) n(%)	132/80/80 (45/27/27)
Type (cTACE / DEB TACE / TAE)	232/56/3 (79/19/1)
Selectivity	
selective/superselective/non selective	197/48/43 (67/16/15)
mRECIST Response, n(%)	
Complete/Partial	69/127 (24 /43)
Stable/Progressive	26/22 (9/8)
Adverse Events, n(%)	
Death	3 (1)
Post TACE syndrome/Decompensation	38/4 (13/1)
Renal dysfunction/other	3/12 (1/4)
Post TACE Treatment, n(%)	59 (20)
Resection/Ablation/PEI/Sirtex	8/33/11/9 (3/11/4/3)

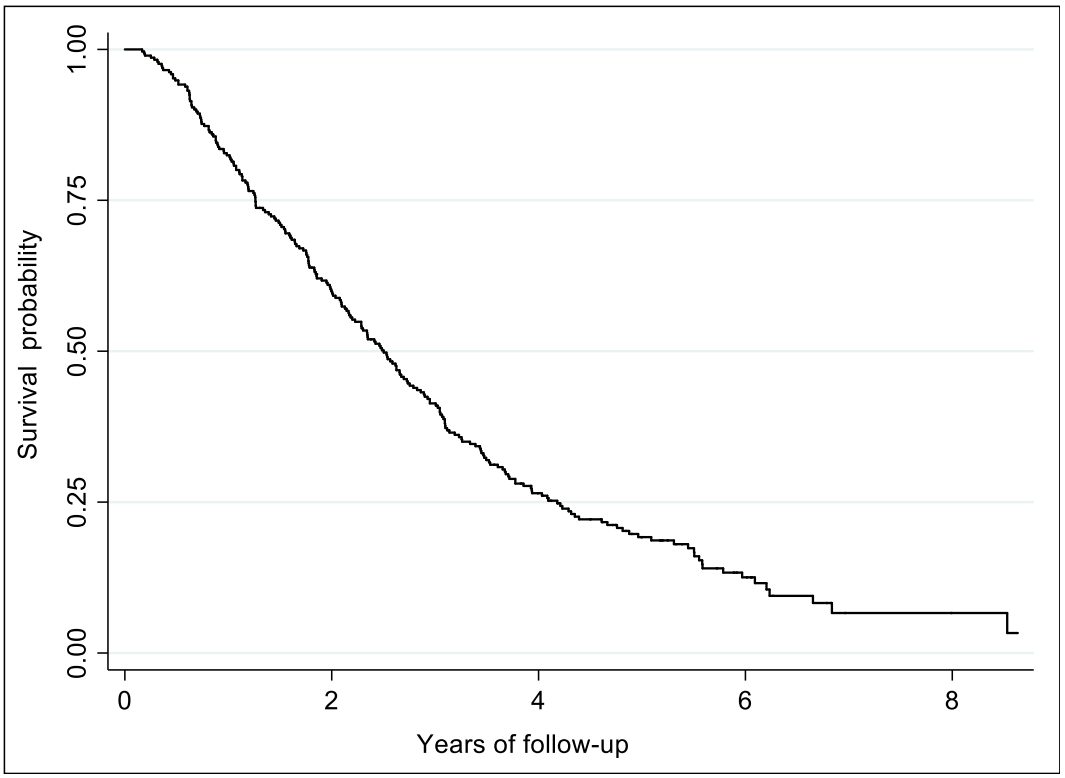
Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional TACE; DEB TACE, drug eluting bead TACE; ETOH, alcohol; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalized ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumours; NAFLD, non-alcoholic fatty liver disease; OS, overall survival; PEI percutaneous ethanol injection; Portal HTN, portal hypertension; PTS, post TACE syndrome; SD, standard deviation; TACE, transarterial chemoembolisation; TAE, transarterial embolisation.

Serum AFP data was available in 260 (89%) patients prior to initial TACE, with the median baseline AFP level being 19 ng/ml (IQR 5-174.5). Of these patients, 135 (52%) had levels below 20 ng/ml, 60 patients (23%) had AFP ≥ 200 and 45 (17%) were ≥ 400 ng/ml prior to initial TACE. Following initial TACE, 110 patients (42%) had AFP of < 20 ng/ml, while 30 (12%) and 23 (9%) had AFP ≥ 200 ng/ml and ≥ 400 ng/ml respectively. In total, 177 (61%) of the overall cohort had AFP data available prior to both their first and second TACE for comparative analysis. Of these 30 patients (17%) had an AFP ≥ 200 ng/ml following initial TACE therapy and 147 (83%) had an AFP < 200 ng/ml.

Overall survival

During a median follow-up of 28 months (IQR 14.8-45.4) after the initial TACE, there were 82 (28%) patients who died. The median overall survival from time of first TACE therapy was 30 months (IQR 15.2 - 50.2) (figure 6.1).

Figure 6.1. Kaplan Meier survival analysis of the overall cohort undergoing repeat TACE (n = 292)



Predictors of overall survival

Univariate analysis: Univariate analysis compared all variables associated with OS encompassing hepatic synthetic function, tumour-related factors both pre- and post-initial TACE and radiological response (mRECIST). Baseline variables pre-initial TACE associated with improved survival in patients undergoing repeat TACE included single tumour (p=0.043), BCLC stage A (p=0.026) and higher serum albumin (p<0.001) (Table 6.2a).

In contrast, variables reflective of lower hepatic reserve prior to both initial and repeat TACE including higher CP score (p<0.001), serum bilirubin (p<0.001), liver decompensation (p<0.001) and ascites (p<0.001) were significantly associated with reduced OS (Table 6.2a, 6.2b). Of note, renal dysfunction following the second TACE was associated with the highest risk of mortality [HR 3.46 (1.07-11.19), p=0.03] (Table 6.2b).

Table 6.2. Univariate analysis of variables associated with overall survival in patients undergoing repeat TACE, with baseline variables (a) and subsequent to initial TACE (b).

(a)

Pre -TACE 1	**OVERALL COHORT n= 292**			
Variable	**Hazard Ratio**	**Lower 95% CI**	**Higher 95% CI**	**P value**
Single Tumour	0.76	0.59	1.00	0.043
Albumin, g/L	0.96	0.94	0.98	<0.001
Bilirubin, µmol/L	1.02	1.01	1.03	<0.001
Ascites	1.94	1.35	2.78	<0.001
Hepatic Encephalopathy	1.70	0.99	2.90	0.048
BCLC stage A	0.75	0.58	0.97	0.026
BCLC stage B	1.36	1.04	1.77	0.020
Child Pugh Score (5/6/7/8/9)	1.25	1.13	1.39	<0.001

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; INR, international normalized ratio; MELD, model for end stage liver disease; TACE, transarterial chemoembolisation.

Analysis of serum AFP as a continuous variable demonstrated a higher serum AFP following initial TACE was associated with lower survival ($p<0.001$) in patients undergoing repeat TACE. For increased interpretability of HR and CI the application of serum cut-off levels of 200 ng/ml and 400 ng/ml, demonstrated a significant relationship between both pre and post treatment serum AFP and overall survival (Table 6.3).

Table 6.3. Univariate analysis of pre and post initial TACE serum AFP levels and association with overall survival.

Variable	n	%	Hazard Ratio	Lower 95% CI	Higher 95% CI	P value
Baseline AFP ≥ 200 ng/ml	260	23%	1.48	1.07	2.04	0.015
Post initial TACE AFP ≥ 200 ng/ml	177	17%	2.19	1.43	3.36	<0.001
Baseline AFP ≥ 400 ng/ml	260	17%	1.36	0.95	1.95	0.088
Post Initial TACE AFP ≥ 400 ng/ml	177	13%	2.41	1.49	3.90	<0.001

Abbreviations: AFP, alpha-fetoprotein; TACE, transarterial chemoembolisation.

Multivariate analysis: On multivariate analysis, factors significantly associated with lower survival in patients undergoing repeat TACE included an increase in number of tumour nodules at baseline ($p=0.02$), a serum AFP ≥200 ng/ml ($p=0.001$) and higher bilirubin following initial TACE ($p=0.007$), and liver decompensation following repeat TACE ($p=0.001$).

