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REVIEW ARTICLE

The management and outcomes of hepatocellular carcinoma in sub-Saharan Africa: a systematic review

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Abstract

Background: Hepatocellular carcinoma (HCC) is a leading cause of mortality in sub-Saharan Africa (SSA). This systematic review aimed to appraise all population-based studies describing the management and outcomes of HCC in SSA.

Methods: A systematic review based on a search in PubMed, PubMed Central, Scopus, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), AfricaWide and Cochrane up to June 2023 was performed. PRISMA guidelines for systematic reviews were followed. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration no: CRD42022363955).

Results: Thirty-nine publications from 15 of 48 SSA countries were identified; 3989 patients were studied. The majority (74%) were male, with median ages ranging from 28 to 54 years. Chronic Hepatitis B infection was a leading aetiology and non-cirrhotic HCC was frequently reported. Curative treatment (liver resection, transplantation and ablation) was offered to 6% of the cohort. Most patients (84%) received only best supportive care (BSC), with few survivors at one year.

Conclusion: The majority of SSA countries do not have data reporting outcomes for HCC. Most patients receive only BSC, and curative treatment is seldom available in the region. Outcomes are poor compared to high-income countries.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and accounted for 4.7% (n = 905 677) of all new cancer diagnoses in 2020.[1] Globally, 80% of HCCs emanate from low- and middle-income countries (LMICs), mostly within sub-Saharan Africa (SSA) and South-East Asia.[2,3]

Presented by Dr. Sanju Sobnach in Poster form at the 15th Biennial Congress of the European-African Hepato-Pancreato-Biliary Association, 6th to 9th June 2023, Lyon Convention Centre, Lyon, France.

In SSA, HCC is the second and third leading cancer in men and women respectively. An estimated 38 629 patients on the subcontinent were diagnosed with HCC in 2020, and 36 592 HCC-related deaths occurred during the same year. Age-standardised incidences of 102 per 100 000 have been reported in parts of SSA.[2,4–9]

In high-income countries (HICs), HCC typically occurs in the elderly with a background of liver cirrhosis (LC). Curative-intended therapies in 40% of these patients have resulted in five-year survival rates of above 70%.[1,4,10–13] This is in stark contrast to SSA where the median age of presentation is 45 years

and median survival 2.5 months. More than 70% of patients present with Barcelona Clinic Liver Cancer Classification (BCLC) Stage D disease and less than 1% are treated with curative intent.[4,6–8,11,14]

Due to the paucity of national registries in SSA, epidemiological data for HCC are predominantly derived from non-population-based institutional registries and national histopathology repositories.[5,9] It is postulated that such epidemiological extrapolations have underestimated the true incidence of HCC in SSA by as much as 20%.[15] To overcome this challenge, countries in SSA need to generate robust epidemiological and outcomes data. An appraisal of all HCC treatment and outcomes data in SSA is therefore a critical step in the development of screening, treatment and surveillance programs.[16,17] Thus, the aim of this systematic review was to appraise and analyse all HCC studies describing the management and treatment outcomes in SSA.

Material and methods

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration no: CRD42022363955).

Search strategy

A systematic search of the published literature was performed. There was no language restriction and only human studies were included. PubMed, PubMed Central, Scopus, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), AfricaWide and Cochrane databases were interrogated from their inception to June 2023. During the search, the following keywords were used in various permutations: 'Hepatocellular Carcinoma,' 'Liver Cell Cancer,' 'Liver Cancer,' 'Hepatoma' and 'sub-Saharan Africa.' The Medical Subject Headings (MeSH terms) used to search the databases are shown in Supplementary Table 1.

Study selection

After a comprehensive search of the databases, two reviewers (SS and UK) entered the publications into the Rayyan online systematic review platform.[19] The collated articles were initially screened by title and abstract, and then compared hierarchically to the predefined inclusion and exclusion criteria listed below. Duplicates were removed. Further studies were identified from the references of the chosen articles. Any disagreement on inclusion was resolved thorough discussions between the two reviewers until consensus was reached. A third reviewer (EJ) assisted in cases of further disagreement.

Quality assessment

Two reviewers (SS and EJ) appraised the methodological quality of the selected studies using the Newcastle–Ottawa Scale (NOS). The three domains included in the NOS were selection of patients, comparability of study groups and assessment of outcomes.[20] Due to the predominantly descriptive nature of this study, the 'selection of the non-exposed = S2' and 'comparability = C1 + C2' were not applicable to most of the appraised publications. Thus, studies with no relevant data pertaining to NOS components S2 and C1 + C2, were termed "not relevant (NR)." Hence, studies that could not be evaluated and rated on the NOS 0–9 score were instead ranked with a maximum of six points.

Inclusion criteria were papers that reported on five or more patients with the following data: (a) patient demographics, (b) HCC treatment modalities, and (c) survival outcomes. The exclusion criteria were as follow: (a) papers not relevant to HCC, (b) non-human clinical studies, (c) publications that included only patients who were less than 18 years of age, (d) studies on African populations outside of SSA, (e) publications examining only fibrolamellar HCC and mixed HCC–cholangiocarcinoma, and (f) letters/case reports/editorials/reviews.

