Original article

Knowledge and practice on magnitude, diagnosis, treatment and prevention strategies of Hepatocellular Carcinoma in Ethiopia: A Systematic Review

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Abstract

Introduction: In Ethiopia, hepatocellular carcinoma (HCC) is the most common cancer with 100% fatality rate. HCC cases in low income countries die within few months following diagnosis. There is lack of information on the burden, risk factors, diagnosis modalities, surveillance strategies and treatment approaches to HCC in Ethiopia.

Objective: To analyze the existing evidence related to burden, risk factors, diagnosis modalities, surveillance strategies, and treatment and prevention strategies of HCC in Ethiopia.

Methods: All studies done on HCC in Ethiopian irrespective of year of publication and study types were included. Literatures were retrieved from electronic database of PubMedand Cochrane library during September/2016 to January 2/2017. Key words and mesh terms such as 'hepatocellular carcinoma', 'hcc', 'hepatoma', 'malignant hepatoma', 'hepatocarcinoma' were used to search for documents. Besides, we searched for articles, guidelines and reviews from world health organizations, lancet and Google scholar sites. Each of the retrieved studies was assessed by two authors for inclusion based on the eligibility criteria, and for quality using the critical appraisal checklist. Qualitative data were synthesized for analyzing the theories of studies. Medley reference manager was used to manage citations.

Results: A total of 1448 literatures were retrieved. Eight studies fulfill the eligibility criteria, however, only three were full-fledged articles. HCC is clinically characterized by exhaustion, loss of appetite, rapid loss of weight, epigastric pain, right upper abdominal quadrant pain with a rapidly growing mass, jaundice, and ascites with or without hepatomegaly and splenomegaly. Data on HCC proportion among liver disease patients lies between 16.1%-19.2%. Cirrhosis followed by hepatotoxic indigenous drugs and viral hepatitis were found to be as major risk factor for HCC. In Ethiopia, there is no surveillance activity and no standard staging systems. Furthermore, there was no policy frame -work for management of HCC.

Conclusion: As compared to other countries, Ethiopia is far behind in addressing HCC. There is no national policy framework and guideline for the management of HCC. Moreover, HCC is a neglected cancer that is considered as a death penalty by the community. Health professionals working in health facilities and health offices should share the data they have to the scientific community and policy makers, for further searching solutions and informed decision, respectively. An intensified public health strategy on health education and early case detection is of critical importance. In addition concerted effort should be made to develop HCC prevention and treatment modality. [*Ethiop. J. Health Dev.* 2017;31(1):44-56]

Key words: Hepatocellular Carcinoma, Ethiopia

Introduction

In 2013, there were 792,000 incidence of liver cancer globally and 818,000 deaths with 44-86% occurrence in developing countries (1,2). Liver cancer is the fifth incident cases and second cause of mortality in developing countries (1–4) but there is still no comprehensive description of the current status of its epidemiology in Africa (5). Mozambique is the highest burden of HCC in Africa; studies showed that HCC has two major patterns in Africa: Hepatitis C virus (HCV) related in Egypt, north of the Sahara, and Hepatitis B Virus (HBV) related in sub-Saharan countries(6). Moreover, it occurs at earlier age in Africa, at a median of 45 years and with advanced stage(5)**.** HCC control in Africa is a daunting prospect because of lack of awareness about risk factors and equipped facilities in terms of human power and infrastructure (6).

In Ethiopia, HCC is the eighth most common cancer with 100% fatality rate among males (7). Most of the HCC cases in low income countries like Ethiopia die within few months (<2.5 months) following diagnosis. This might be due to lack of facility for cancer screening ,lack of skill to differentially diagnose HCC

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from other diseases and late arrival of cases in seeking medical care (4,7).

Observation of HCC case struggling to live with HCC prompted us to review associated situations and countries' response to it. Moreover, there is lack of information on the burden, risk factors, diagnosis modalities, surveillance strategies and treatment approaches to HCC in Ethiopia.

Thus, the purpose of this review was to analyze existing evidence related to burden, risk factors, diagnosis modalities, surveillance strategies, and treatment and prevention strategies of HCC in Ethiopia.

Methods

***Eligibility Criteria*: S**tudies that assessed the HCC proportion, clinical and laboratory features, associated factors, diagnostic methods, treatment and prevention strategies in Ethiopia were included. Those papers published in English Language were reviewed.

Search Methods: Literatures were retrieved from electronic database of PubMed and Cochrane library between September/2016 and January 2/2017 using key words and mesh terms related to HCC prevalence, diagnostic modalities, and treatment and prevention strategies in Ethiopia .The key words include 'hepatocellular carcinoma', 'hcc', 'hepatoma', 'malignant hepatoma', 'hepatocarcinoma,'magnitude', 'prevalence','proportion','clinical diagnosis', 'laboratory diagnosis','radiological diagnosis','pathological diagnosis','Treatment', 'control', 'prevention', 'Ethiopia'. The search was limited to articles published in English language in human subject (Table 1). Moreover, we also hand searched articles, guidelines and reviews from World Health Organizations (WHO), lancet and Google scholar.