Table 6.4. Multivariate analysis of variables associated with overall survival in patients undergoing repeat TACE.

Overall cohort n= 292				
Variable	**Hazard Ratio**	**Lower 95% CI**	**Higher 95% CI**	**P value**
Baseline tumour number, 1, 2,3, > 3	1.18	1.03	1.36	0.020
Bilirubin post TACE 1	1.02	1.00	1.03	0.007
AFP ≥ 200 ng/ml post TACE 1	2.13	1.34	3.40	0.001
Decompensation post TACE 2	4.50	1.86	10.89	0.001

Abbreviations: AFP, alpha-fetoprotein; TACE, transarterial chemoembolisation.

Relationship between AFP and overall survival

On further subgroup analysis patients with a higher serum AFP ≥ 200 ng/ml following initial TACE had a significantly lower overall survival with median OS of 18.2 months (IQR 9.2 to 26.1) compared to those with serum AFP < 200 ng/ml of 31.1 months (IQR 18.7 to 55.4) (Figure 6.2). Further comparative analysis of the characteristics of these two subgroups (Table 6.5) found that patients with AFP ≥ 200 ng/ml had greater tumour burden at baseline as identified by BCLC stage C (p=0.017), larger mean tumour size (p=0.002), and macrovascular invasion (p=0.035) compared to patients with AFP < 200 ng/ml following initial TACE. In comparison, patients with serum AFP < 200 ng/ml were less likely to have underlying HCV (p=0.0-4) or HBV (0.05), higher rates of T2DM (p=0.05) and lower inflammatory response following TACE with lower serum neutrophils (p=0.001) and ALT (p=0.03).

Figure 6.2. Kaplan Meier survival analysis of patients with an serum AFP above or below 200ng/ml post initial TACE (AFP1).

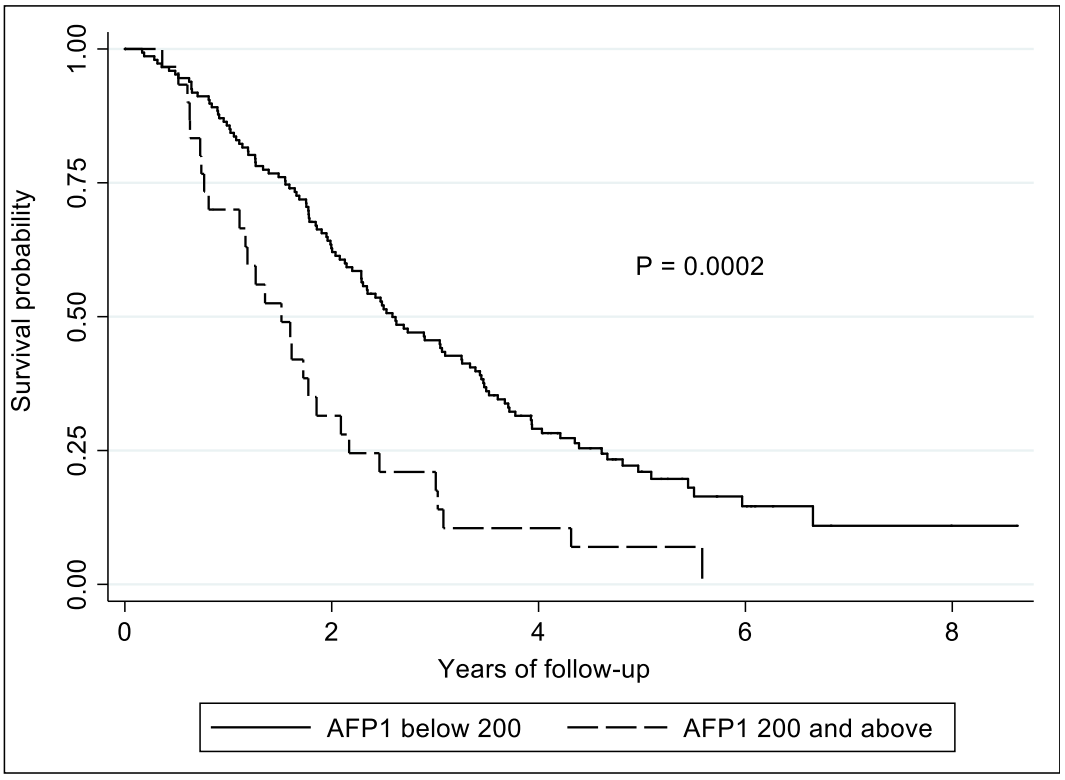


Table 6.5. Characteristics of patients following initial TACE with AFP ≥ 200 ng/ml vs. < 200 ng/ml.

Repeat serum AFP subgroup n= 177					
Variable	**n**	**AFP < 200 ng/ml**	**n**	**AFP ≥ 200 ng/ml**	**P value**
Pre-TACE, % (n)					
Caucasian	147	83.7% (123)	30	63.3% (19)	0.011
HCV	147	41.5% (61)	30	70% (21)	0.004
HBV	147	17.7% (26)	30	33.3% (10)	0.05
T2DM	147	34.7% (51)	30	16.7% (5)	0.05
BCLC stage C	147	2% (3)	30	13.3% (4)	0.017
Macrovascular invasion	147	1.4% (2)	30	10% (3)	0.035
tumour size, (cm), mean (SD)	147	3.84 (2.55)	30	5.64 (3.89)	0.002
Post initial TACE, median (IQR)					
Neutrophils, x10^9/L	91	2.9 [2.3-3.72]	23	4.2 [2.9-5.1]	0.001
ALT, U/L	146	38.5 [24-72]	29	65 [34-100]	0.03
Na, mmol/L	145	138 [136-140]	28	137 [135-139]	0.048

Abbreviations: ALT, alanine transaminase ; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; T2DM, type 2 diabetes mellitus; Na, serum sodium; SD, standard deviation.

To further explore the relationship between OS and AFP levels, we analysed the survival of patients according to the pattern of change in serum AFP levels < and ≥ 200 ng/ml pre- and post-initial TACE. Notably, the median survival of patients with an AFP ≥ 200 ng/ml both pre- and post-initial was similar to subjects whose level fell below 200 ng/ml after TACE (18.6 vs 19.9 months) (Table 6.6). In comparison, the median OS of patients whose AFP remained < 200 ng/ml both pre- and post-initial TACE was significantly higher at 34.7 months compared to the groups whose AFP level was either ≥ 200 ng/ml at baseline or increased to ≥ 200 ng/ml after initial TACE (p=0.0001) (Table 6.6).

Table 6.6. Median survival time by AFP level < or ≥ 200ng/ml pre and post initial TACE, labelled as AFP0 and AFP1 respectively.

AFP groups	n	Median Survival time, months(IQR)	P value
AFP0 < 200 and AFP1 < 200	135	34.7 (19.9 - 56.1)	0.0001
AFP0 < 200 and AFP1 ≥ 200	5	19.4 (14.2 - 29.6)	
AFP0 ≥ 200 and AFP1 < 200	12	19.9 (13.3 - 27.7)	
AFP0 ≥ 200 and AFP1 ≥ 200	25	18.2 (9.2 - 26.1)	

Abbreviations: AFP, alpha-fetoprotein

DISCUSSION

TACE is an effective treatment in eligible patients with uHCC, however the majority of patients treated with TACE will require repeat therapy due to a partial response or tumour recurrence. Treatment outcomes after TACE are influenced by both the severity of underlying liver dysfunction and tumour burden[1–3,32], and as such the indications and criteria for repeat TACE remain variably defined and adopted in International guidelines.[5,26,33,34] We therefore explored the factors associated with overall survival in patients having repeat TACE in a real-world multicenter cohort focusing particularly on the prognostic role of serum AFP level.