Data extraction

Data were sought from the selected articles and transferred onto a predefined electronic data extraction form (Microsoft Excel 365 ProPlus). The extracted data included country of study, first author, year of publication, study period, mean/median age of patients, Hepatitis B Virus (HBV) incidence, proportion of patients with LC, presence of portal vein tumour thrombosis (PVTT), metastatic disease at presentation, HCC treatment and survival outcomes.

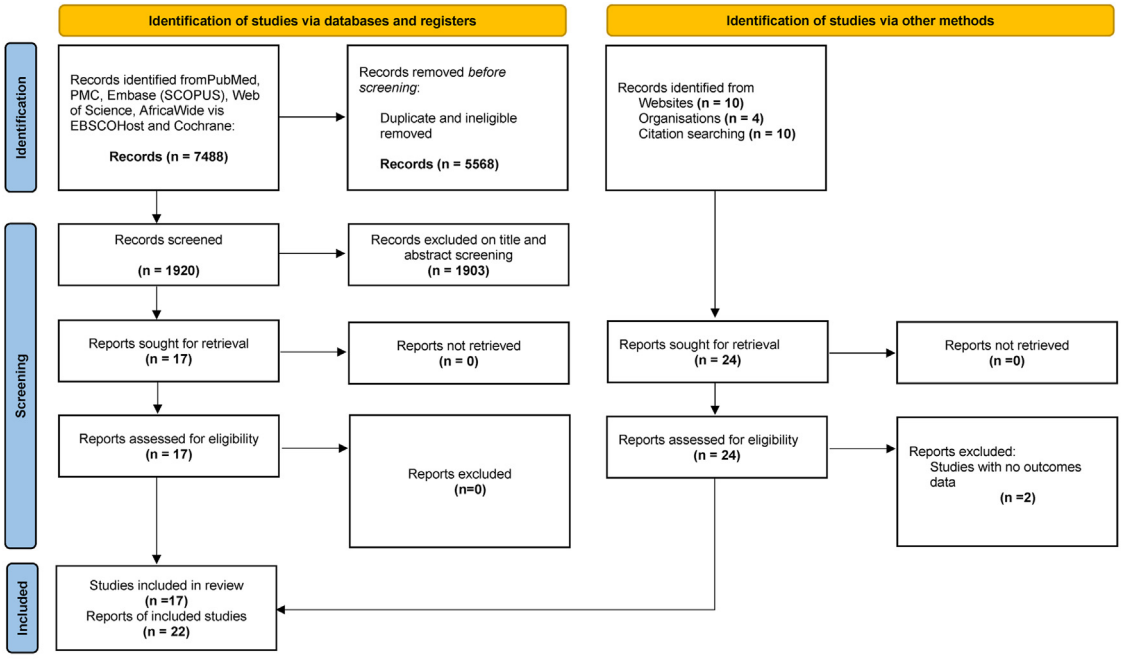
Statistical analysis

The results and outcomes are tabulated as originally reported in the sourced articles. Due to the heterogeneity of the included studies, and variations in the reporting of treatment and respective outcomes, a meta-analysis was not performed.

Results

The results of the systematic literature search are shown in Fig. 1. There were 39 publications from 15 of the 48 SSA countries (Table 1).[21–59] The NOS appraisal of the papers is shown in Table 2. Close to three quarters of all the studies were from Nigeria (10 papers), Ethiopia (five), South Africa (five), Sudan (three), Togo (three) and Uganda (three). Eight countries had a single publication (Fig. 2).

This systematic review comprised 3989 patients, of whom 74% were male. The mean and median ages ranged from 32 to 62, and 28 to 54 years respectively. When HBV testing was performed, the positivity rate peaked at 80%.[21,23,25–29,31–42,46,48,51,52,54–57,59] In 26 studies, five to 80% of HCCs occurred in non-cirrhotic livers.[21–35,37,42,47–50,54,56–59] In nine studies, five to 41% of the patients had PVTT.[25–27,29,31,39,42,51,57] The presence of extrahepatic metastases was documented in two to 59%



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1 PRISMA statement

of patients; the lungs were the most frequent site of spread.[21,23,25–27,29,30,32–36,41–43,50,54,56,57]

The spectrum of treatment offered to patients is detailed in Fig. 3. In 20 studies, patients were offered a single modality of care.[21,23,24,30,31,34,37,39,41,45–52,54,55,58,59] In 21 papers, best supportive care (BSC) was the sole treatment in 90% of the patients.[21–23,28–31,33–39,41,42,50–52,56,57] No publication reported on all available treatment modalities. Notably, 12 studies reported on 1142 patients (29%) treated before 1990.[20–22,28,30–32,41,52–55] Many of these treatments are now obsolete and of historical value only.