Table 1: **Search strategy used to retrieve appropriate literatures using Mesh terms, Bahir Dar, Ethiopia, 2017.**

Database/ Search date	**Search strategy/mesh terms**	**Number of papers retrieved**
Cochrane Database of Systematic Reviews: Issue 12 of 12, December 2016/ **Sep 1/2016 - January 2/2017**	#1"hepato-carcinoma":ti,ab,kw or "HCC":ti,ab,kw or "hepatoma":ti,ab,kw and "Ethiopia" with Hepato-Biliary Group in Review Groups (Word variations have been searched) #2"hepatocellular carcinoma":ti,ab,kw or "HCC":ti,ab,kw or "hepatoma":ti,ab,kw and "diagnosis":ti,ab,kw and "Ethiopia":ti,ab,kw with Hepato-Biliary Group in Review Groups (Word variations have been searched) #3"hepatocellular carcinoma":ti,ab,kw or "HCC":ti,ab,kw or "hepatoma":ti,ab,kw and "treatment":ti,ab,kw and ethiopia:ti,ab,kw with Hepato-Biliary Group in Review Groups (Word variations have been searched) (#1and #2 and #3)	524
PubMed/ **Sep 1/2016 - January 2/2017**	((((("Carcinoma, Hepatocellular"[Mesh]) OR "HCC1 autoantigen" [Supplementary Concept]) OR ("Adenoma, Liver Cell"[Mesh] OR "Liver Neoplasms, Experimental"[Mesh])) AND ("Cross-Sectional Studies"[Mesh] OR "epidemiology" [Subheading] OR "Epidemiology"[Mesh] OR "Prevalence"[Mesh])) AND "Ethiopia"[Mesh]	5
	((((("Carcinoma, Hepatocellular"[Mesh]) OR "HCC1 autoantigen" [Supplementary Concept]) OR ("Liver Neoplasms, Experimental"[Mesh] OR "Adenoma, Liver Cell"[Mesh])) AND ("Diagnosis"[Mesh] OR "Early Diagnosis"[Mesh] OR "Diagnosis, Computer-Assisted"[Mesh] OR "Immunologic Tests"[Mesh] OR "Early Detection of Cancer"[Mesh] OR "Clinical Laboratory Techniques"[Mesh] OR "diagnostic imaging" [Subheading])) AND "Ethiopia"[Mesh]	4
	(((((("Carcinoma, Hepatocellular"[Mesh]) OR "HCC1 autoantigen" [Supplementary Concept]) OR ("Liver Neoplasms, Experimental"[Mesh] OR "Adenoma, Liver Cell"[Mesh])) AND "Therapeutics"[Mesh]) OR "prevention and control" [Subheading]) AND "Ethiopia"[Mesh]	803

***Study Selection*:** All of the identified studies were listed. Studies retrieved from PUBMED independently assessed the fulfilment of the inclusion criteria by two of the authors (Biadglegne F and Derbie A). Studies retrieved from Cochrane library independently assessed the fulfilment of the inclusion criteria by two of the authors (Zenebe Y and Adem Y). Disagreements regarding the inclusion or exclusion of publications were resolved by discussion.

Critical appraisal of studies for quality: Two authors (Mekonnen D and Biadglegne F) assessed the quality of selected studies using the critical appraisal checklist published by the critical appraisal skills programme (CASP), Oxford, UK(8). We assessed the risk of bias by assessing the methodological quality of the studies and level of evidence for the research question. Disagreements on grading the level of evidences were resolved by discussion (Table 2).

Table 2: **Critical appraisal of articles included in the review, Bahir Dar, Ethiopia, 2017**

S/N	Papers (Full Title)	Level of evidence based on the study design (High, moderate, low, very low) Reflections, concerns, on limitations or strengths	Final evaluation on level of evidence for our research question
1	A review of a five (5) years experience (Sept. 2004-Aug. 2009) with hepatic resections at Gonda rUniversity Hospital (GUH). Worku et al *Ethiop Med J*. 2013 Jan;51(1):59-65	**Very low** Not representative, no history of follow up data for other patients' , service is interrupted now	Very low
2	Major Risk Factors, Clinical and Laboratory Characteristics of Patients With HCC: A retrospective Study at Tikur Anbassa Hospital, Ethiopia. Mekonnen et al *Ethiop Med J, 2015*	**Very low** Few sample size, Incomplete data, Differential /non differential/ bias	Very low
3	Hepatitis C virus infection and chronic liver disease in Ethiopia where hepatitis B infection is hyper endemic. Tsega et al. *Trans R Soc Trop Med Hyg*. 1995	**Very low** Very small sample size, Too old, selection bias, Inconsistency	Very low
4	Primary carcinoma of the liver in Ethiopia. A study of 38 cases proved at post-mortem examination. Pavlica D & Samuel I. *Br J Cancer.* 1970 Mar; 24(1):22-9.	**Very low** Information bias, Very old data No laboratory data	Very low
5	Chronic liver disease in Ethiopia: A clinical study with emphasis on identifying common causes. Tsega et al. *Ethiop Med J*. 1992 Apr;30(2 Suppl):1-33	**Moderate** Small sample size, selection bias	Low
6	Hepatocellular carcinoma in Ethiopia. A prospective clinical study of 100 patients. Tsega E *East Afr Med J*. 1977 May;54(5):281-92	**Low** Selection bias, Confounding bias, Sampling bias, Lost to follow up, No full text article, Too old data	Very Low
7	Current views on liver diseases in Ethiopia. Tsega E *Ethiop Med J.* 1977	**Very low** No full article, Sample size not known, Too old data	Very low
8	Histopathological features of liver disease in hospitalized Ethiopian patients. Fekade D. *Ethiop Med J.* 1989	**Very low** No full text article, Too old data Information bias, Researcher bias	Very low