Serum AFP as a marker of tumour burden has been previously proposed as a prognostic marker in patients undergoing TACE for uHCC.[35–38] However, the prognostic role of serial changes in serum AFP levels following TACE has been controversial as not all HCC produce AFP, and false positive results not infrequently occur such as in active viral hepatitis.[36,39–41] Consequently, a wide variety of serum cut off values have been postulated ranging from 20-400 ng/ml, as well as variations in serum AFP response ranging from 20% to 50% based on the AUROC of the derivation cohort.[42–48] Notably, application of these percentage change values in pre and post treatment AFP had no significant prognostic effect on OS in our cohort,

and may reflect the inherent differences in our characteristics at baseline and also the inability of the delta value to capture the wide variations in serum AFP levels associated with HCC. [49]

In contrast several recent studies including a meta-analysis have demonstrated a significant association of specific serum levels of AFP with HCC treatment outcomes including treatment response and overall survival.[43,50,51] In a recent prognostic model Wang et al found the serum AFP of 400 ng/ml was a useful cut off value in a population with predominantly HBV related liver disease.[38,45] They found the AFP response following TACE independently associated with prognosis in BCLC stage B patients, however further analysis regarding combination therapy with other treatments such as ablation or systemic therapies was not available.

When applied to our cohort, we found serum AFP cut off level of 200 ng/ml had the greatest stratification compared to an AFP <20 ng/ml that was seen in 135 (52%) and AFP < 400 ng/ml in 215 (83%) of patients. This AFP value has the potential advantage over the lower cut off value of < 20 ng/ml in being less likely to include those with an elevated level due to active liver disease such as such as with chronic viral hepatitis.[36,41] A serum AFP < 200 ng/ml was a significant prognostic marker both pre and post initial TACE associated with better overall survival outcomes (figure 6.2). Patients that maintained an AFP < 200 ng/ml at baseline and following initial TACE had a significantly better survival outcome (p=0.0001) compared to patients that had a higher baseline AFP ≥ 200 ng/ml regardless of a post treatment change in levels. The poorer prognosis in patients with AFP ≥ 200 ng/ml following TACE may relate to the greater tumour burden at baseline including tumour size (p=0.002) and macrovascular invasion (p=0.035) along with greater inflammatory response to treatment with higher serum ALT (p=0.03) and neutrophil count (0.001). Further detailed analysis of serum AFP pre and post TACE is limited by small number of patients in each subgroup.

Our results are consistent with recent updates in international guidelines[26,52] that have endorsed the revised cut off of 200 ng/ml from the previously used 400 ng/ml due to superior sensitivity and specificity and nearly 99% positive predictive value.[36,49,53] In particular explant studies have demonstrated higher AFP levels ≥ 200 ng/ml are associated with higher risk of both microvascular and macrovascular invasion, along with poorly differentiated tumours as was demonstrated in our analysis (Table 6.3).[21,54] However, the reduced availability of repeat AFP data in 61% of our overall cohort limits the generalisability of our findings particularly in cases of non-AFP producing HCC.

Along with AFP level, we found like others on multivariate analysis that markers of both hepatic reserve and tumour burden are key prognostic markers being associated with poorer survival following repeat TACE. [14,55–59] In particular, decreasing liver reserve had the greatest impact on mortality in our cohort with post TACE liver failure and decompensation associated with the highest risk of reduced survival [HR 4.50, (95% CI 1.86-10.89), (p=0.001)]. Although this occurred in only 1% of our patients and is generally thought to be low in incidence (2-7%),[60–62] the frequency of liver decompensation may be as high as 18% following TACE depending on the definition used.[30,63–65] We also found like others that decline in liver function as measured by higher serum bilirubin prior to repeat TACE was associated with reduced survival.[66–68] This again highlights the prognostic importance of liver reserve following TACE because discontinuation of TACE due to liver decompensation and/or biochemical decline carries a poorer prognosis than when it is due to radiological progression. Indeed, most patients with significant hyperbilirubinaemia are unsuitable for or intolerant of further therapies such as systemic therapy and are managed with best supportive care. [69–71]

In addition, the number of tumour nodules prior to initial TACE was a significant and independent prognostic marker following repeat TACE in our cohort being associated with a higher risk of mortality. This is similar to the findings of several previous studies.[57,72,73] Furthermore, greater tumour size at baseline was significantly associated with higher serum AFP ≥ 200 ng/ml following initial TACE which was one of the key prognostic determinants associated with lower OS on multivariate analysis (Table 6.4).

As noted above an important limitation of our study was the reduced availability of serial AFP levels before and after the initial TACE to explore the relationship with survival further. However, there was only minimal differences in the characteristics in those without follow up AFP levels, with lower rates of HCV infection (p=0.024), higher NAFLD (p=0.03), and higher proportion of single HCC (p=0.03) (data not shown). Other study limitations include the retrospective analysis of data with resultant variations in the timing of serum collection pre and post TACE as well as variations in on-site specific protocols, and this may impact on the interpretation of results that are influenced by post treatment hepatic dysfunction and inflammation such as serum AFP.[36,41]

Our study also includes patients undergoing combination therapies with TACE and a small number of BCLC stage C (4%) patients that underwent TACE outside of current guidelines, consistent with contemporary real-world studies analysing global patterns of TACE utilisation.[15,16] Despite these limitations this is a large study analyzing prognostic factors in patients undergoing repeat TACE on demand for uHCC over a significant period of 6 years across six large tertiary referral centres. As such these results have greater clinical relevancy to current clinical practice as the data incorporates variations in patient selection, TACE type (conventional or DEB), and technique (selective or super selective).

CONCLUSION

Patient selection for repeat TACE requires a careful balance between the risks of complications and benefits with evaluation of factors associated with poor outcomes including baseline tumour burden, and decline in liver reserve following repeat treatment. In particular serum AFP ≥ 200 ng/ml post initial TACE is a useful prognostic marker associated with significantly poor outcomes in those following repeat TACE.

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CHAPTER 7

Conclusion and Future Directions

Hepatocellular carcinoma has a growing global health burden with increasing incidence and mortality. This is largely due to the presentation and diagnosis of this tumour at a non-curative stage of disease, with the additional competing mortality associated with underlying chronic liver disease. As a result, TACE has become the recommended treatment for patients with unresectable HCC to achieve control of disease and in some cases to facilitate curative therapies such as ablation and liver transplantation through down staging tumour burden. The technique of administering and delivering TACE has had significant improvements in last 40 years, along with increased standardisation of guidelines for patient selection led by multidisciplinary teams. However, despite these advances there remains significant variation in survival outcomes. As a result, multiple prognostic scores have been developed to improve clinical assessment, with variable performance in external validation studies, and a paucity of data comparing current and emerging prognostic models in our Australian cohort.

Thus, this thesis and its included papers evaluated the factors associated with prognosis in patients with HCC undergoing TACE through the application of novel scoring algorithms to an Australian cohort. Firstly, a comprehensive meta-analysis and systematic review was carried out of the ALBI grade, a novel prognostic score that has gained significant international attention due to its potential to enhance clinical stratification of risk and thus improve allocation of HCC treatment for patients. In particular the ALBI grade has been trialled as an adjunct to the Child Pugh Score for assessing hepatic reserve at some tertiary centres, including Australia.

Our systematic review and metanalysis of the ALBI grade demonstrated that the ALBI grade is a clinically useful prognostic tool that can assist clinicians in patient selection with validation in a large cohort of patients derived from a heterogenous international population

with HCC treated with TACE. However, its performance in comparison to currently used tools for assessing hepatic reserve such as the Child Pugh score was variable across the included patient cohort, suggesting that its performance may not be superior across an international population of patients undergoing TACE. This may relate directly to the differences between the original derivation cohort and the characteristics of the patient pool in the meta-analysis, with greater proportion of patients with early stage HCC and preserved liver function. Further subgroup analysis of the more heterogeneous group of intermediate stage patients undergoing TACE was limited due to availability of data regarding BCLC staging in the included studies.

The subsequent chapter of this thesis reports the results of a multicentre retrospective study capturing TACE treatment in current clinical practice, and evaluates the variables associated with overall survival. This study is the first large multi-centre Australian study of TACE therapy outcomes for unresectable HCC. Our analysis found that the technique and mode of TACE delivery varied across the participating centres, including the type of TACE, embolization materials and selectivity of angiographic catheterisation of the hepatic arterial branches (supplementary table 4.1a-b). Reassuringly these differences in TACE practice did not significantly influence overall survival outcomes in our cohort.

