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Outcomes of jaundice in advanced hepatocellular carcinoma – a sub-Saharan perspective

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Background: Jaundice is a marker of advanced disease and poor outcomes in hepatocellular carcinoma (HCC). The aim of this study was to describe and analyse the management and outcomes of jaundiced HCC patients at a large academic referral centre in sub-Saharan Africa (SSA).
Methods: Treatment-naïve adult HCC patients who presented with jaundice between 1990 and 2023 were analysed.
Results: During the inclusion period, 676 HCC patients were treated at Groote Schuur Hospital. The mean age of the 126 (18.6%) who were jaundiced was 48.8 (± 13.2) years. Eighty-nine (70.6%) were male. Ninety-four (74.6%) patients with jaundice secondary to diffuse tumour infiltration had best supportive care (BSC) only. Thirty-two had obstructive jaundice (OJ); four were excluded because of missing hospital records. In 28 of these patients, 16 underwent biliary drainage (BD) and 12 received BSC only. The mean overall survival (OS) of the 126 patients was 100.5 (± 242.3) days. The patients with diffuse tumour infiltration had an OS of 105.9 (± 273.3) days. The patients with OJ survived 86.5 (± 135.0) days. There was no significant difference in OS between the three patient groups ($p = 0.941$). In the OJ group, patients who underwent BD survived longer than the BSC group (117.9 ± 166.4 vs. 29.2 ± 34.7 days, $p = 0.015$).
Conclusions: In this cohort of SSA patients, jaundice was a marker of advanced HCC with limited treatment options and poor OS. However, in carefully selected patients with OJ, BD is beneficial and improves survival.
Keywords: hepatocellular carcinoma, sub-Saharan Africa, South Africa, outcomes, jaundice, biliary drainage

Introduction

The global incidence of hepatocellular carcinoma (HCC) is rising and by 2040, HCC will account for an estimated 1.3 million deaths annually.[1] Eighty per cent of all new HCC originate from low- and middle-income countries (LMICs), most of which are in South-East Asia and sub-Saharan Africa (SSA).[2-7] In SSA, HCC is typically a fatal disease of the young. The age at presentation is between 28 and 54 years, and 84% present with advanced disease. Most patients receive best supportive care (BSC) as the sole modality of care, and only six per cent are alive at one year. Chronic hepatitis B virus (HBV) infection is the main aetiology of HCC on the African sub-continent. Over the last thirty years, many studies have attributed the HCC disease profile in young SSA patients (large tumours in non-cirrhotic livers, high metastatic burden and frequent tumour-related complications) to the hepatocarcinogenic potential of HBV. The high prevalence of vascular invasion and extrahepatic metastases also support the impact of this HBV carcinogenic pathway.[3-5,8]

Jaundice is a marker of advanced HCC and occurs in 5–44% of patients during the course of the disease.[9-12] Diffuse hepatic tumour infiltration and end stage liver disease (ESLD) are the most frequent aetiologies. Jaundice in HCC is associated with other poor prognostic factors such as multifocal disease and vascular invasion, particularly portal vein tumour thrombosis (PVTT) and hepatic vein tumour thrombosis (HVTT).[12-17]

Obstructive jaundice (OJ) on the other hand occurs infrequently in HCC. Biliary obstruction may result from intra-biliary tumour growth, haemobilia, tumour encasement or extrinsic compression of the biliary system by tumour or lymph nodes.[12-20] Such patients may benefit from biliary drainage (BD) (endoscopic retrograde pancreatography (ERCP); percutaneous transhepatic cholangiography (PTC); endoscopic ultrasound (EUS)-guided drainage) as palliative modality or as a bridge to further HCC therapies such as trans-arterial embolisation (TACE) or ablation.

There is a paucity of data on the management of jaundice in HCC. Currently, studies are limited to case series and publications from high volume centres in Asia.[12-17,21-27] There are currently no studies from SSA, where the disease profile is unique and typified by large tumours in young non-cirrhotic patients.[3-7,11,28,29]

The aim of this study is to describe and analyse the presentation, management and outcomes of HCC patients with jaundice referred to a large academic centre in South Africa.

Patients and methods

In this retrospective single-centre cohort study, treatment-naïve adult patients with HCC who presented with jaundice at their index admission between 1990 and 2023 were analysed. Data were collected prospectively and stored on a faculty-secure database. Extracted data included age, gender, performance status (PS), symptoms, signs, comorbidities, routine laboratory investigations (full blood count, liver function tests, HBV and Hepatitis C (HCV) testing, international normalised ratio (INR), alpha-fetoprotein levels), imaging findings (ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI). The Child-Pugh score (CPS), model for end stage liver disease-sodium (MELD-Na) score and Barcelona Clinic Liver Cancer (BCLC) staging were calculated and compared across categories.