Curative intended treatment

Of the 3989 patients, only 228 (6%) were treated with curative intent.

Liver resection

Liver resection (LR) was a treatment modality in 12 studies.[22,27,32,33,42,45,49,53,56–59] Eight of these were single-centre retrospective studies where the proportion of patients undergoing liver resection ranged from 1% to 28%.[22,27,32,33,42,53,56,57] Only one of these reported on LR-related outcomes. This was an appraisal of 60 HCC cases from Nigeria of whom five underwent LR. There were no survivors at a 26-month follow up.[32]

Of the remaining four publications, two were case-control studies and two were cohort studies.[45,49,58,59] The two latter studies were both from Cape Town. Lemmer *et al.* reported on 14 patients who underwent LR with one, three and five-year survival rates of 85%, 75% and 62% respectively.[58] In a follow-up study of 16 patients with NC-HCC from the same centre, Bhaijee *et al.* showed that the one, three and five-year survival rates were 100%, 56% and 38% respectively.[45] In a case-control study of 44 resected patients from Sudan, the 30-day mortality was 9% and there were no long term survivors.[49] Finally, in eight patients who underwent LR in Togo, the peri-operative mortality was 25% but no long term follow up was reported.[59]

Ablation

Ablation for HCC was documented in two studies.[42,48] In a review of 229 HCC cases from Senegal, radiofrequency ablation (RFA) or percutaneous alcohol injection (PAI) were used in 1% and 2% of the patients respectively.[42] A trial by Elsanousi *et al.* from Sudan used PAI as adjunct treatment in 21 patients who had previously undergone hepatic artery ligation for large HCCs. The median survival was 14 months and the one, three and five-year survival rates were 71%, 24% and 5% respectively.[48]

Transplantation

Only one study from South Africa reported the outcomes of LT for HCC in SSA. Thirty-one patients were transplanted with one- and five-year survival rates of 77% and 61% respectively.[46]

Table 1 Quality assessment of included studies

Study	Year	Selection			Comparability		Exposure			No. of stars
		S1	S2	S3	C1	C2	E1	E2	E3	
Nsonde Malanda, J	2018	*	NR	*	NR	NR	*	*	0	4
Ayol-Petty, M	1990	*	NR	*	NR	NR	*	*	0	5
Tsega, E	1977	*	NR	*	NR	NR	*	*	*	5
Tsega, E	1984	*	NR	*	NR	NR	*	*	*	5
Aby, ES	2020	*	NR	*	NR	NR	*	*	*	5
Seid, AS	2020	*	NR	*	NR	NR	*	*	*	5
Abza, GB	2023	*	NR	*	NR	NR	*	*	*	5
Gyedu, A	2015	*	NR	*	NR	NR	*	0	0	3
Rakotozafindrabe, A	2022	*	NR	*	NR	NR	*	0	0	3
Norredam, K	1977	*	NR	*	NR	NR	*	0	0	3
Diarra, M	2006	*	NR	*	NR	NR	*	*	*	5
Muhammad, I	1991	*	NR	*	NR	NR	*	*	0	4
Enwezor, C	1992	*	NR	*	NR	NR	*	*	*	5
Olubuyide, I	1992	*	NR	*	NR	NR	*	*	*	5
Ndububa, D	2001	*	NR	*	NR	NR	*	*	0	4
Mustapha, S	2007	*	NR	*	NR	NR	*	*	0	4
Okonkwo, U	2011	*	NR	*	NR	NR	*	0	0	3
Okonkwo, U	2016	*	NR	*	NR	NR	*	0	0	3
Adekanle, O	2019	*	NR	*	NR	NR	*	*	*	5
Adebayo, O	2020	*	NR	*	NR	NR	*	0	0	3
Okeke, E	2020	*	NR	*	NR	NR	*	*	*	5
Diallo, I	2021	*	NR	*	NR	NR	*	*	*	5
Diallo, S	2022	*	NR	*	NR	NR	*	*	0	4
Berman, C	1967	*	*	*	*	*	*	*	*	8
Madden, M	1993	*	*	*	*	*	*	*	*	8
Lemmer, E	1998	*	NR	*	NR	NR	*	*	*	5
Bhaijee, F	2011	*	NR	*	NR	NR	*	*	*	5
Dempster, M	2019	*	NR	*	NR	NR	*	*	*	5
Elsanousi, O	2018	*	NR	*	NR	NR	*	0	0	3
Elsanousi, O	2019	*	NR	*	NR	NR	*	0	0	3
Elsanousi, O	2021	*	NR	*	NR	NR	*	*	*	5
Jaka, H	2014	*	NR	*	NR	NR	*	0	0	3
Yapo, P	2011	*	NR	*	NR	NR	*	*	*	5
Bouglouga, O	2012	*	NR	*	NR	NR	*	0	0	3
Dossouvi, T	2022	*	NR	*	NR	NR	*	*	*	5
Harrison, N	1973	*	NR	*	NR	NR	*	*	*	5
Olweny, C	1975	*	NR	*	NR	NR	*	*	*	5
Olweny, C	1980	*	NR	*	NR	NR	*	*	*	5
Kiire, C	1988	*	NR	*	NR	NR	*	*	0	4