***Data extraction and management*:** The proportions of HCC, clinical characteristics, risk/associated/ factors, laboratory characteristics presented in the studies were collected. Three authors (Mekonnen D, Elfu B and Hailu D) extracted all data independently. Disagreements on the synthesized data were resolved by discussion. In addition, qualitative data were collected from 12 senior internists and 4 surgeons using them as key informants; to document the current practices and help as an illustration to the review. Semi-structured questionnaire was used to identify gaps and guided the interview (Table 3). Moreover, a case history of one HCC patient also summarized. Mendley reference manager was used to manage citations.

Results

Study selection: A total of 1448 literatures were retrieved (912 from PubMed, 524 from Cochrane library, 5 from lancet, 5 from Google scholar and 2 from WHO). After removing the duplicates and screening, 27 articles were assessed for eligibility based on the criteria. Eight studies fulfill the eligibility criteria (Figure 1).

Table 3: **Results of the key informant interviews regarding HCC, Bahir Dar, Ethiopia, 2017**

S/n	Discussion points	Summarized key informant responses
1	Staging system	American Association for the study of Liver diseases (AASLD) Okuda Tumor node metastasis (TNM)
2	Risk Factors	Liver cirrhosis Chronic infection with Hepatitis B Chronic infection with Hepatitis C viruses Aflatoxin intoxication
3	Preventions	HBV vaccination
4	Imaging technique	Ultrasound Computed tomography
5	Pathological technique	Ultrasound guided fine needle aspiration
6	Lab Techniques	Alpha-1 fetoprotein
7	Surveillance Strategies	No Surveillance Strategies
8	Treatment	No treatment except supportive treatment
9	National guideline	No
10	operational policy, strategy or action plan	No

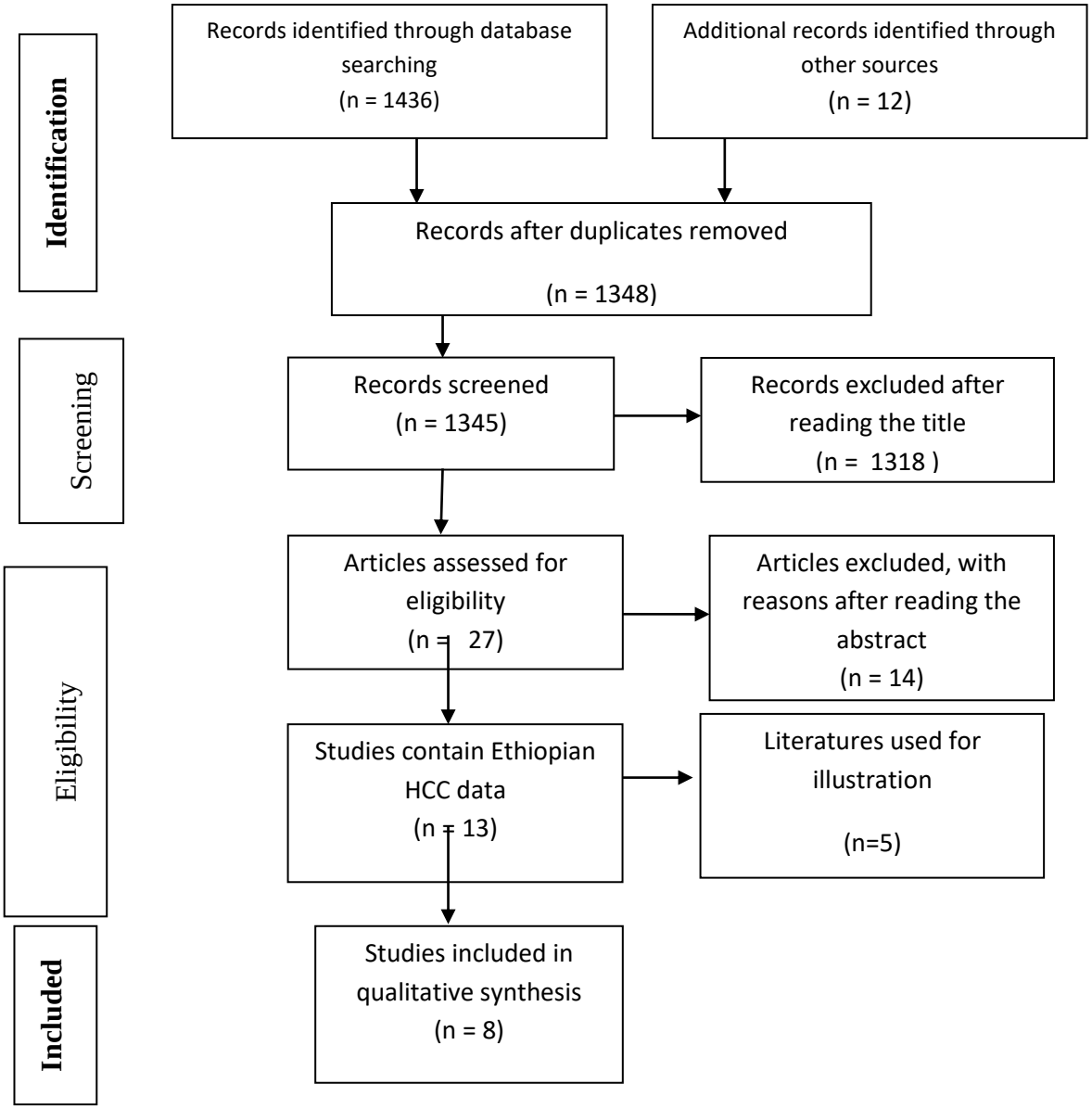
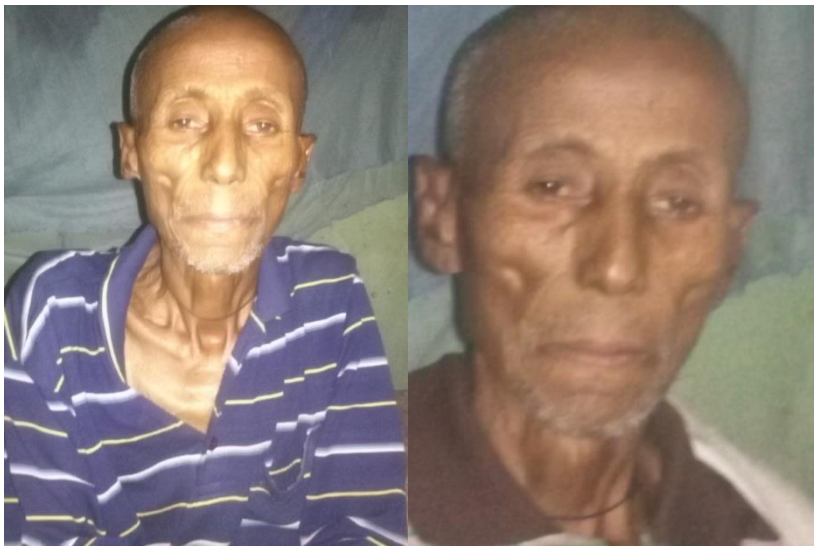


