Epidemiologic, humanistic and economic burden of hepatocellular carcinoma in the USA: a systematic literature review

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Aim: To describe the epidemiologic, humanistic and economic burdens of hepatocellular carcinoma (HCC) in the USA. Materials & methods: Studies describing the epidemiology and economic burden from national cohorts, any economic models, or any humanistic burden studies published 2008–2018 were systematically searched. Results: HCC incidence was 9.5 per 100,000 person-years in most recent data, but was ~100-times higher among patients with hepatitis/cirrhosis. Approximately a third of patients were diagnosed with advanced disease. Patients with HCC experienced poor quality of life. Direct costs were substantial and varied based on underlying demographics, disease stage and treatment received. Between 25–77% of patients did not receive surgical, locoregional or systemic treatment. Conclusion: Better treatments are needed to extend survival and improve quality of life for patients with HCC.

First draft submitted: 11 June 2020; Accepted for publication: 1 July 2020; Published online: 21 July 2020

Keywords: epidemiology • hepatocellular carcinoma • pharmacoeconomics • risk factors • staging

Liver cancer is the sixth most common cancer diagnosis and fourth most common cause of cancer deaths in the world [1]. In the USA, cancer of the liver and bile duct was estimated to incur over 42,000 new cases and over 31,000 deaths in 2019, with men experiencing approximately two- to three-times as many new cases and deaths as women [2]. Approximately 70% of liver cancer cases are thought to be associated with modifiable risk factors, such as viral hepatitis, alcohol, smoking and obesity [3]. Despite declines in overall incidence and deaths from all cancers in the USA, liver cancer incidence and mortality are rising [4].

Hepatocellular carcinoma (HCC) accounts for 75–85% of all liver cancers, making HCC a major cause of cancer and cancer-related deaths [5]. Similar to liver cancers overall, the risk of HCC increases dramatically in patients with pre-existing liver disease caused by hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcohol abuse, nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) [6]. A study using data from the Surveillance, Epidemiology and End Results (SEER) Program suggests that there will be over 38,000 HCC cases in 2020 and over 56,000 HCC cases in 2030 in the USA [7].

The treatment decision for HCC depends upon disease stage and patient characteristics. Potentially curative options include liver transplant and surgical resection (cure fractions based on overall survival of 74 and 41%, respectively) [8]. However, these options are appropriate only for patients with early stage disease [9–11]. Additionally, in cases of liver-donor shortages or ineligibility for resection due to underlying liver dysfunction and/or portal hypertension, ablation may be a curative option. For patients with inoperable disease due to performance status or comorbidity, or for those with locoregional disease with or without minimal extrahepatic disease, guideline-recommended locoregional options include ablation (e.g., radiofrequency ablation, microwave ablation or cryoablation), radiation, or liver-directed treatment (e.g., conventional or drug-eluting bead [DEB] transarterial chemoembolization [TACE], transarterial radioembolization [TARE]). Systemic treatment (e.g., sorafenib, lenvatinib, atezolizumab + bevacizumab, regorafenib, cabozantinib, ramucirumab, nivolumab, pembrolizumab) is recommended by guidelines for patients with advanced HCC disease (i.e., metastatic disease or when patients expe-
rience extensive liver tumor burden) who have preserved liver function (i.e., Child-Pugh A) and good performance status (i.e., Eastern Cooperative Oncology Group [ECOG] 1–2) [9–11].

Approximately half of HCC patients in the USA do not undergo any treatment; factors commonly correlated with not receiving treatment include older age, African-American race, and being enrolled in Medicaid or having no insurance [12]. Left untreated, the median survival is 13.4 months for early stage patients, 9.5 months for intermediate stage patients, 3.4 months for advanced stage patients and 1.6 months for end stage patients [13]. Survival is associated with both clinical (e.g., tumor size and extent, evidence of metastasis, patient age, surgical treatment) and nonclinical (e.g., income, education) factors [14].

Since liver cancer incidence and mortality are rising, and HCC accounts for the majority of all liver cancers, we sought to gain a comprehensive understanding of the epidemiological, economic and humanistic burden among patients with any stage of HCC in the USA who are not eligible for liver transplant or resection.