Palliative treatment

Trans-arterial therapies

The use of trans-arterial chemo-embolisation (TACE) in the management of HCC was reported in three studies from Ethiopia and one from Senegal.[25–27,42] In the three Ethiopian studies, TACE was used in 47%, 16% and 2% of the patient cohorts respectively.[25–27] In a study of 15 HCC patients from Addis Ababa, Aby *et al.* used TACE followed by Sorafenib in 47% of the cohort.[25] In the Senegalese study, TACE accounted for 3% of all treatments.[42] The only TACE outcomes in SSA

Table 2 Characteristics of included studies

Country	Publication	Study period	No. of patients (males) (females)	Mean (± SD) median age (range) yr	HBV (%)	Liver cirrhosis	PVTT (%)	Metastatic disease at presentation	HCC treatment	Outcomes
Congo (Brazzaville)	Nsonde Malanda J et al., SAJ Cancer Sci 2018	2010–2014	286 (201) (85)	Median age: 45 (20–72)	76%	20%	NSP	49%	BSC (100%)	6-mo survival: 27% (biopsies in 167 patients: HCC-159, CholangioCA-6, Mixed-2)
Democratic Republic of Congo	Ayol-Petty M et al., Med Afr Noire 1990	1962–1989	84 (72) (12)	Mean age: 38 (8–70)	NSP	39%	NSP	NSP	BSC (90%) Chemotherapy with Endoxan, Imuran & 5-FU (8%) Liver resection (2%)	6-mo survival: 26% Histology: HCC (95%), CholangioCA (4%), Mixed (1%)
Ethiopia	Tsega E, East Afr Med J. 1977	1972–1974	100 (75) (25)	No mean/ median age mentioned (22–87)	50% (Only 46 tested)	Out of 36 biopsied 22%	NSP	8%	BSC (100%)	In hospital mortality: 21% 8 mo survival: 1%
	Tsega E, Ethiop. Med. J. 1984	NSP	13 (9) (4)	Mean age: 46 (30–62)	NSP	85%	NSP	NSP	i.v. adriamycin	Median survival (mo.): 8 (1–13)
	Aby ES et al., Eur J Gastroenterol Hepatol. 2020	NSP	15 (7) (8)	Median age: 45 (34–50)	60%	73%	40%	13%	TACE + sorafenib (47%) Sorafenib only (54%)	Median survival (days): 106 (62–152)
	Seid AS et al., Expert Rev Gastroenterol Hepatol. 2020	2016–2018	46 (23) (23)	Median age: 54 Range: (45–62)	41%	85%	33%	NSP	Surgery (2%) TACE (17%) Sorafenib (20%) Palliative (33%) Lost to follow up (28%)	Median survival (days): 68 (17–334)
	Abza GB et al., Cancers 2023	2016–2021	369 (246) (123)	Mean age: 52 (±16)	71% (Out of 165 tested)	58%	29%	43% *366 screened	Surgery (8%) TACE (2%) Sorafenib (16%) Chemotherapy (5%) Palliative (69%)	OS: 141 days (CI: 117–165) 1-yr. survival: 26% 3-yr. survival: 8%
Ghana	Gyedu A et al., World J Surg 2015	2007–2013	206 (138) (68)	Mean age: 44 (±14)	52%	63%	NSP	NSP	BSC (98%) Chemotherapy (2%)	50% of cohort demised in hospital during initial presentation
Madagascar	Rakotozafindrabe ALR et al., ecancer 2022	2012–2017	42 (29) (13)	Mean age: 57 (±16) (21–82)	43%	100%	14%	45%	Curative (2%) BSC (98%)	In hospital mortality rate: 24%
Malawi	Norredam K, Trop. Geogr. Med 1977	1971–1972	24 (19) (5)	Mean age: 43 (21–65)	NSP	46%	NSP	29%	BSC (100%)	In hospital mortality: 3% Mean hospital survival: 5 wk.
Mali	Diarra M et al., Med Afr Noire 2006	2000–2001	81 (78) (3)	Mean age: 52 (±15) (14–90)	66%	95%	20%	NSP	BSC (100%)	1 yr survival: 1%
Nigeria	Muhammad I et al., J.R. Coll.Surg. Edinb. 1991	1975–1987	35 (26) (9)	Mean age: 44 (20–70)	70%	94%	NSP	23%	Wedge excision (77%) Hepatic artery ligation (14%) Liver resection (9%)	46% of patients died within 35 days of laparotomy (mean survival: 22 days) 6-mo survival: 6%
	Enwezor CJ et al., Int Surg. 1992	1988	60 (48) (12)	(20–40)	80%	85%	NSP	2%	Liver resection (8%) BSC (92%)	Liver resection group: 0% survival at 26 mo. BSC group: 0% survival at 15 mo.