Figure 1: **A flow diagram for selection of identified studies, Bahir Dar, Ethiopia, 2017**

Study characteristics: Eight studies were included in the review (Table 4). However, full test article was retrieved only for three of the studies (9–11). Furthermore, except two studies (9,12), the year of publication lies between 1970-1995 G.C which is relatively old (10,11,13–16). Except three studies (10,11,14), all the remaining are published in Ethiopian Medical Journal (9,12,13,15,16). Six studies are retrospective and/or cross sectional study in design (9–12,15,16) and the other two are follow up types (13,14).The numbers of participants under each study were very small. Mekonnen et al (2015) review basic demographic factors, risks, laboratory profiles and imaging reports of 51 HCC patients. Of those 39 were male and 12 were female with age group ranged between 18 to 65 years(9). Tsega et al (1995) studied 51 males and 17 females HCC patients with mean age of 49±13.1 (10). In the Pavlica D & Samuel I (1970) study, 35 male and 3 female were included and their age lies between 23-67 years (11). Worku et al (2013) report 9 HCC cases with resection history (12). Tsega et al (1992) define clinical features and associated risk factor for 112 young male HCC cases admitted to hospital between July 1986 and April 1989 (13). Tsega E (1977) assessed the clinical and laboratory features, and associated risk factors of 100 HCC patients, of whom one-third were under the age of 40(14). Fekade D (1989) analyzed 704 patients' biopsy done at Addis Ababa University hospital with liver diseases; of whom HCC accounted 135 (19.2%) of study subjects (16) (Table 4).

Risk of bias within and across the studies: One or more types of bias such as information, selection and confounding bias were observed within studies (Table 2). Six studies are retrospective and/or cross sectional study in design (9–12,15,16) and the other two are follow up types (13,14).The sample size in each study was very low. Furthermore, most of the results did not use any statistical method and were of qualitative reports. Thus, bias is likely high in all reports. There was also heterogeneity across studies' report.