Patients were managed by a multi-disciplinary team (MDT) of oncologists, hepatologists, radiologists, palliative care physicians, hepatobiliary and transplant surgeons, and treatment decisions were made at an MDT meeting. The BCLC management guidelines were generally followed, with the exception of resection and TACE where extended criteria were applied in some patients.[30] The University of California San Francisco (UCSF) criteria were applied for selecting candidates for liver transplantation.[31]

In jaundiced patients with biliary dilatation on cross-sectional abdominal imaging, BD was considered. Patients with an expected survival of less than 30 days were offered BSC only. Indications for BD procedures included cholangitis, intractable pruritus and the need to improve BD before TACE or local ablation. ERCP was the preferred method of BD. When ERCP drainage was not feasible or unsuccessful, percutaneous transhepatic biliary drainage (PTBD) or EUS-guided BD was performed. Drainage was achieved by placement of plastic or self-expandable metallic stents (SEMS). Jaundiced patients with diffuse tumour infiltration of the liver and/or ESLD were managed medically.

In patients with OJ, cross sectional and cholangiogram images were retrospectively reviewed by a hepatobiliary surgeon and radiologist, and classified as obstructive icteric type (OIT) I, II or III as proposed by Lau et al.[12] OIT I is caused by intraluminal tumour casts and/or fragments, OIT II by intraluminal blood clots filling the biliary tree and OIT III by tumour compression of the common hepatic duct/common bile duct.

Survival was compared for patients with diffuse tumour infiltration and those with OJ. In the latter, a sub-group analysis was performed for those undergoing BD compared to patients treated with BSC only.

Statistical analysis

Descriptive statistics, including median values with 95% confidence intervals (CI) were used to assess the distribution of continuous variables. Categorical variables were tabulated, and variations assessed in proportions using the Pearson's chi-squared test. The Kaplan Meier method was used to assess overall survival (OS) and the log rank test to compare survival curves between groups. Additionally, a Mantel-cox regression analysis was done to further explore the impact of various factors on OS. Assumptions underpinning all statistical tests performed, including the proportional hazards assumption for the Cox regression model, were assessed and confirmed to be met. The analyses were conducted using SPSS version 26 (IBM. SPSS Armonk, NY2019).

Results

A total of 676 HCC patients were treated at Groote Schuur Hospital during the inclusion period. One hundred and twenty-six (18.6%) patients were jaundiced at the time of diagnosis (Figure 1). Baseline characteristics of these patients are summarized in Tables I and II. Eighty-nine (70.6%) patients were male, and the mean age was 48.8 years. Pain and weight loss were the most frequently associated symptoms in 72.9% and 60.5% of patients respectively. The mean duration of symptoms was 75.4 days. Seventy-three (57.9%) patients tested positive for HBV and five (3.9%) were HCV positive. Most (51.6%) patients had BCLC Stage D disease, 46.8% were CPS C and the mean MELD-Na was 21.7. Fifty-four (42.9%) patients had more than six HCC lesions on cross-sectional abdominal imaging. Extrahepatic metastases were reported in 22.2% of the 126 patients. Furthermore, 23.8% had main PVTT. Fourteen (11.1%), 13