In contrast the severity of underlying liver dysfunction and tumour burden along with aetiology of underlying liver disease were the most significant factors that influenced treatment outcomes. These results are in keeping with previously published literature, however the association of chronic hepatitis B with favourable TACE response was likely influenced by lower rates of cirrhosis and advanced liver disease in addition to participation in established screening programs.

The baseline data in our Australian population allowed for application and comparison of both current and emerging prognostic scoring models that have been recently developed and validated in patients with HCC undergoing TACE. We analysed the performance emerging novel makers, including the HAP score, ALBI and PALBI grade, in comparison to the current widely used clinical tools, including the BCLC stage, CPS, and MELD score. Notably the HAP score, incorporating the serum biomarker of AFP had the highest discriminatory value as measured by the Harrel C-index, whilst the currently used BCLC staging system had the lowest performance. However, overall none of the prognostic scores and models that were analysed had clinically satisfactory performance in our cohort and therefore reinforce the requirement for further development of novel and clinically useful scoring systems for patients undergoing TACE.

As the majority of patients in our cohort underwent repeat TACE therapy, we also evaluated prognostic factors associated with overall survival in this subgroup of patients. Our analysis demonstrated that in addition to tumour burden and hepatic function, the serum tumour biomarker, AFP, is a significant prognostic factor associated with overall survival. In particular, patients that maintained an AFP < 200 ng/ml pre and post initial TACE therapy had significantly better post treatment survival, consistent with recent studies and supportive of incorporation of AFP in clinical guidelines for patient selection for those considered for repeat TACE. However, further large validation studies are required to derive the optimal serum cut off values, and investigation into other serum biomarkers associated with HCC as AFP is not detectable in a significant proportion of HCC.

The significance of serum AFP as a prognostic marker in our cohort and as a key component of the novel HAP score underlines the ongoing deficits in our current prognostic staging

systems. These include the omission of other key variables such as post treatment mRECIST response and decompensation that were significant in our cohort on univariate analysis. In contrast other factors such as ECOG based performance status did not carry any significant prognostic value despite their incorporation into the currently BCLC staging and treatment algorithm. This may reflect the clinical challenge of differentiating between functional impairments due to underlying chronic liver disease, from the superimposed burden of tumour related symptoms.

Based on these results we plan future development of a TACE specific prognostic model, incorporating additional prognostic variables significant on multivariate analysis in our cohort. The prognostic model would be tested in patients undergoing both initial and repeat TACE, with further external validation in a larger multicentre study of patients treated with TACE derived from external tertiary treatment centres.

The main limitation of our study is the retrospective nature of data capture across the six tertiary sites from which our cohort is derived. As such all analysis of results require consideration of the inherent treatment and reporting bias due to site specific availability of equipment and technical expertise. This includes the treatment and assessment of response by unblinded clinicians, and Radiologists as per routine standard of care.

Combination therapies both pre and post initial TACE were utilised in over one third of our study cohort, capturing the limitations of current treatment algorithms with regards to optimal timing of stage migration. The benefit in survival outcomes observed in patients undergoing post TACE ablation and resection are likely due to the selection bias of patients with relatively preserved liver function and utilisation of TACE for downstaging tumour burden.

Thus, we aim to further analyse factors associated with prognosis in patients undergoing combination therapies in future subgroup analysis.

Similarly, a small proportion of patients with advanced stage HCC were also treated with TACE, consistent with international cohort studies of TACE utilisation beyond the BCLC algorithm. This practice is influenced by site specific practice, and the variable definition of TACE refractory status and failure in current guidelines. In particular, enrolment of patients into clinical trials or systemic therapy can be based on combination of both clinical and biochemical response to treatment and time to tumour progression. As such subgroup analysis of our baseline cohort excluding advanced HCC stage (BCLC stage C) and combination therapies was important to elucidate the true benefit of TACE when applied to the 'ideal' candidate patient.

Overall, the survival outcomes of patients undergoing TACE for unresectable HCC in Australia are comparable to international cohorts, however there remains significant variability in outcomes and clinical practice. The four studies outlined in this thesis demonstrate the importance of careful patient selection including assessment of both underlying hepatic reserve and tumour parametres when evaluating suitability of patient's with unresectable HCC for TACE treatment. Further large prospectively designed studies are required to validate the performance of prognostic models outlined in the previous chapters, and to develop a scoring system that optimally stratifies the widely heterogenous population of patients with unresectable HCC undergoing TACE.

APPENDIX A – SUPPLEMENTARY DATA

Supplementary Table 3.1 – Subgroup analysis comparing the overall performance of the ALBI grade with the CPC, BCLC stage for all studies (A-H) included in the meta-analysis.

A) Huo et al [32]

Cohort	Classification system	N	Median survival (months)	Lower 95% CI	Higher 95% CI	Harrell's C	AIC
Taiwan	ALBI grade 1	297	38.09	31.33	44.67	0.544	8093.12
	ALBI grade 2	540	21.28	17.13	22.86		
	ALBI grade 3	44	11.32	4.25	15.76		
	C-P A	698	27	23.74	30.25	0.527	8111.09
	C-P B	163	14	10	17.91		
	C-P C	20	5	0	10.28		
	BCLC A	157	42	33.2	50.79	0.575	8038.44
	BCLC B	227	29	23.24	34.75		
	BCLC C	413	13	10.45	15.55		
	BCLC D	0					
	MELD < 10	613	26	22.81	29.18	0.497	8125.11
	MELD 10-14	202	23	18.52	27.49		
	MELD > 14	66	13	9.15	16.85		
	ALBI grade 1 (within C-P A)	293	39	32.46	45.54	0.545	6091.2
	ALBI grade 2 (within C-P A)	405	22	18.93	25.07		
	ALBI grade 3 (within C-P A)	0	0	0	0		
	ALBI grade 1 (within C-P B)	4	16	1.3	30.7	0.455	1125.79
	ALBI grade 2 (within C-P B)	131	14	10.04	17.96		
	ALBI grade 3 (within C-P B)	28	13	0	30.97		
	ALBI grade 1 (within C-P C)	0	0	0	0	0.382	76.53
	ALBI grade 2 (within C-P C)	4	1				
	ALBI grade 3 (within C-P C)	16	5	0	10.07		
	ALBI grade 1 (within BCLC A)	50	56	31.91	80.09	0.547	897.84
	ALBI grade 2 (within BCLC A)	103	42	31.01	52.99		
	ALBI grade 3 (within BCLC A)	4	26	5.20	46.8		
	ALBI grade 1 (within BCLC B)	105	43	34.02	52	0.589	1617.37
	ALBI grade 2 (within BCLC B)	120	23	18.81	27.194		
	ALBI grade 3 (within BCLC- B)	2	7				
	ALBI grade 1 (within BCLC C)	125	21	15.32	26.67	0.493	3461.88
	ALBI grade 2 (within BCLC C)	268	12	9.95	14.01		
	ALBI grade 3 (within BCLC C)	19	10	0	26.96		

B) Waked et al [34]