(*continued on next page*)

Table 2 (*continued*)

Country	Publication	Study period	No. of patients (males) (females)	Mean (± SD) median age (range) yr	HBV (%)	Liver cirrhosis	PVTT (%)	Metastatic disease at presentation	HCC treatment	Outcomes
	Olubuyide IO, Cent Afr J Med. 1992	1987–1989	89 (60) (29)	Mean age: 50 (15–78)	70%	81%	NSP	52%	BSC (100%)	Mean survival: 6 mo. (3 wk–2 yr.)
	Ndububa DA et al., Nig J Med. 2001	1987–1999	154 (104) (50)	Mean age: 46 (±15) (16–80)	61% Only 90 tested	78%	NSP	17%	BSC (97%) Chemotherapy (5FU and/or doxorubicin) 3%	Mean survival: 14 (3–82) wk. Based on 62 documented deaths
	Mustapha SK et al., The Internet Journal of Gastroenterology 2007	2002–2006	100 (79) (21)	Mean age: 49 (±15) (21–75)	67%	NSP	NSP	15%	BSC (99%) Chemotherapy (5FU) (1%)	In hospital mortality: 42% Mean survival: 15 (6–58) wk.
	Okonkwo UC et al., Niger J Med 2011	2007–2008	60 (38) (22)	Mean age: 50 (±15) (19–86)	37%	62%	NSP	NSP	BSC (100%)	In hospital mortality: 58% (Mean duration from symptom onset to death: 20 wk)
	Okonkwo U et al., ijSci 2016	2012–2015	100 (70) (30)	Mean age: 43 (±15) Median age: 40 (12–90)	48%	NSP	NSP	NSP	BSC (97%) Chemotherapy (3%)	33% of cohort demised at 2 mo follow up
	Adekanle O et al., ESJ 2019	01/2010–06/2016	149 (120) (29)	Mean age: 45 (±15) (18–87)	66%	NSP	5%	NSP	BSC (100%)	Median Survival: 20 days OS: 59% at 2 wk. OS: 34% at 1 mo. OS: 7% at 2 yr.
	Adebayo O et al., Ann Ibd. Pg. Med 2020	2011–2014	206 (147) (59)	Mean age: 41 (±15) (17–85)	NSP	NSP	NSP	NSP	BSC (41%) Discharged against medical advice (13%) Death (38%) Surgical care (2%)	38% of cohort died within 15 days of diagnosis
	Okeke E et al., Trop Med Int Health 2020	09/2017–04/2019	101 (72) (29)	Median age: 48 (35–60)	57%	NSP	NSP	13%	BSC (100%)	Median time to death: 70 (23–163) days
Senegal	Diallo I et al., Pan Afr Med J 2021	2012–2017	229 (199) (30)	Mean age: 47 (21–88)	69%	71%	41%	12%	BSC (91%) Hepatectomy (3%) RFA (1%) Percutaneous alcohol injection (2%) TACE (3%)	In hospital mortality: 38% 39% died within 3 mo of diagnosis 14% lost to follow up
	Diallo S et al., Adv Res Gastroenterol Hepatol 2022	01/2018–07/2019	104 (89) (15)	Mean age: 47 (18–78)	66%	95%	37%	59%	BSC (94%) Hepatectomy (4%) TACE (2%) Sorafenib (2%)	Mean survival: 5 (2–13) mo.
South Africa	Berman C et al., SAMJ 1967	1965	25 (All males)	Mean age: 47 (±15) Median age: 28 (20–55)	NSP	NSP	NSP	40%	Pulmonary metastases group-Rx with Epodyl (n = 10) No extrahepatic disease (n = 8)-Rx with Radiotherapy only No extrahepatic disease (n = 7)-Rx with Natulan and Radiotherapy	5-mo. survival: 0% 3-mo. survival: 0% 6-mo. survival: 14%
	Madden MV et al., Gut 1993	1987–1991	50 (46) (4)	Chemotherapy group: 48 (24–70) Symptomatic treatment group: 49 (18–70)	NSP	NSP	NSP	0	Chemotherapy (5-epidoxorubicin) via HAI (n = 25) BSC (n = 25)	Median survival: 48 days Median survival: 51 days

Table 2 (*continued*)