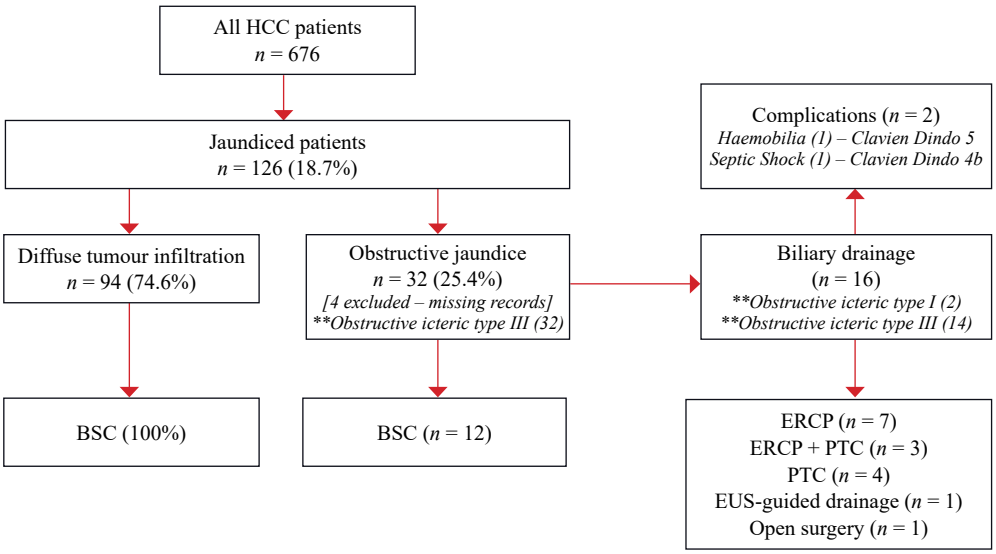

Figure 1

Table I: Baseline characteristics

Baseline characteristics	Total (n = 126)		Diffuse (n = 94)		Obstructive (n = 28) *			
					BD (n = 16)		No BD (n = 12)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	48.8	13.2	47.7	12.8	48.9	12.0	54.8	16.4
Symptom duration	75.4	77.6	70.6	66.4	116.8	129.4	51.3	39.0
MELD-Na	21.7	5.6	21.3	5.6	22.1	5.8	24.1	5.2
	n	%	*n*	%	*n*	%	*n*	%
Gender								
Male	89	70.6	70	74.5	14	87.5	7	58.3
Female	37	29.4	24	25.5	2	12.5	5	41.7
PS								
0	4	3.1	2	2.2	1	6.2	0	0
1	39	30.7	29	31.5	6	37.5	1	8.4
2	41	32.3	31	33.7	5	31.2	3	25.0
3	34	26.8	25	27.2	4	25.0	4	33.3
4	9	7.1	5	5.4	0	0	4	33.3
Viral serology+ve								
HBV	73	57.9	56	59.6	9	56.3	7	58.3
HCV	5	3.9	4	4.3	0	0	1	8.4
HIV	14	11.1	10	10.6	3	18.8	1	8.4
CPS								
A	4	3.2	4	4.5	0	0	0	50.0
B	60	47.6	39	44.3	12	75.0	6	50.0
C	59	46.8	45	51.1	4	25.0	6	50.0
BCLC grade								
A	4	3.2	2	2.2	1	6.3	0	0
B	2	1.6	1	1.1	1	6.3	0	0
C	55	43.7	40	43.5	9	56.2	4	33.3
D	65	51.6	49	53.3	5	31.2	8	66.7
EHM	28	22.2	20	21.3	2	12.5	7	58.3
> 6 lesions on CT	54	42.9	39	55.7	5	31.3	11	91.7
Vascular invasion								
PVTT								
Right	36	28.6	26	27.7	3	18.8	8	66.6
Left	32	25.4	19	20.2	5	31.2	9	75.0
Main trunk	30	23.8	18	19.1	5	31.2	8	66.6
HVTT								
Right	14	11.1	11	11.7	3	18.8	1	8.4
Left	13	10.3	10	10.6	1	6.3	2	16.6
Middle	15	11.9	12	12.8	1	6.3	2	16.6

BD – Biliary drainage, MELD-Na – Model for end-stage liver disease-sodium, PS – Performance status, CPS – Child Pugh score, BCLC – Barcelona clinic liver cancer, EHM – Extrahepatic metastases, CT – Computed tomography, PVTT – Portal vein tumour thrombosis, HVTT – Hepatic vein tumour thrombosis

(10.3%) and 15 (11.9%) patients had right, left and middle HVTT respectively. Ninety-four (74.6%) patients were jaundiced due to diffuse hepatic tumour infiltration.

Of the 32 patients with OJ, four were excluded from further analyses due to missing hospital records. In the remaining 28 patients, 12 had very poor PS and received BSC only.

Sixteen HCC patients with OJ underwent BD (Table III). Fourteen patients had OIT III and two had OIT I HCCs. Cholangitis and bridging to TACE were the most frequent indications for BD. In 11 patients who underwent endoscopic biliary drainage (EBD), 10 patients had ERCP, and one patient had EUS-guided BD. The technical success rate was 72.7%. Three patients required PTBD. Two patients developed complications following PTBD (cholangitis and septic shock in one patient, and a second developing haemobilia, both resulting in death). In five patients who underwent BD as a bridge to TACE, only three eventually received TACE, surviving 127, 237 and 644 days respectively. Surgical exploration and biliary drainage were performed in one patient.