***Synthesis of results*:** Data on HCC proportion among liver disease patients lies between 16.1% (11) and 19.2% (16). The clinical feature of HCC patients reported were exhaustion, loss of appetite, rapid loss of weight, epigastric pain, right upper abdominal quadrant (RUQ) pain with a rapidly growing mass, jaundice, and ascites with or without hepatomegaly and splenomegaly (9,13–15). This, clinical case definition is in line with the case reported below. Mr. Mekonnen Nigus was a hard working farmer living in rural village Raya Kobo Woreda, Amhara National Regional State, Ethiopia. He had a history of splenomegally and frequent malaria infection at his young age. He didn't have previous history of hepatitis. He sometimes drinks local beer. As a farmer, he frequently cultivates and harvests Maize, Teff, Sorgum and Pepper. He repeatedly visited the nearby health centers for medical intervention. However, health professionals diagnosed him as gastritis. When his condition worsens, he was taken to Dessie private hospital; there, he diagnosed with advanced stage of HCC. The physician advised his families for house rest and palliative care. His chief complaint was exhaustion, loss of appetite, rapid loss of weight, epigastric pain, a big, hard, tender and grossly palpable nodular liver. Mr Mekonnen Nigus died one month after he diagnosed; on June 6, 2015 G.C at the age of 74 years.



Mr Mekonnen Nigus (1941-2015 G.C).

Except two studies, the remaining six studies reported one or more associated factors for HCC (9–11,13–15). Cirrhosis as a risk factor for HCC have been reported by four studies (11,13–15) and hepatotoxic indigenous drugs by three studies (11,14,15), viral hepatitis by three studies (9,14,15) with one conflicting result (10) (Table 4).

Table 4: **Summary of local scientific evidences on HCC Bahir Dar, Ethiopia, 2017**

Authors, year of publication	Papers (Full title)	Major findings
Mekonnen *et al* 2015 (9)	Major Risk Factors, Clinical and Laboratory Characteristics of Patients With HCC: A retrospective Study at Tikur Anbassa Hospital, Ethiopia	**Risk Factors** ❖ Hepatitis B and C viruses =48% ❖ History of alcohol abuse was =45% **Clinical features** ❖ right upper abdominal pain =88.2 % ❖ as cites =21.6 % ❖ portal vein thrombosis =41.2 % ❖ hepatomegaly=70.6 % ❖ splenomegaly =19.6 % **Laboratory characteristics; AFP level of** ❖ 500 = 19 (43.2 %) ❖ < 20 =11 (25 %) ❖ 200-500= 8 (18.2 %)
Tsega *et al* 1995(10)	Hepatitis C virus infection and chronic liver disease in Ethiopia where hepatitis B infection is hyper endemic.	❖ For both HBV and HCV their association with HCC was not significant, P>0.05
Pavlica D & Samuel I 1970 (11)	Primary carcinoma of the liver in Ethiopia. A study of 38 cases proved at post-mortem examination	**Proportions** ❖ 38/236 HCC cases identified ❖ PHCC account for 20%death in medical ward **Associated factors** ❖ Cirrhosis ❖ Histotoxic agents like Mycotoxin and indigenous drugs
Worku *et al* 2013 (12)	A review of a five (5) years of experience (Sept. 2004-Aug. 2009) with hepatic resections at Gondar University Hospital (GUH)	**Proportion** ❖ 2/9 resections death reported
Tsega *et al* 1992 (13)	Chronic liver disease in Ethiopia: a clinical study with emphasis on identifying common causes	**Clinical Features** ❖ Exhaustion, loss of appetite, rapid loss of weight, epigastric pain, a big, hard, tender and grossly nodular liver with bruit, signs of portal hypertension, and/or hepatic encephalopathy **Laboratory Features** ❖ Serum anti-nuclear factor, anti-mitochondrial anti-bodies and anti-smooth muscle anti-bodies were absent ❖ Hepatitis B virus markers =78% HCC patients ❖ The HBsAg carrier state =23% ❖ 58 (52%) HCC have >500 mg/ml AFP **Risk Factor** ❖ 85% of HCC =macro nodular cirrhosis
Tsega E 1977 (14)	Hepatocellular carcinoma in Ethiopia.Apro spective clinical study of 100 patients	**Clinical Features** ❖ Upper abdominal pain with a rapidly growing mass, jaundice, and ascites ❖ In 12 patients, fever was the primary admission complaint. ❖ Hepatic bruit over an enlarged liver =80% of patients ❖ Liver function tests and analysis of ascitic fluid were unpredictable. ❖ None of the paraneoplastic syndromes were observed in the 100 patients. **Laboratory Features** ❖ 65% of the patients but none of the control group were positive for alpha-fetoglobulin. ❖ 50% of the patients and 7% of the control subjects had demonstrable HBsAg in their sera ($p<0.001$). **Risk Factors** ❖ Medicinal herbs and/or dietary hepatotoxins ❖ Viral hepatitis ❖ Cirrhosis
Tsega E 1977 (15)	Current views on liver diseases in Ethiopia	**Clinical Features** ❖ Anorexia, weight loss, persistent, burning, right upper quadrant pain, and a hard, nodular, tender RUQ mass. Over 5% of malignancies seen were HCC **Risk Factors** ❖ viral hepatitis, cirrhosis, Herbal medicines, aflatoxins
Fekade D 1989 (16)	Histopathological features of liver disease in hospitalized Ethiopian patients	Proportion HCC for accounted 135 (19.2%) of all diagnoses

Key informants interview result showed that different staging system is used by different clinicians due to lack of governing guideline. Moreover, liver cirrhosis, HBV, HCV and afla toxin intoxication mentioned as a risk factor. There are no regular surveillance activities. Furthermore, there is no policy framework and national guideline for management of HCC (17). Alfa feto protein (AFP) was the most widely used diagnostic marker; Ultrasound (US) guided fine needle aspiration was rarely used (Table 3).