Methods

Methods of the literature review were specified in advance and documented in an internal study protocol. The systematic literature review (SLR) was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Search strategy

A systematic search was conducted to identify all available literature investigating the epidemiological, humanistic and economic burden associated with HCC patients in the USA (Supplementary Table 1). The population of interest was persons of any age in the USA with confirmed HCC; studies only describing patients with liver transplant or resection were excluded. Studies describing patient characteristics, epidemiology, or economic burden required national sampling for inclusion. Included citations for all outcomes were limited to observational studies (e.g., cross-sectional/surveys, retrospective or prospective cohort, case–control) and economic modeling studies, with SLRs/meta-analyses reviewed for study identification purposes only. The search was conducted in the MEDLINE® (1946–present) and Embase® (1947–present) databases for articles and conference abstracts, respectively, written in the English language and published between 1 January 2008 and 15 December 2018 (Supplementary Table 2). The publication limit of 2008 was intended to ensure that the treatment landscape was relatively consistent throughout the time periods in which data were collected in the included studies. The search for epidemiological studies was limited by an observational study design filter and a publication date after 1 January 2013, to ensure the more recent and relevant information was captured. Additional references were identified by searching the bibliographies of SLRs. Targeted keyword searches were performed on 5 August 2019, to identify citations published since the systematic search (15 December 2018) to ensure the most up-to-date information was captured. No study authors were contacted to identify additional studies or to confirm data.

Study selection & data extraction

Results of all searches were compiled into a common Excel database. Study inclusion and exclusion at each screening step were based on pre-defined criteria. Eligible records were screened first at the title and abstract level and then as full-texts by one reviewer, and quality control of records was performed by a second, senior reviewer. Conference abstracts with data that were subsequently published as manuscripts were excluded from further review as ‘duplicates’. An Excel data extraction template was developed and piloted to ensure usability. The extraction sheet was then populated to capture study characteristics, study populations, HCC patient characteristics, epidemiology, humanistic burden, and economic burden data from each study (Supplementary Table 3). Full text review and extraction were performed by two independent reviewers, and any discrepancies were reconciled. A third independent reviewer was consulted as necessary and adjudicated where consensus could not be reached.

Outcomes evaluated

The main outcomes of interest were HCC patient characteristics, epidemiology, humanistic burden and economic burden. Comparable data points from each study were presented alone or as ranges; no summary measures combining studies were calculated. Epidemiology outcomes included incidence and prevalence. Patient-related characteristics included sex, ethnicity, age, comorbidities, insurance/payer, disease stage at diagnosis and survival. Humanistic outcomes included health-related quality of life (measured using generic or disease-specific instruments), symptom burden and treatment burden. Economic outcomes included direct costs (medical and nonmedical), indirect costs,
inpatient length of stay (LOS), specialist visits and treatments, as well as a brief survey of economic modeling study inputs and results.

Risk of bias
Risk of bias was assessed at the outcome level by determining whether each study population represented a special, 'selected' cohort (i.e., a cohort selected based on receiving a specific intervention, having an underlying etiology, or having other special characteristics) or a 'nonselected' cohort. Within each outcome of interest, results are reported from citations describing nonselected cohorts and by payer when possible. No assessment of risk of bias affecting cumulative evidence was performed.

Results
Patient/study selection
The searches identified 5228 journal articles from MEDLINE and 4555 conference abstracts from Embase for a total of 9795 citations for title and abstract review. From 9795 total citations screened, 99 citations were included (Figure 1).

Epidemiology
Incidence
A total of nine studies presented incidence among nonselected cohorts (i.e., SEER and US Cancer Statistics registry, Medicare, and Veterans Affairs) [16–24], of which five studies presented incidence for individual years (Figure 2) [16,19,21,23,24]. Using the most recent data available (year 2015), the incidence of HCC in the USA among all payers was 9.5 per 100,000 person-years (PY) [19]. Based on the national population of 329 million people in 2019, an incidence of 9.5 per 100,000 PY equated to 31,255 annual HCC cases. The most recent incidence was higher in Medicare and Veterans Affairs patients (22.3 and 45 per 100,000 PY, respectively) [16,21]. In one study using data from SEER, incidence varied among groups by sex, race and age (Figure 3): across all racial groups,
the incidence among men was approximately three-times higher than the incidence among women; by race, the incidence among Asians (18.6 per 100,000 PY), African-Americans (15.0 per 100,000 PY) and Hispanics (11.8 per 100,000 PY) was higher than Caucasians (7.0 per 100,000 PY); and persons aged 50 years and older typically had higher incidence than younger patients [24].