The OS for the various patient categories is depicted in Figure 2. The mean OS for the entire cohort of 126 patients

Table II: Baseline laboratory findings in study cohort

Baseline characteristics	Total cohort (n = 126)	Aetiology of jaundice in 126 patients	
		Diffuse tumour infiltration (n = 94)	Biliary obstruction (n = 32)
Alpha fetoprotein [g/L]			
Mean	185827.7	221646.2	82214.4
SD	± 393275.0	± 448925.8	± 146901.1
Sodium [mmol/L]			
Mean	133.6	133.8	133.6
SD	± 5.0	± 4.8	± 5.0
Creatinine [umol/L]			
Mean	85.8	85.7	87.4
SD	± 60.5	± 59.7	± 66.0
Total bilirubin [umol/L]			
Mean	153.4 2	128.3	224.3
SD	± 125	± 104.4	± 155.2
Albumin [g/L]			
Mean	29.5	29.4	29.4
SD	± 7.4	± 6.9	± 8.5
INR			
Mean	1.5	1.5	1.6
SD	± 0.5	± 0.5	± 0.5

was 100.5 (± 242.3) days. In the 94 patients with jaundice secondary to diffuse tumour infiltration, it was 105.9 (± 273.3) days. The 32 patients with OJ survived on average 86.5 (± 135.0) days. There was no significant difference in OS between those three patient groups (p = 0.941). However, within the OJ group, patients who underwent BD survived significantly longer than those who were treated with BSC only (117.9 ± 166.4 vs. 29.2 ± 34.7 days, p = 0.015) (Figure 3).

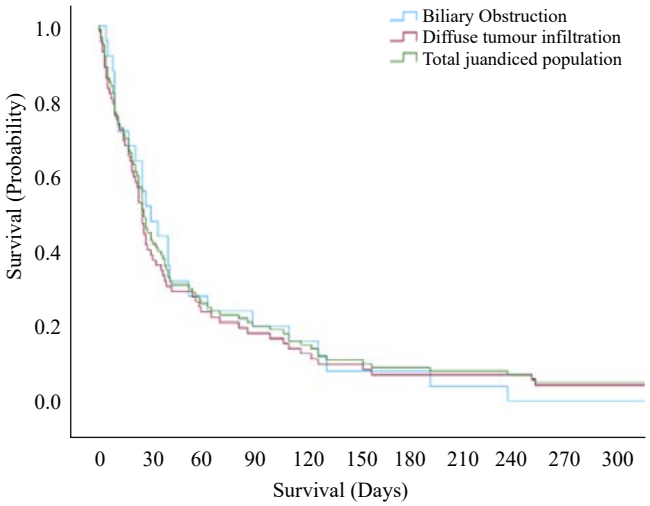

Figure 2

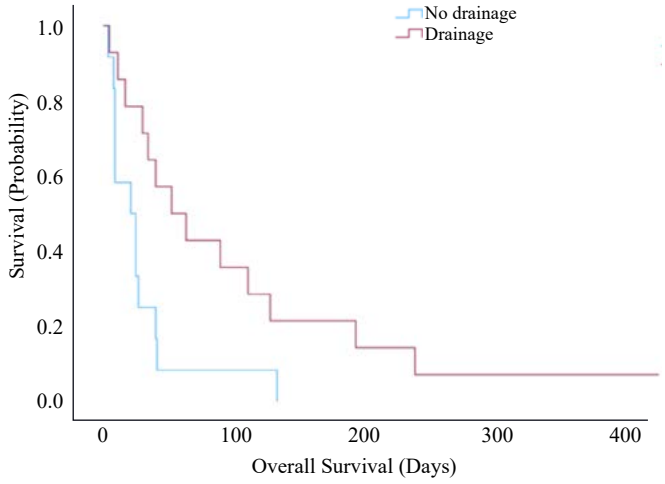

Figure 3

Table III: Summary of 16 hepatocellular carcinoma patients who underwent biliary drainage for symptomatic obstructive jaundice