Discussion

Updated scientific literatures regarding the HCC epidemiology, risk factors and clinical and laboratory characteristics in Ethiopia is very limited. Moreover, diagnostic modalities, surveillance strategies, and prevention and treatment options are none. Only eight literatures identified, of which six are too old to represent the current situation. Moreover, the studies were very limited in scope; focused on prevalence, clinical markers for HCC and associated factors (Table 2). Furthermore, studies were retrospective in design with very small subjects. Despite that, our review showed that HCC is clinically, a well characterized disease and shouldn't confused with other diseases. However, according to the case reported here, they often miss diagnosed (13). This might be due to lack of awareness about HCC among low and middle level health professionals.

The proportion of HCC among patients with liver disease was between16.1% (11) and 19.2% (16). However, these studies used small sample size; lack appropriate methodology, and too old to represent the current prevalence. Thus, both institution and community based survey is required to clearly show the incidence and prevalence of HCC in Ethiopia.

According to this review, Cirrhosis (11,13–15) followed by hepatotoxic indigenous drugs (11,14,15) and viral hepatitis were found to the major risk factor for HCC in Ethiopia. Moreover, data from our informants review showed that liver cirrhosis, chronic infection with HBV and HCV, and aflatoxin were the major associated factors with HCC. Unlike our review and key informant report, recent data emerged from lancet emphasizing the role of viral hepatitis (5,6) and underscore the role of hepatotoxic indigenous drugs and aflatoxin.

Data on the prevalence of HBV were surplus and lies between 3.7and 16.8% (18). Different small scale cross sectional study showed the increased rate of HCV which lies between 3.6 to 10 % (19–23). One study in Ethiopia aimed at analyzing the levels and frequency of AFT contamination in consumed cereals using a total of 595 food samples (24). Aflatoxin B and G was the predominant form, 30% and 6%, respectively. The highest levels of AFB were observed in peanut and sorghum samples (24). Thus, large scale follow up study is mandatory to identify the prevailing factors in Ethiopia.

Data on diagnostic modalities used in Ethiopia are none in our review except AFP. The key informant interview report showed that US and AFP frequently used diagnostic modalities among presumptive liver disease patients in Ethiopia. However, the use of biopsy as a diagnostic tool is discouraged. This might be due to lack of technically equipped pathologists and/or lack of pathologist. Moreover, it should be always guided with US and only recommended for lesions larger than 1 cm (25–27). Furthermore, with biopsy, there is inherent limitation in differentiating between high-grade dysplastic nodules and HCC (25–27). And also in patients with indeterminate biopsy result, repeat biopsy and/or imaging are recommended (28). Thus, the use of biopsy is very limited. Computed topography (CT) and magnetic resonance Imaging (MRI) was only found in a few health facilities (Table 3).

Except some beginning at the University of Gondar (12), there was no any treatment modalities (Table 3, 4). This might be due to resources constraints, competitive priorities of the country, less political commitment to fight HCC and lack of policy recommendations by the scientific communities. Most of early detected HCC cases referred to other countries like South Africa, Thailand and India which are unaffordable. With this experience, most people consider HCC as diseases of death penalty. However, as part of HCC prevention, HBV vaccination was integrated in to the national immunization programme since 2007 (29) and currently reaches to 72% coverage in infant (17).

Like Ethiopian data, the global epidemiology showed that cirrhosis is the prime risk factor for HCC development (30,31). Cirrhosis is defined as the fibrosis of the liver cells and characterized by decreased proliferation and loss of regenerative capacity. Approximately 80% of the HCCs develop in cirrhotic livers (30). Additional promoting factors include, shortening of telomere (31–35), activation of satellite cells (36), loss of function of the *p53* tumor suppressor gene (37), inactivation of the p27 cell cycle regulator (38), loss of heterozygosity of the insulin-like growth factor 2 receptor locus (39), and loss of protein expression of the p16 cell cycle inhibitor (38,39).

Hepatitis B virus is the second associated factors for HCC in three different ways. First, its chronic nature of infection leads to cirrhosis (40). Second, HBV-host genome integration leads to mutation (31,39,41) and third, by producing HBx protein. HBx protein inhibits P53, apoptosis and repair system (39,42,43). Of the genotypes, C and D carries two to three fold higher risk for developing HCC (44–50).

Hepatitis C virus is another virus associated with HCC. In the presence of alcohol, there will be greater HCV replication, changes in the hyper variable region of the viral genome, resistance to interferon therapy and inhibition of hepatic expression of *Bcl-2*, resulting in increased apoptosis and more severe liver injury and increased oxidative stress (39,51). The non-structural proteins of

HCV; NS3, and NS5A are key mediators for these role (39). Chronic consumption of more than 80 g of ethanol per day for more than 10 years increased the risk of HCC 5-fold in men and 10 g/day in women are associated with 24-fold risk for the development of HCC (47,52). HCC accounts 25% of all liver deaths in human immunodeficiency virus (HIV) patients. Moreover, there are reports indicating HCC developing in HIV/HCV co-infected patients to be more aggressive, to present at an earlier age and to be less curable than HCV mono infected patients. However, a direct oncogenic effect of HIV is not clearly defined yet (53,54).