Country	Publication	Study period	No. of patients (males) (females)	Mean (± SD) median age (range) yr	HBV (%)	Liver cirrhosis	PVTT (%)	Metastatic disease at presentation	HCC treatment	Outcomes
	Lemmer ER et al., S Afr Med J 1998	1990–1996	14 (7) (7)	Median age: 40 (18–74)	38% (Out of 8 tested patients)	29%	NSP	0%	Liver resection	1-yr. DFS: 85% 2-yr. DFS: 75% 3-yr. DFS: 62%
	Bhaijee F et al., SAJS 2011	1990–2008	16 (6) (10)	Median age: 55 (22–79)	Nil	0%	NSP	0%	Liver resection	1-yr. survival: 100% 3-yr. survival: 56% 5-yr. survival: 38%
	Dempster M et al., SAJS 2019	2006–2018	31 (26) (5)	Median age: 57 (8–74)	26%	NSP	0%	0%	Liver transplantation	1-yr. survival: 77% 5-yr. survival: 61%
Sudan	Elsanousi OM et al., IJS 2018	2002–2013	44 (32) (12)	Mean age: 59 (±8) (40–75)	NSP	48%	0%	NSP	Liver resection (100%)	30-day mortality: 9%
	Elsanousi OM et al., IJS 2019	01/2013–05/2018	20 (17) (3)	Mean age: 62 (38–76)	6%	85%	NSP	NSP	hepatic artery ligation and extrahepatic collaterals division (HALED) of the liver lobe	30-day mortality: 5%
	Elsanousi OM et al., Ann Med Surg (Lond). 2021	2013–2018	21 (18) (3)	Mean age: 62(±9) (38–76)	52%	81%	NSP	0%	Combined surgical and injection of alcohol	Median survival: 14 mo. 1-yr. survival: 71% 3-yr. survival: 24% 5-yr. survival: 5%
Tanzania	Jaka H et al., World J Surg Oncol. 2014	2009–2013	142 (98) (44)	Median age: 45 (14–76)	66%	66% (Out of 94 biopsied)	NSP	27%	BSC (100%)	In hospital mortality: 46%
Togo	Yapo P et al., Rev int sc méd. 2011	1997–2005	8 (6) (2)	Mean age: 45 (32–63)	50%	40%	NSP	0%	Liver resection (100%)	Peri-operative mortality: 25%
	Bouglouga O et al., Rev. med. Madag. 2012	2004–2010	155 (115) (40)	Mean age: 48 (15–90)	22%	80%	36%	NSP	BSC (100%)	6-mo survival: 60%
	Dossouvi T et al., Surg Res 2022	2018–2020	98 (65) (33)	Mean age: 49	50%	100%	NSP	NSP	BSC (100%)	12-mo survival: 2%
Uganda	Harrison NW et al., BJS 1973	1969–1972	120 Only 36 analysed in study (24) (12)	Mean age: 38 (16–65)	NSP	NSP	NSP	0%	Liver resection (28%) Hepatic artery infusion (44%) Systemic chemotherapy (21%) BSC (21%)	Liver Resection: Median survival of 7 mo. Hepatic artery infusion: Median survival of 6 mo. BSC: Median survival of 1 mo.
	Olweny CLM et al., Cancer 1975	1973	14 (All males)	Mean age: 45 Range: (34–68)	21%	71%	NSP	14%	i.v. Adriamycin	Median survival: 8 (range: 1–13) mo.
	Olweny CLM et al., Cancer 1980	1973–1979	139 (107) (32)	Mean age: 35 (9–75)	45% (Out of 55 tested)	NSP	NSP	NSP	Intra-arterial Adriamycin ± (dichloromethotrexate, 5-azacytidine, rezoxane and cyclophosphamide)	Complete responders (n = 7), Mean survival:9 (1–48) mo. Partial responders (n = 130), Mean survival: 3 (1–9) mo.

(*continued on next page*)

Table 2 (*continued*)

Country	Publication	Study period	No. of patients (males) (females)	Mean (± SD) median age (range) yr	HBV (%)	Liver cirrhosis	PVTT (%)	Metastatic disease at presentation	HCC treatment	Outcomes
Zimbabwe	Kiire CF, Trop Gastroenterol 1988	1984–1987	439 (390) (49)	Mean age: 32 (4–74)	44% (Out of 210 tested)	80% (in 268 biopsied patients)	NSP	12%	BSC (99%) Hemi-hepatectomy (1%)	In hospital mortality: 50% Mean survival time from diagnosis: 7 (0–30) wk.

Abbreviations: 5 fluorouracil (5FU), best supportive care (BSC), cholangiocarcinoma (CholangioCA), confidence interval (CI), disease free survival (DFS), hepatitis B virus infection (HBV), hepatocellular carcinoma (HCC), intravenous (i.v.), month (mo.), not specified (NSP), overall survival (OS), portal vein tumour thrombosis (PVTT), trans-arterial chemo-embolisation (TACE), weeks (wk.), year (yr.).

were reported by Seid *et al.*; the median survival was 353 days.[26] Hepatic artery infusion (HAI) was used as palliative therapy in two studies.[44,53] In an analysis of 36 HCC patients from Uganda, 17% underwent HAI with a median survival of seven months.[53] In a landmark randomised controlled trial from Cape Town of BSC versus HAI for advanced HCC, Madden *et al.* showed that patients receiving HAI with 5-epidoxorubicin did not survive longer.[44] There were no reports of trans-arterial embolisation (TAE) or trans-arterial radio-embolisation (TARE) in SSA.

Oncologic therapy

The use of sorafenib was mentioned in only two Ethiopian studies.[25,26] In patients who received Sorafenib, the median survival was 106 days.[25] No studies reported on treatment with novel biological targeted therapies.