Age (years) and gender	PS	HCC features	OIT **	CPS	MELD-Na	BCLC	PVTT
69M	2	Multifocal	Type III	B7	12	C	Yes
40M	1	Hilar compression	Type III	B7	38	A	No
66F	3	Multifocal	Type III	C13	22	D	Yes
34M	1	Large non-cirrhotic HCC	Type III	B7	20	B	No
52 F	3	Multifocal	Type III	B8	21	D	Yes
58 M	3	Large non-cirrhotic HCC	Type III	B8	22	C	No
28M	3	Cirrhotic HCC	Type III	C11	25	D	No
40M	1	Large non-cirrhotic HCC	Type III	B7	23	C	No
37M	2	Multifocal	Type III	C10	23	D	Yes
47M	1	Multifocal	Type III	B8	23	C	Yes
63M	1	Large non-cirrhotic HCC	Type III	B8	20	C	No
42M	2	Hilar compression	Type III	C11	28	D	No
59M	1	Intraductal invasion	Type I	B7	21	C	No
46M	0	Hilar compression	Type III	B7	17	C	No
56M	2	Intraductal invasion	Type I	B9	14	C	No
45M	2	Multifocal	Type III	B9	24	C	Yes

** Obstructive icteric type (OIT) Classification proposed by Lau et al.,[12] PS – Performance Status, HCC – Hepatocellular carcinoma, CPS – Child Pugh score, MELD-Na – Model for end-stage liver disease-sodium, BCLC – Barcelona liver clinic stage, PVTT – Portal vein tumour thrombosis

Discussion

In this study, we report on our experience with the management of jaundice in HCC at a high-volume centre in SSA. The incidence of jaundice in this cohort of 676 patients was 18.6%, and comparable to previously published studies.[12-18,20,32-36] More than half of the patients had chronic HBV infection and advanced HCC. Extrahepatic metastases and vascular invasion (PVTT and HVTT) occurred frequently. As expected, the OS was poor, with patients surviving on average 100 days. These findings are similar to results from a recent systematic review by our group, where the treatment and outcomes of HCC in SSA were reported and in which up to 59% and 41% of patients presented with extrahepatic metastases and PVTT respectively.[28] Most strikingly in the study the in-hospital mortality was 58% and the one-year survival rate was 1–2% in patients who received only BSC.

We identified two distinct groups of HCC patients who present with jaundice. In the first and larger group, jaundice is caused by diffuse hepatic tumour infiltration and/or ESLD. Given the poor PS, the multifocality of disease, the high burden of extrahepatic disease and frequent vascular invasion, these patients were managed with BSC only. Although radioembolisation, sorafenib and novel biological targeted therapies are potential treatment options, these are not available at state health care facilities in South Africa.[3-5]

The second group comprised patients with OJ. The OJ incidence was 25.4% in this present study, much higher than the 0.5–13% previously reported in the literature.[33,34,37,38] This finding emphasises the fact that the HCC disease profile in SSA is associated with more aggressive and advanced disease compared to high-income countries, thus requiring a different treatment approach.[3-7,11,28,29,39] In the analysed 28 OJ patients, only 16 underwent BD. There has been a gradual shift from PTBD to EBD in the treatment of OJ in HCC to improve quality of life.[2,12,14-17,20,32,33,36,38,40] At our institution, EBD is performed under conscious sedation by hepatobiliary surgeons. In our experience, this has granted HCC patients easier and more timeous access to EBD. The technical success rate of EBD (72.7%) in our cohort was similar to reported data in the literature.[12-16,32,33,35,36]

Given the high incidence of multifocal disease, unsurprisingly OIT III HCCs were most frequently seen. There was no difference in OS between patients with OJ and those with diffuse hepatic tumour infiltration. This is mostly probably because the presence of jaundice at the time of HCC diagnosis inherently signifies very advanced disease with poor outcomes.[6,7,10-19,28,33,36-38]

In the SSA context, it is well recognised that over 80% of HCC patients are offered BSC as the sole modality of care.[3-8,11,28,29] Effective palliative care in these patients should go beyond standard opioid administration and hospice care. Symptoms of intractable pruritus and cholangitis should be actively managed to improve quality of life and prolong survival in selected patients. It is also worthwhile noting that due to the lack of sorafenib and novel biologic agents at state healthcare facilities, palliative TACE is more often used.[3-5] In this paper, we have shown that carefully selected HCC patients with OJ who underwent BD had improved survival.

Conclusion

To the best of our knowledge, this is the first large experience describing the management of jaundice in HCC outside of Asia. In this cohort of patients, jaundice remains a marker of advanced HCC with limited treatment options and poor survival. However, in carefully selected patients with OJ, BD is beneficial.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

This study was approved by the University of Cape Town Human Research Ethics Committee (HREC Ref no.: 758/2023).

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