Cohort	Classification system	N	Median survival (months)	Lower 95% CI	Higher 95% CI	Harrell's C	AIC
Europe	ALBI grade 1	384	26.18	22.93	28.09	0.5749	11269.51
	ALBI grade 2	731	14.61	13.39	15.92		
	ALBI grade 3	82	9.7	5.8	14.01		
Japan	ALBI grade 1	85	38.91	27.27	51.35	0.566	5816.71
	ALBI grade 2	462	22.43	19.61	25.39		
	ALBI grade 3	106	15.33	9.34	20.46		
Egypt	ALBI grade 1	156	30	20		0.5808	4443.53
	ALBI grade 2	690	18	17	20		
	ALBI grade 3	152	13	9	14		
Hong Kong (China)	ALBI grade 1	34	30.2	16.84	47.17	0.5898	995.50
	ALBI grade 2	98	18.65	12.6	25.59		
	ALBI grade 3	11	6.05	1.22	14.18		
All cohorts	BCLC A	N/A					
All cohorts	BCLC B	N/A					
All cohorts	BCLC C	N/A					
All cohorts	BCLC D	N/A					
Europe	C-P A	865	18.68	17.27	20.72	0.5446	10877.14
	C-P B	286	13.26	11.32	15.03		
	C-P C	17	5.3	2.73	26.84		
Japan	C-P A	341	26.32	23.49	31.55	0.5662	5849.668
	C-P B	270	19.77	15.89	22.2		
	C-P C	44	15	7.47	27.04		
Egypt	C-P A	475	24	20	27	0.6161	4392.089
	C-P B	468	15	14	17		
	C-P C	55	5	4	9		
Hong Kong (China)	C-P A	110	23.16	16.88	30.07	0.5684	1003.309
	C-P B	31	7.53	3.09	20.13		
	C-P C	2					
Europe	ALBI grade 1 (within C-P A)	366	26.45	23.22	28.09	0.5661	7524.7
	ALBI grade 2 (within C-P A)	487	15.39	13.59	17.27		
	ALBI grade 3 (within C-P A)	5					
Japan	ALBI grade 1 (within C-P A)	83	38.91	27.27	51.97	0.542	2582.401
	ALBI grade 2 (within C-P A)	257	24.51	19.9	28.32		
	ALBI grade 3 (within C-P A)	1					
Egypt	ALBI grade 1 (within C-P A)	143	30	20		0.5422	1558.429
	ALBI grade 2 (within C-P A)	326	22	18	24		
	ALBI grade 3 (within C-P A)	6					
Hong Kong (China)	ALBI grade 1 (within C-P A)	34	30.2	16.84	47.17	0.5568	722.9373
	ALBI grade 2 (within C-P A)	76	21.61	14.41	25.92		
	ALBI grade 3 (within C-P A)	0					
Europe	ALBI grade 1 (within C-P B)	7	6.38	0.95		0.5393	2086.791
	ALBI grade 2 (within C-P B)	216	13.85	12.24	15.26		
	ALBI grade 3 (within C-P B)	60	9.57	5.79	15.66		
Japan	ALBI grade 1 (within C-P B)	2	12.6	12.6		0.5327	2096.108
	ALBI grade 2 (within C-P B)	193	20.66	16.81	23.55		
	ALBI grade 3 (within C-P B)	73	17.27	9.67	20.86		
Egypt	ALBI grade 1 (within C-P B)	13	16	5		0.5246	1994.459
	ALBI grade 2 (within C-P B)	338	16	14	18		
	ALBI grade 3 (within C-P B)	117	14	12	16		
Hong Kong (China)	ALBI grade 1 (within C-P B)	0				0.5749	139.5191
	ALBI grade 2 (within C-P B)	22	8.09	3.09	26.71		
	ALBI grade 3 (within C-P B)	9	6.05	0.1	22.5		

Europe	ALBI grade 1 (within C-P C)	0				0.5965	56.50737
	ALBI grade 2 (within C-P C)	5	19.74	2.96			
	ALBI grade 3 (within C-P C)	12	4.84	1.18	26.84		
Japan	ALBI grade 1 (within C-P C)	0				0.556	212.5407
	ALBI grade 2 (within C-P C)	12	15.3	6.74	56.78		
	ALBI grade 3 (within C-P C)	32	14.21	4.21	27.3		
Egypt	ALBI grade 1 (within C-P C)	0				0.548	208.3027
	ALBI grade 2 (within C-P C)	26					
	ALBI grade 3 (within C-P C)	29	5	3	6		
Hong Kong (China)	ALBI grade 1 (within C-P C)	0				0.5	1.3863
	ALBI grade 2 (within C-P C)	0					
	ALBI grade 3 (within C-P C)	2	1.74	1.74			

C) Aravind et al [37]

Cohort	Classification system	N	Median survival (months)	Lower 95% CI	Higher 95% CI	Harrell's C
Europe	ALBI grade 1	208	26.1	19.5	32.6	
	ALBI grade 2	196	18.6	14.9	21.5	
	ALBI grade 3	27	11.7	6.1	17.3	
	C-P A **	365				
	C-P B	63				
	C-P C	2				
	BCLC A**					
	BCLC B					
	BCLC C					
	BCLC D					
	ALBI grade 1 (within C-P A)**	204	26	19.5	32.6	
	ALBI grade 2 (within C-P A)	151	19.1	14.7	23.5	
	ALBI grade 3 (within C-P A)	7	7.6	2.27	12.9	

** No OS data for CPC substratification and BCLC, however majority of patients were CPC - A

D) Hiraoka et al [38]

Cohort	Classification system	N	Median survival (months)	Lower 95% CI	Higher 95% CI	Harrell's C
Japan	ALBI grade 1	88	44.1	35.1	49.9	
	ALBI grade 2	124	16.2	21.8	32.8	
	ALBI grade 3	0				
	C-P A **	212				
	C-P B	0				
	C-P C	0				
	BCLC A	0				
	BCLC B**	212				
	BCLC C	0				
	BCLC D	0				
	ALBI grade 1 (within C-P A)**	88	44.1	35.1	49.9	
	ALBI grade 2 (within C-P A)	124	16.2	21.8	32.8	
	ALBI grade 3 (within C-P A)	0				
	ALBI grade 1 (within BCLC B)**	88	44.1	35.1	49.9	
	ALBI grade 2 (within BCLC B)	124	16.2	21.8	32.8	
	ALBI grade 3 (within BCLC-B)	0				

** All patients are CP A and BCLC B in this study

E) Pinato et al [28]

Cohort	Classification system	N	Median survival (months)	Lower 95% CI	Higher 95% CI	Harrell's C
USA	ALBI grade 1	41	15.4	11	20	0.57
	ALBI grade 2	209	11	8.3	14	
	ALBI grade 3	65	4.5	3	6	
Europe	ALBI grade 1	139	39	33	44	0.58
	ALBI grade 2	251	18	14.3	21.6	
	ALBI grade 3	30	18	14.8	21.1	
Asia	ALBI grade 1	156	51.8	45	57	0.58
	ALBI grade 2	482	34	30	39	
	ALBI grade 3	85	21	14	28	
USA	C-P A	220	11.77	9.48	14.06	0.57
	C-P B	94	5.47	4.23	6.70	
	C-P C	0				
Europe	C-P A	262	30.00	24.70	35.30	0.56
	C-P B	112	16.00	12.78	19.22	
	C-P C	0	N/A			
Asia	C-P A	488	41.80	37.05	46.55	0.55
	C-P B	146	26.10	19.84	32.36	
	C-P C	4	10.20	4.84	15.56	
USA	ALBI grade 1 (within BCLC A)	1	1.67	.	.	0.58
	ALBI grade 2 (within BCLC A)	31	14.43	5.34	23.52	
	ALBI grade 3 (within BCLC A)	11	5.17	0.67	9.66	
USA	ALBI grade 1 (within BCLC B)	40	15.40	11.48	19.33	
	ALBI grade 2 (within BCLC B)	178	9.13	6.20	12.06	
	ALBI grade 3 (within BCLC B)	53	4.43	2.63	6.23	
USA	ALBI grade 1 (within BCLC C)	0				
	ALBI grade 2 (within BCLC C)	0				
	ALBI grade 3 (within BCLC C)	0				
Europe	ALBI grade 1 (within BCLC A)	17	120.00	0.00	241.73	0.65
	ALBI grade 2 (within BCLC A)	44	46.73	40.31	53.15	
	ALBI grade 3 (within BCLC A)	7	18.07	15.82	20.31	
Europe	ALBI grade 1 (within BCLC B)	85	39.00	32.91	45.09	
	ALBI grade 2 (within BCLC B)	138	18.00	12.48	23.53	
	ALBI grade 3 (within C-P B)	11	82.00			
Europe	ALBI grade 1 (within BCLC C)	37	18.00	10.85	25.15	
	ALBI grade 2 (within BCLC C)	69	9.00	4.68	13.32	
	ALBI grade 3 (within BCLC C)	12	12.00	6.03	17.98	
Asia	ALBI grade 1 (within BCLC A)	53	9.33	42.31	78.89	0.65
	ALBI grade 2 (within BCLC A)	179	3.04	40.44	52.36	
	ALBI grade 3 (within BCLC A)	38	13.67	21.20	74.80	
Asia	ALBI grade 1 (within BCLC B)	91	2.95	46.01	57.59	
	ALBI grade 2 (within BCLC B)	262	3.07	23.58	35.63	
	ALBI grade 3 (within BCLC B)	37	3.65	5.95	20.25	
Asia	ALBI grade 1 (within BCLC C)	12	17.10	6.68	27.52	
	ALBI grade 2 (within BCLC C)	41	16.60	10.24	22.96	
	ALBI grade 3 (within BCLC C)	10	13.27	2.11	24.43	