Aflatoxin is a class of mycotoxins produced by moulds of the Aspergillus parasiticus and Aspergillus flavus. Aflatoxin B1 (AFB1) is the most potent naturally occurring chemical liver carcinogen and it accounts 4.6-28.2% of all HCC cases (55). Aflatoxins grow on whole grains such as rice, corn and wheat as well as on peanuts, almonds, walnuts, sunflower seeds, and spices such as black pepper and coriander (30).

Studies also demonstrate the link between HCC and overweight, obesity, diabetes, hereditary hemochromatosis (HH), oral contraceptives, and tobacco smoking (56–58). If an obese person chronically infected with HBV and /or HCV, there is 100 fold increased risk of HCC (56–59) .Literatures showed a 200-fold increased risk of HCC among patients with HH (60).

Studies demonstrate that being male (61–63) and younger age especially children in developing countries (38) are more affected. In women, estrogen effects might suppress interleukin (IL)-6-mediated inflammation that, reduce both liver injury an d compensatory proliferation. on the contrary, in men, testosterone effects could increase androgen receptor signaling, promoting liver cell proliferation (64, 65).

The diagnostic modalities of HCC are based on various imaging techniques, histological analysis and serum markers. Scientific literatures outside Ethiopia dictate widely use of latest and improved imaging techniques. The most commonly used imaging techniques are summarized in Table 5.

Alpha-1 fetoprotein is a protein that can be expressed by hepatic cancer cells, with extremely complicated biologic activities. Studies have shown that AFP plays double roles in both inhibiting the immune system and promoting the growth of cancer cells. Thus, an increased in the serum concentration of AFP is primarily used as a tumor marker for HCC evaluation (68). However, AFP can be elevated in other primary liver malignancies and become within normal limits in a large proportion of patients with known HCC (69–72). Due to its low specificity, AASLD didn't recommend AFP in the diagnosis of HCC (72,73). However, other literature recommended AFP for monitoring of recurrent disease. Because successful removal of tumor by surgical means is usually followed by an immediate fall in AFP levels to normal values in 3–5 days (74,75). A level of 400-500 ng/ml was considered diagnostic (66). Other candidate serum markers used globally are listed in table 6.

Table 5: **Comparative use of imaging techniques for diagnosis of HCC, Bahir Dar, Ethiopia, 2017 (66,67)**

Ultrasound scanning	**Screening test and not a diagnostic test**
Colour Doppler Ultrasound	Gives the mean velocity of blood flow within a vessel by color coding the flow, Better than US
Contrast enhanced ultrasound	Used to improve sonographic visualization of hepatic tumor vascularity
***Multiphasic helical* computed tomography**	Deemed the imaging technique of choice for the detection and staging of HCC
Magnetic resonance imaging	Accurate than CT or US in detecting HCC and estimating the actual tumor size
***Multi-detector helical* computed tomography**	Better than MRI for early detection of small HCC during the follow-up of patients with chronic hepatitis and cirrhosis
Angiography	Often used to delineate hepatic anatomy before resection or as guidance for transarterial chemoembolization of HCC lesions

Table 6: **Serum markers for HCC, Bahir Dar, Ethiopia, 2017 (66)**

➢ **Lectin reactive AFP (AFP-L3)**
➢ **Des-gamma carboxyprothrombin (DCP)**
➢ **α-L-fucosidase**
➢ **Glypican-3**
➢ **Squamous cell carcinoma antigen (SCCA)**
➢ **Golgi protein 73 (GP73)**
➢ **Hepatocyte growth factor (HGF)**
➢ **Transforming growth factor-b1 (TGF-b1)**
➢ **Vascular endothelial growth factor (VEGF)**
➢ **Serum proteomics**

HBV vaccination is the most effective measure to avert HCC. Vaccine against HCV is not yet available and would be an active area of research. Reports showed that IFN (76–78) and Lamivudine (79,80) reduces the risk of HCC.

Many studies have reported the positive and negative association of some foods with HCC. Coffee (81,82) tea (83) , vegetables and fruits (84) consumption have shown to reduce HCC. Vitamin K2 inhibits the growth of hepatoma cells, by causing cell-cycle arrest and apoptosis through different mechanisms (85).

Different surveillance strategies applied for detection of very early stage HCC (86) (Table 7). Surveillance by US, CT, MRI was employed by most developed nations for screening every 6-12 months (78). And also some countries used a combination of AFP and US for HCC surveillance in clinical practice (87). The most appropriate subject but not limited includes: HBV and HCV carriers, primary biliary cirrhosis, genetic chromatosis and alpha-1- antitrypsin deficiency (62,88). Optimal interval of surveillance is around 3-12 months (88).