Eleven studies reported on palliative chemotherapy, including Adriamycin, 5-Fluoracil in combination with Doxorubicin, Procarbazine and Triethylene glycol diglycidyl ether.[22,24,27,28,35,36,38,43,53–55] Patients treated with Adriamycin had a median survival of seven to eight months.[24,54] In a study by Berman *et al.*, the use of Triethylene glycol diglyceridyl ether showed no survival benefit in patients with pulmonary metastases. In the same study, none of the patients treated with radiotherapy were alive at three months.[43]

Best supportive care

This was the most frequently reported treatment modality. In eleven papers, BSC was the sole treatment administered. The outcomes were poor with an in-hospital mortality ranging from 3% to 58%. Only 1%–2% of patients were alive at one year.[21,23,30,31,34,37,39,41,50–52]

Discussion

Hepatocellular carcinoma is the malignancy with the highest annual fatality ratio (0.96) in SSA and predominantly affects young Africans.[1,4,8,60,61] With a population of just over 1.2 billion and a peak crude incidence rate of 15 per 100 000, it is concerning that over the last four decades there have only been 39 published HCC outcomes studies from SSA.[62,63] This systematic review confirms this paucity of data, provides invaluable insights into the disease burden and its management in SSA. Furthermore, the data reiterate the significant differences that exist between HICs and SSA, particularly with regards to demographics, disease presentation, treatment strategies and survival outcomes.

This literature review yielded 39 studies and included 3989 patients. Data were available from only one third of all SSA countries.[21–59,63,64] The paucity of national registries in SSA presents a significant obstacle for the accurate estimation of the true incidence of HCC in the region.[15] The reliance on non-population-based institutional registries and national histopathology repositories are likely to underestimate HCC incidence. Patients in SSA were younger than those from Asia, North America and Europe, where the median age at diagnosis is over 60 years.[12,13,65,66] The male preponderance was in keeping with previous reports.[10,11,13,60,61,66–68] Chronic HBV infection is endemic in many parts of Africa and remains the predominant aetiology of HCC.[4,5,8] Over the last three decades, many 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.[2,69–73] The frequent occurrence of NC-HCC in combination with the high prevalence of PVTT (41%) and extrahepatic metastases (59%) in this systematic review support the impact of this HBV carcinogenic pathway.[21–23,27,29–32,34,43,45,47–49,57]

Unfortunately, HCC remains a fatal disease of the young in SSA with a median survival of 2.5 months.[7] This emphasises the urgent need for better disease surveillance in those at risk, improved access to standardised therapies and palliative care services for HCC patients in the region. Moreover, HBsAg screening of pregnant women and the provision of Tenofovir

Figure 2 Countries in sub-Saharan Africa with and without published studies

prophylaxis in the second trimester to highly viraemic women (HBV DNA > 200 000 IU/ml) together with the integration of the HBV birth dose vaccination into national vaccination programs within all public health care facilities is a critical step in preventing mother-to-child transmission of Hepatitis B (PMTCT). This is essential as the early age of chronic hepatitis B infection is associated with increased risk of cirrhosis and HCC and PMTCT will help address the HCC pandemic throughout Africa.[4,74–77] One of the striking differences between HCC care in HICs and SSA is undoubtedly the limited access to curative-intended therapies in the latter. The routine availability of LR, LT and ablation in HICs has resulted in five-year survival rates of above 70% for HCC. This is in contradiction to SSA where less than 1% of patients receive curative treatment because of late presentation, limited resources and lack of specialised centres.[7] In this systematic review, the higher proportion of patients benefiting from curative-intended therapies (6%) is likely due to the selective patient populations reporting. Most patients (84%) received only BSC and there were almost no survivors at one year. Adding to the burden is a general lack of good palliative or end of life care. It is alarming that the survival in those managed with BSC was not dissimilar to the natural history of untreated