F) Hansmann et al [35]

Cohort	Classification system	N	Median survival (months)	Lower 95% CI	Higher 95% CI	Harrell's C
USA	ALBI grade 1	0				N/A
	ALBI grade 2	79	20.3	10.5	N/A	
	ALBI grade 3	101	10.7	3.5	21.6	
	C-P A	44	20.3	11.1	36.7	N/A
	C-P B	105	14.7	5.1	29.4	
	C-P C	31	7.9	2.9	10.7	
	BCLC A ^	68				N/A
	BCLC B	53				
	BCLC C	27				
	BCLC D	32				
	ALBI grade 1 (within C-P A)	0				N/A
	ALBI grade 2 (within C-P A)*	44				
	ALBI grade 3 (within C-P A)	0				
	ALBI grade 1 (within C-P B)	0				0.892
	ALBI grade 2 (within C-P B)	34	14.7	9.6		
	ALBI grade 3 (within C-P B)	71	12.2	3.5	22.7	
	ALBI grade 1 (within C-P C)	0				N/A
	ALBI grade 2 (within C-P C) **	1				
	ALBI grade 3 (within C-P C)	30	6.9	2.9	10.7	
	ALBI grade 1 (within BCLC A)	0				0.887
	ALBI grade 2 (within BCLC A)	35	no analysis as most patients alive at time of analysis (46%)			
	ALBI grade 3 (within BCLC A)	32	21.6	8.4	29.1	
	ALBI grade 1 (within BCLC B)	0				0.917
	ALBI grade 2 (within BCLC B)	31	20.1	11.2	33.9	
	ALBI grade 3 (within BCLC-B)	22	12.2	3.5	17.9	
	ALBI grade 1 (within BCLC C)	0				0.839
	ALBI grade 2 (within BCLC C)	12	12.9	4.2		
	ALBI grade 3 (within BCLC C)	15	3.5	2.4	5.2	
	ALBI grade 1 (within BCLC D)	0				N/A
	ALBI grade 2 (within BCLC D) **	1				
	ALBI grade 3 (within BCLC D)	32	7.9	3.7	10.9	

^ No BCLC data

*No substratification of CP-A as all patients ALBI grade 2

**only one patient, no analysis

G) Hickey et al [36]

	ALBI grade 1	19	N/A			
	ALBI grade 2	241	19.2	16.1	22.2	0.584
	ALBI grade 3	77	11.3	8.4	14.1	
	C-P A	186	21	16.1	25.8	
	C-P B	146	17.8	11.9	23.7	0.524
	C-P C	5	11.3	0	24	
	BCLC A *	160				
	BCLC B	127				
	BCLC C	50				
	BCLC D	0				
	ALBI grade 1 (within C-P A)	14	N/A (small numbers)			
	ALBI grade 2 (within C-P A)	170	19.2	15.8	22.5	
	ALBI grade 3 (within C-P A)	2	N/A (small numbers)			
	ALBI grade 1 (within C-P B)	34				
	ALBI grade 2 (within C-P B)	56	20.7	10.8	30.5	
	ALBI grade 3 (within C-P B)	56	11	7.4	14.5	
	ALBI grade 1 (within C-P C)	0				
	ALBI grade 2 (within C-P C)	0				
USA	ALBI grade 3 (within C-P C)	5	11.3	0	24.2	
	ALBI grade 1 (within BCLC A)	11	majority (80%) alive at study termination			
	ALBI grade 2 (within BCLC A)	113	45.4	26.3	64.4	
	ALBI grade 3 (within BCLC A)	36	majority (80%) alive at study termination			
	ALBI grade 1 (within BCLC B)	8	majority alive			
	ALBI grade 2 (within BCLC B)	82	18.7	16.3	21.1	0.739
	ALBI grade 3 (within BCLC-B)	23	10.7	9.3	12.1	
	ALBI grade 1 (within BCLC C)	0				
	ALBI grade 2 (within BCLC C)		7.2	3.7	10.7	
	ALBI grade 3 (within BCLC C)		3.5	2.6	4.3	
	C-P A (within BCLC A)**		majority alive			
	C-P A (within BCLC B)	68	19.2	16	22.4	
	C-P A (within BCLC C)		8.6	5.1	12	
	C-P B (within BCLC A)		majority alive			
	C-P B (within BCLC B)	43	17.4	8.8	26	0.735
	C-P B (within BCLC C)		3.5	2.6	4.4	
	C-P C (within BCLC A)		majority alive			
	C-P C (within BCLC B)					
	C-P C (within BCLC C)					

*No data for BCLC overall,

**additional substratificationo of BCLC with CPC for comparison of BLCC strafied by ALBI

H) Carling et al [39]

Cohort	Classification system	N	Median survival (months)	Lower 95% CI	Higher 95% CI	Harrell's C
Europe	ALBI grade 1	21	26.9	3.6	62	
	ALBI grade 2	27	12.8	1.7	37.7	
	ALBI grade 3	1	4.5	NA	NA	
	C-P A	49	14.9	1.7	62	
	C-P B	0				
	C-P C	0				
	BCLC A	3				
	BCLC B	26				
	BCLC C	20				
	BCLC D	0				
	ALBI grade 1 (within C-P A) *	21	26.9	3.6	62	
	ALBI grade 2 (within C-P A)	27	12.8	1.7	37.7	
	ALBI grade 3 (within C-P A)	1	4.5	NA	NA	
	ALBI grade 1 (within BCLC A)**					
	ALBI grade 2 (within BCLC A)					
	ALBI grade 3 (within BCLC A)					
	ALBI grade 1 (within BCLC B)					
	ALBI grade 2 (within BCLC B)					
	ALBI grade 3 (within BCLC-B)					
	ALBI grade 1 (within BCLC C)		14.3			
	ALBI grade 2 (within BCLC C)		8.6			
	ALBI grade 3 (within BCLC C)					

*all patients are CPA in this cohort, no C-index of comparison for ALBI grade substratification of other CPC grades)

**small numbers

Abbreviations: ALBI, albumin bilirubin grade; BCLC, Barcelona clinic liver cancer stage; CI, confidence interval; C-P, Child Pugh class.

Supplementary Table 4.1. Univariate analysis of baseline and post treatment variables associated with OS following initial TACE overall cohort (a) and TACE only subgroup (b).

a)