HCC is curative diseases with timely treatment. Curable treatments include resection, liver transplantation and percutaneous local ablative treatment. These are appropriate for asymptomatic patients with very early and early stage of HCC. Trans -arterial chemo embolization is indicated for patients with asymptomatic, multi-nodular HCC (intermediate, or stage B), whereas chemotherapy with Sorafenib is the only recommended treatment for patients with advanced (stage C) HCC. The best supportive care is recommended for patients with terminal (stage D) HCC (89,90) (Table 7).

Immunotherapy is a new field of liver immunology which aimed at treatment of HCC using immunological cells, immune mediators and other HCC biomarkers. Adoptive immune therapy work by introducing effective immune cells to directly remove tumor cells (91,92).To date immunotherapy showed at least some benefits when combined with other treatment modalities such as chemotherapy and curative therapies (93). More is to come in the near future in the field of immunotherapy.

Table 7: **Staging system and treatment strategy of HCC, Bahir Dar, Ethiopia, 2017 (66)**

Very early stage (0)	**Early stage (BCLC A)**	**Intermediate stage (BCLC B)**	**Advanced stage (BCLC C)**	**Terminal stage (BCLC D)**
•Child-Pugh A •Asymptomatic •single lesion < 2cm •No portal hypertension	• Single lesion > 2 cm or • 3 nodular lesions,each < 3 cm • Asymptomatic	• One, large lesion • AMD • No vascular invasion • No EH lesions	• Symptomatic tumours and/or • Invasive tumours or • EH involvement	• Severe HD • Child-Pugh C
Treated By: resection	Resection, percutaneous ablation, transplantation	TACE	Sorafenib	Symptomatic treatment
• The 5-year survival is > 90% and • The tumor rarely recurs	Five-year survival >50% after curative treatment	• Survival≈ 16M. • palliative care	• Survival ≈10.7 M. • palliative care	• Survival<6 M. • No intervention • Symptomatic

BCLC: *Barcelona clinic liver cancer staging system;* ***AMD:*** *Asymptomatic multifocal disease****;*** ***TACE****: Trans-catheter arterial chemoembolization*; ***M****: Months;* ***EH:*** *Extra hepatic;* ***HD:*** *hepatic dysfunction.*

Limitation

The scopes of studies were limited and assessed only clinical characteristics, laboratory features, proportion of HCC and associated factors. Methodologically, there is also inherent limitation. Moreover, studies are too old and used very small sample size. Thus, they were unable to represent the current situation.

Conclusions:

Literatures regarding HCC in Ethiopia are very limited and suffer from representativeness. Facilities are limited, trained human resource is also quite limited. The country has no any policy framework and guideline for management of HCC. On the other hand, according to unpublished hospital reports, HCC and other types of cancer are alarmingly increasing.

Sensitive and specific and affordable point of care diagnostic technologies is one of the urgent needs for HCC control. Besides diagnosis issue, treatment options are also not available in our country indicating that much efforts is need to bring hopes to affected populations.

These seems a decade assignment for the country. Thus, the country should have cross-cutting strategies to avert the situation. Based on the information obtained from our review, we forwarded the following recommendations:
First, in the absence of well-organized health facilities and early screening strategies, timely information on prevention and control mechanism is the most cost effective means of reducing HCC risk factors. This can be addressed through health education on alcohol misuse, metabolic syndromes (diabetes, overweight and obesity), infection prevention of HBV and HCV, fruit and vegetable intake, prevention of food contaminations by AFT. These healthy life style education package can be spread to the communities by community leaders, health extension workers, local opinion leaders, community radio programs, faith based organizations, social media, anti-cancer associations and annual scientific conferences. Moreover, communities must be made aware of HCC, of its possible symptoms, and of the necessity of early diagnosis to ensure that HCC is curable if identified early.

Second, HBV vaccination should be expanded to all eligible risk groups. Moreover, diagnostic services must be expanded for earlier identification.

Third, there should be political commitment to improve health systems and invest wisely in cancer services. Regional cancer centers should be established and enabled for full range of services.

Fourth, sustained capacity building skim should be established. There should be task shifting from oncology to trained physicians and nurses, from radiology to radiography technicians and from pathologist to laboratory technologists.

Fifth, the current investments on chemicals, pesticide, fertilizers and brewery industry should be monitored for their environmental friendliness. Farmers should be aware on how to handle pesticides and fertilizers. Environmental biotechnology should be functional to monitor the environment from mutagenic chemical and plastic wastes.

Sixth, forming care and treatment guidelines should be a major part of the strategy to reduce cancer related mortality in Ethiopia.

Curbing cancer epidemic should not be the responsibility of only to health professionals and governments. Rather, it should be national agenda. Health professionals, biotechnologists, engineers, agricultural professionals, chemists, musicians and poets and many more should consort together.

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Authors' contributions
DM conceived the study and drafted the review, appraise the quality of evidences. FB appraised the quality of evidences and select literatures from PubMed. AD select literatures from PubbMed. YA and YZ select literatures from Cochrane library. DH, BE extract the data from the selected literatures using data extraction sheet.US provide selected literatures, review guidelines and contribute substantially for scientific content of the review. HM, AG, AS, FB, AM contribute substantially for the scientific content of the review. All the authors read and approved the final review.

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