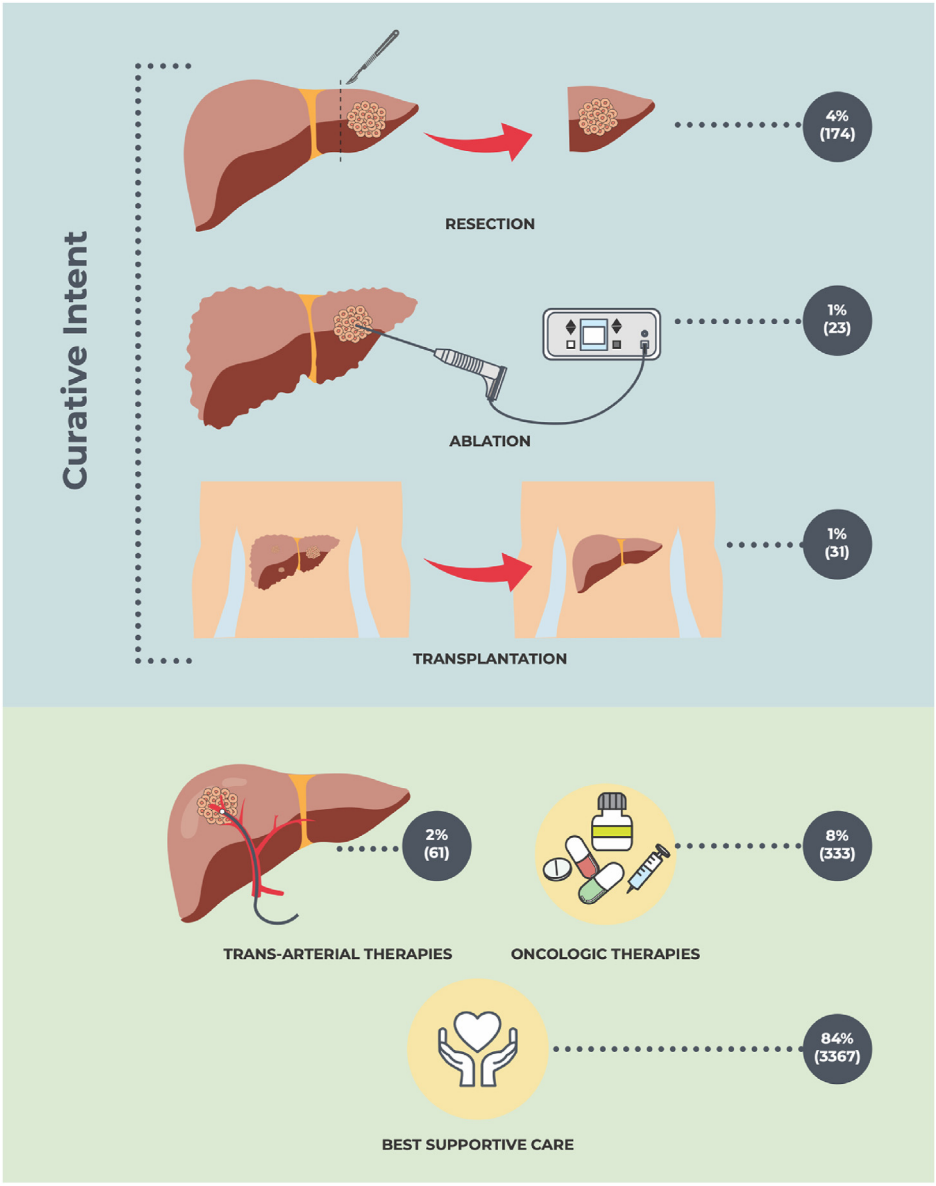


Figure 3 Hepatocellular carcinoma treatment in 3989 patients

HCC.[21,23,30,31,34,37,39,41,51–53] This was well substantiated in a study of untreated HCC patients from Nigeria, where the mean survival from hospital admission to death was three weeks. Mortality resulted mainly from hepatic failure and tumour rupture.[34]

This exposé highlights the need for developing and implementing cost-effective and sustainable therapies for HCC in SSA. Using a 'one size fits all' approach and applying the BCLC criteria to all HCC patients in SSA is not an appropriate strategy.[8,11] The occurrence of large tumours in normal livers, presentation at young age, frequent PVTT and metastatic disease, poor response to conventional therapies and high mortality may indicate poor biology.[21–59,64,65,70,71,74] This systematic review includes seven studies that investigated drugs and surgical strategies to manage HCC in SSA, four of which were reported before 1990.[24,43,44,47,48,54,55]

This systematic review highlights several areas for future research which could guide and facilitate changes in healthcare policy to optimally address the challenges in HCC care in SSA. The establishment of comprehensive national registries and improved data collection systems will allow for more accurate and representative epidemiological data collection. This will consequently support the modelling required for the estimation of need for different treatment strategies to direct infrastructure development. Modelling based on the prevalence of risk factors, in particular chronic HBV infection and the impact of primary prevention on

the prevalence over time, as well as the impact of screening on surveillance of patients at risk for HCC on stage migration will aid in the design and planning of health care strategies and facilities. Research on novel biological targeted therapies, trans-arterial therapies, and advanced oncologic treatments in the SSA population is essential. It has been reported that less than 1% of trials on systemic and local therapies are done in Africa.[78]

This data will foster advocacy for improving healthcare infrastructure, including diagnostic facilities, treatment centres, and multidisciplinary care teams which are all vital in optimising management of HCC. Identifying HCC at an earlier stage will improve treatment outcomes and patient survival.

In conclusion, our systematic review provides important perspectives into the management and outcomes of HCC in SSA. The incidence, presentation of patients with advanced disease and limited access to curative treatments underpin the crucial need for new approaches in SSA. Strategic planning must include broad-based concerted investments in preventive strategies, early detection, improved access to curative therapies, advancements in research and a deepened understanding of the disease on the continent. Africa must lead collaborative efforts between regional policy makers, healthcare authorities and local and international researchers to improve the outcomes and reduce the burden of HCC in SSA.

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.09.015.