Variable	Hazard Ratio	Lower 95% CI	Upper 95% CI	P value
Baseline variables				
Age	1.00	0.99	1.01	0.49
Weight	1.00	1.00	1.01	0.261
Height	1.00	0.99	1.02	0.617
Asian ethnicity	0.59	0.43	0.82	0.001
Caucasian ethnicity	1.55	1.16	2.07	0.003
Other ethnicity	1.00	0.58	1.73	1.000
Male	1.06	0.77	1.48	0.706
Type 2 Diabetes Mellitus	1.11	0.88	1.40	0.362
NAFLD	1.01	0.78	1.30	0.951
Hepatitis B	0.65	0.49	0.88	0.004
Hepatitis C	1.06	0.85	1.33	0.587
Treatment of viral hepatitis	0.47	0.22	1.01	0.048
Haemochromatosis	0.99	0.53	1.82	0.965
Alcohol	1.20	0.96	1.50	0.096
HCC size (cm)	1.05	1.00	1.09	0.025
Single HCC	0.75	0.60	0.94	0.011
Two HCC	0.97	0.74	1.27	0.812
Three HCC	1.22	0.82	1.82	0.312
> 3 HCC	1.39	1.09	1.77	0.008
Extrahepatic spread	1.30	0.68	2.47	0.420
Macrovascular invasion	1.51	0.87	2.61	0.131
PEI	1.05	0.46	2.40	0.906
Ablation	0.83	0.56	1.24	0.358
Resection	0.89	0.60	1.32	0.566
Portal Hypertension	1.35	0.96	1.91	0.081
Hepatic Encephalopathy	1.66	1.06	2.62	0.024
Ascites	2.29	1.71	3.05	0.000
Overall Child Pugh Score (CPS)	1.30	1.19	1.42	0.000
CPS A	0.48	0.38	0.60	0.000
CPS B	2.06	1.63	2.60	0.000
MELD	1.04	1.01	1.07	0.009
Overall BCLC stage	1.35	1.14	1.60	0.000
BCLC stage A	0.66	0.53	0.83	0.000
BCLC stage B	1.44	1.15	1.81	0.001
BCLC stage C	1.33	0.86	2.05	0.191
ECOG of 0	0.91	0.73	1.13	0.369
ECOG of 1	0.99	0.79	1.24	0.923
ECOG of 2	1.43	0.99	2.08	0.055
ECOG of 3	1.54	0.37	6.38	0.543
serum AFP	1.00	1.00	1.00	0.873
serum Albumin	0.94	0.92	0.96	0.000
serum ALT	1.00	1.00	1.00	0.070
serum Bilirubin	1.02	1.01	1.03	0.000
serum Creatinine	1.00	1.00	1.00	0.488
serum Haemoglobin	0.99	0.99	1.00	0.016
serum GGT	1.00	1.00	1.00	0.001
serum Na	0.96	0.92	1.00	0.026
serum Neutrophils	1.04	0.96	1.12	0.347

TACE treatment characteristics				
Embolisation with particles or gelfoam	1.12	0.89	1.41	0.329
non selective TACE	1.25	0.91	1.70	0.158
selective TACE	0.94	0.75	1.19	0.616
super selective TACE	0.95	0.71	1.26	0.698
cTACE	0.78	0.60	1.01	0.056
DEB TACE	1.30	0.99	1.70	0.051
TAE	1.47	0.46	4.71	0.506
Post TACE variables				
mRECIST CR	0.71	0.56	0.90	0.005
mRECIST PD	2.04	1.43	2.92	0.000
mRECIST PR	1.05	0.84	1.32	0.642
mRECiST SD	1.05	0.73	1.51	0.789
MELD score	1.08	1.05	1.12	0.000
Overall Child Pugh Score (CPS)	1.35	1.24	1.46	0.000
CPS A	0.54	0.43	0.67	0.000
CPS B	1.82	1.45	2.30	0.000
CPC C	2.48	1.50	4.11	0.000
ECOG of 0	0.86	0.69	1.08	0.193
ECOG of 1	1.04	0.83	1.29	0.736
ECOG of 2	1.27	0.90	1.81	0.168
ECOG of 3	2.02	0.63	6.45	0.227
Complication	1.26	0.97	1.63	0.075
Decompensation	2.09	1.20	3.61	0.007
Ascites	2.17	1.65	2.85	0.000
Hepatic Encephalopathy	1.74	1.16	2.61	0.006
Other complicaton	1.11	0.70	1.76	0.647
Portal Hypertension	1.34	0.95	1.89	0.084
Post TACE syndrome	1.14	0.82	1.57	0.424
Renal dysfunciton	1.35	0.63	2.91	0.429
Post TACE combination treatment	0.53	0.38	0.74	0.000
Ablation	0.51	0.32	0.81	0.003
Resection	0.20	0.08	0.50	0.000
PEI	1.14	0.62	2.10	0.675
serum Creatinine	1.00	1.00	1.00	0.385
serum Platelets	1.00	1.00	1.00	0.041
serum Neutrophils	1.01	0.95	1.08	0.719
serum Sodium	0.93	0.90	0.96	0.000
serum Haemoglobin	0.99	0.99	1.00	0.011
serum INR	1.75	1.27	2.40	0.000
serum GGT	1.00	1.00	1.00	0.041
serum AST	1.00	1.00	1.00	0.380
serum ALT	1.00	1.00	1.00	0.782
serum Bilirubin	1.02	1.02	1.03	0.000
serum Albumin	0.93	0.91	0.95	0.000

b)

Variable	Hazard Ratio	Lower 95% CI	Upper 95% CI	P value
Baseline Variables				
Male gender	0.95	0.65	1.39	0.793
Caucasian ethnicity	1.75	1.20	2.54	0.003
Asian Ethnicity	0.56	0.37	0.84	0.004
Born in Australia	1.28	0.95	1.71	0.101
Other ethnicity	0.79	0.34	1.81	0.570
Single HCC	0.77	0.59	1.02	0.061
Two HCC	1.11	0.79	1.55	0.545
Three HCC	1.13	0.62	2.04	0.690
> 3 HCC	1.24	0.92	1.69	0.152
HCC extrahepatic mets	2.21	0.30	16.49	0.429
Hepatitis C	1.03	0.78	1.36	0.837
Hepatitis B	0.76	0.52	1.10	0.139
Viral hepatitis Treatment	0.27	0.10	0.75	0.010
Type 2 Diabetes	1.25	0.93	1.67	0.127
Haemochromatosis	1.09	0.50	2.35	0.829
NAFLD	0.98	0.72	1.35	0.914
Other cause of cirrhosis	1.35	0.74	2.45	0.315
Weight	1.01	1.00	1.02	0.115
Height	1.00	0.98	1.02	0.904
Portal hypertension	1.06	0.65	1.73	0.817
Ascites	1.92	1.35	2.72	0.000
Hepatic Encephalopathy	1.52	0.90	2.57	0.107
Overall Child Pugh Score (CPS)	1.32	1.19	1.47	0.000
CPS A	0.45	0.34	0.60	0.000
CPS B	2.16	1.62	2.89	0.000
MELD score	1.04	1.01	1.08	0.020
ECOG of 0	0.88	0.67	1.15	0.336
ECOG of 1	0.87	0.65	1.16	0.335
ECOG of 2	1.38	0.88	2.17	0.152
ECOG 3	1.43	0.34	5.93	0.617
Ablation	1.58	0.21	11.77	0.649
Resection	0.47	0.06	3.49	0.450
BCLC stage A	0.68	0.52	0.90	0.006
BCLC stage B	1.47	1.11	1.94	0.006
serum Albumin	0.94	0.92	0.97	0.000
serum GGT	1.00	1.00	1.00	0.037
serum AFP	1.00	1.00	1.00	0.682
serum ALT	1.00	1.00	1.00	0.233
serum Haemoglobin	0.99	0.98	1.00	0.006
serum Bilirubin	1.02	1.01	1.03	0.001
serum Creatinine	1.00	1.00	1.01	0.719
serum Sodium	0.97	0.93	1.03	0.304
serum Neutrophils	1.02	0.92	1.12	0.710
serum platelet count	1.00	1.00	1.00	0.031

TACE Treatment Characteristics				
Embolisation with gelfoam or particles	1.06	0.79	1.42	0.707
non selective TACE	1.15	0.77	1.70	0.493
Selective TACE	0.94	0.70	1.26	0.689
TACE delivery super selective	1.09	0.77	1.56	0.621
TAE only	0.72	0.10	5.34	0.741
cTACE	0.84	0.61	1.18	0.307
DEB TACE	1.20	0.86	1.68	0.270
Post TACE- Variables				
Overall Child Pugh Score (CPS)	1.37	1.23	1.52	0.000
CPS A	0.53	0.40	0.70	0.000
CPS B	1.97	1.48	2.64	0.000
CPS C	2.32	1.17	4.61	0.014
Post TACE complications	1.03	0.74	1.43	0.862
Portal HTN	1.06	0.66	1.72	0.800
Renal complication	1.40	0.57	3.48	0.454
Post TACE syndrome	0.96	0.63	1.48	0.861
Hepatic Encephalopathy	1.62	1.02	2.58	0.036
Ascites	1.88	1.35	2.60	0.000
Decompensation	2.23	1.20	4.16	0.010
Other complications	0.83	0.47	1.49	0.531
MELD score	1.08	1.03	1.12	0.000
ECOG of 0	0.88	0.67	1.15	0.336
ECOG of 1	1.11	0.85	1.47	0.435
ECOG of 2	1.02	0.66	1.59	0.925
ECOG of 3	1.84	0.57	5.91	0.296
mRECIST CR	0.84	0.62	1.15	0.267
mRECIST of PD	1.84	1.18	2.87	0.006
mRECIST of SD	1.46	0.93	2.30	0.095
mRECIST PR	0.84	0.63	1.12	0.218
serum Albumin	0.93	0.91	0.96	0.000
serum platelet count	1.00	1.00	1.00	0.121
serum ALT	1.00	1.00	1.00	0.221
serum AST	1.00	0.99	1.00	0.546
serum Bilirubin	1.02	1.01	1.02	0.000
serum Creatinine	1.00	1.00	1.01	0.205
serum GGT	1.00	1.00	1.00	0.810
serum Haemoglobin	0.99	0.98	1.00	0.005
serum INR	1.88	1.26	2.79	0.002
serum Na	0.94	0.90	0.98	0.004
serum Neutrophils	1.00	0.92	1.09	0.955

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional TACE; CR, complete response; DEBTACE, drug eluting bead TACE; ECOG, Eastern Cooperative Oncology Group; EHS, extra hepatic spread; HCV, hepatitis C virus; HBV, hepatitis B virus, INR, international normalized ratio; MELD, model for end stage liver disease; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MVI, macrovascular invasion; N/A, not applicable; Na, sodium; NAFLD, non alcoholic fatty liver disease; OS, overall survival; PD, progressive disease; PEI, percutaneous ethanol injection; Portal HTN, portal hypertension; PR, partial response; PTS, post TACE syndrome; SD, stable disease; TACE, transarterial chemoembolization; TAE, transarterial embolization.

Supplementary Table 4.2. The interrelationship between aetiology of chronic liver disease secondary to HBV and other co-factors including patient ethnicity.

Variable	non HBV (n=349)	HBV (n=82)	P value
Age (years), mean (SD)	67.3 (10.4)	61.9 (10.5)	<0.0001
Caucasian (n,%)	304 (87%)	39 (48%)	<0.0001
Asian (n,%)	31 (8.9%)	37 (45%)	<0.0001
HCV (n,%)	149 (43%)	18 (22%)	0.001
NAFLD (n,%)	95 (27%)	10 (12%)	0.004
ETOH (n,%)	163 (47%)	23 (28%)	0.001
Serum Markers (median, IQR)			
Albumin, g/L	34 (31-38)	37 (33-41)	0.004
Bilirubin, µmol/L	18 [12-27]	15 [10-22]	0.015
INR	1.2 [1.1-1.3]	1.1 [1-1.2]	0.004
Platelets, 10^9/L	114 [80-161]	137 [98-177]	0.02
Size of largest HCC (mean, SD)	3.84 (2.21)	4.58 (3.75)	0.021
Child Pugh Class (median, IQR)	6 [5-7]	6 [5-6]	0.019
Child Pugh A (n,%)	233 (67%)	65 (79%)	0.027
Child PughB (n, %)	112 (32%)	17 (21%)	0.043
MELD (median, IQR)	9 [7-12]	8 [7-10]	0.005
Portal HTN (n,%)	307 (89%)	64 (78%)	0.013

Abbreviations: ETOH, alcohol; HCC, hepatocellular carcinoma; HCV, hepatitis C; HTN, hypertension; INR, international normalised ratio; IQR, interquartile range; MELD, model for end stage liver disease; NAFLD, non-alcoholic fatty liver; SD, standard deviation.

APPENDIX B - OTHER PUBLISHED WORK

The following work was completed during PhD enrolment and has been published in peer-reviewed journals or presented at national and international Gastroenterology conferences. The following publications further develop the main theme regarding management of hepatocellular carcinoma and treatment including TACE.

1. Treatment choice for early stage hepatocellular carcinoma in real world practice: Impact of treatment stage migration to transarterial chemoembolisation and treatment response on survival.

   S Roberts, A Gazzola, J Lubel, P Gow, S Bell, A Nicoll, A Dev, MA Fink, S Sood, V Knight, G Mishra, T Hong, E Paul, A Majeed, and W Kemp for the Melbourne Liver Group. *Scandinavian Journal of Gastroenterology 2018*. *Oct - Nov;53(10-11):1368-1375.*

2. Clinical Utility of ALBI grade as a prognostic marker in patients with HCC undergoing TACE: a systematic review and meta-analysis.

   G. Mishra, A. Majeed, A. Dev, G. Eslick, S. Roberts.

   Oral presentation, Australian Gastroenterology Week Conference 2019

   Scientific Poster, Australian Gastroenterology Week Conference 2019

   Scientific Poster, American Association of Liver Disease Conference 2019

3. Prognostic factors associated with survival in patients with HCC undergoing TACE: an Australian multicentre cohort study.

   G. Mishra, A. Dev, E. Paul, S. Roberts, on behalf of Melbourne Liver Group.

   Scientific Poster, Australian Gastroenterology Week Conference 2019

4. Liver function assessment in patients with HCC: a comparison of current and emerging scores.

   G. Mishra, M. Suen, S. Dave, E. Paul

   Scientific Poster, Australian Gastroenterology Week Conference 2019

5. The SITAR study: SIRT versus DEB-TACE in identifying good prognostic indicators.

   Hirsch R.D., Sawhney R., Bird V., Sood S., Mishra G., Dev A., Gow P., Kemp W., Roberts S.K., Ryan M., Nicoll A.J.

   Journal of Gastroenterology and Hepatology. Vol 33 (Supplement 2) (pp 48), 2018. Date of Publication: September 2018.

6. Survival outcomes of patients with two hepatocellular carcinoma lesions diagnosed synchronously or sequentially.

   AD Pham , RV Apostolov, ZS Ardalan, A Majeed, G Mishra, NM Kam, K Patwala, N Kutaiba, AG, Testro, PJ Gow.

   Scientific Poster: American Association of Liver Disease Conference 2018

Other published works

1. The Efficacy and Safety of High vs Low Dose Ursodeoxycholic Acid for Primary Sclerosing Cholangitis: A Meta-Analysis with Update of Recent Literature.

   A Bloom*, G Mishra*, S Sood, S Le, and S Pianko. (Co-first Author).

   Scientific Poster. Australian Gastroenterology Week Conference 2017

   J. Gastroenterol. Hepatol. 2017 Aug; 32:87-87

   J. Hep. 2017: 66:S521

2. Mycophenolate for the treatment of autoimmune hepatitis in patients not responsive or intolerant to standard therapy: the Australian TAPESTRY study.

   A. Gazzola, R. Lim, S. Strasser, A. Nicoll, J. Mitchell, W. Siow, T. Mitchell, Z. Hamarneh, M. Weltman, N. Janko, E. Tse, G. Mishra, E. Cheng M. Levy, W. Cheng, S. Sood, R. Skoien, A. Zekry, J. George, G. MacQuillan, A. Wigg, K. Stuart, W. Sievert, G. McCaughan, S. K. Roberts on behalf of ALA CRN.

   Scientific Poster: American Association of Liver Disease Conference 2016.

   Oral presentation: Australian Gastroenterology Week Conference 2016

   Clin Gastroenterol Hepatol. 2018 Feb;16(2):268-277

3. Real world evaluation of Viekira Pak (Ritonavir boosted Paritaprevir, Ombitasvir and Dasabuvir +/ - Ribavirin) in HCV Genotype 1 targeting advanced liver disease (The REV1TAL Study).

   J. S. Lubel, S. Pianko, A. Thompson, S. Strasser, K. Stuart, P. Gow, J. Mitchell, S. Chivers, G.Mishra, S. Nazareth, T Jones, J. Gough, S. Bollipo, A. Wade, E. Tse, J. George, S. Roberts and REV1TAL STUDY GROUP.

   Scientific Poster: American Association of Liver Disease Conference, Australian Gastroenterology Week Conference 2016, and for International Liver Conference for the European Association for the Study of Liver Diseases 2017

   J. Gastroenterol. Hepatol. 2016 Oct; 31:77-78