Incidence was reported in 11 studies among etiology-related cohorts [25–35], of which six reported incidence irrespective of treatment with direct-acting antivirals (Figure 2) [25–30]. Estimates varied by study; however, the incidence of HCC in patients with HCV, HBV, or cirrhosis was approximately 100-times higher than incidence in
Epidemiology & burden of HCC in USA

Prevalence

Six studies reported prevalence of HCC among nonselected cohorts [16,18,20,24,33,36]. In the most recent and generalizable study cohort, the prevalence of HCC in 2003–2011 was 0.0096%, with higher prevalence among Asian (0.0164%) populations than African-American (0.0109%), Caucasian (0.0082%) and Hispanic (0.0098%) populations [24]. The study authors did not have additional information on underlying disease etiologies and other risk factors and were unable to definitively state reasons for these racial discrepancies in prevalence. Furthermore, the similarity in incidence and prevalence rates was not explained by study authors, who noted that prevalence rates increased more from 2003 to 2011 than incidence rates, possibly due to improved treatment of underlying etiologies and better screening and surveillance programs. Prevalence of HCC was reported in 20 studies among etiology-related cohorts [16,26–33,38–49]. The prevalence of HCC among patients with HCV, HBV, NAFLD/NASH, cirrhosis or chronic liver disease was 1–10%.

Patient characteristics

Demographics & etiology

A total of 41 studies with national sampling presented demographic and etiology information [16,17,20,21,25,26,29,32,35,39,46,50–79], of which 21 studies presented data for nonselected cohorts (Figure 4) [16,17,20,21,33,50,54,55,58–60,62,65,66,68–70,72,74,75,77,79]. Reported values from the largest study including both inpatients and outpatients (n = 50,723) [77], with ranges provided from other studies, described patients with HCC as mean age 64 (50–75) years and 74% (57–100%) male (57–74% male if excluding studies from Veterans Affairs). Prevalence of HCC etiologies varied widely between cohorts, with ranges of 1–14% with HBV, 17–68% with HCV, 5–55% with alcoholism/alcoholic cirrhosis, 13–56% with other cirrhosis, 0–35% with NASH and 0–56% with diabetes (Figure 4).
Payers

Cohorts from inpatient databases were used to identify the prevalence of different payers among patients with HCC, because all other data sources providing this information were based on databases from a single payer (e.g., SEER-Medicare, Veterans Affairs). Therefore, it is important to caveat that the only data available that described the proportions of payers for patients with HCC relates to those who were admitted as inpatients. A total of four studies presented payer data for inpatients (Figure 5) [55,59,66,72]. Among inpatients, payers included Medicare (37–45%), commercial insurance (27–33%), Medicaid (16–19%) and self-pay/other (8–12%) [55,59,66,72].

Disease stage

A total of ten studies described disease staging at diagnosis [53,56,60,64,65,69,70,77–79], of which six presented data for nonselected cohorts (Figure 6) [60,65,69,70,77,79]. Based on staging criteria from American Joint Committee on Cancer (AJCC) or Barcelona Clinic Liver Cancer (BCLC), approximately two-thirds of patients had early or intermediate stage disease at diagnosis, while a third had advanced stage disease [60,65,69,70,77,79].

Survival

Fifteen studies reported survival (mean, median or proportion at timepoint) among patients with HCC [17,52,53,56,60,64,65,69,70,73,77,79–82]. Several of these studies described survival in a selected population, such as selection based on intervention (e.g., rounds of TACE; rounds of systemic treatment) or patient characteristics (e.g., inpatient vs outpatient; underlying HBV vs HCV). The largest study describing overall survival at specific timepoints in a nonselected population relied upon data from SEER [24]. The authors found that overall survival ranged 44–53% at 1 year, 27–33% at 3 years and 21–26% at 5 years among African-American, Asian, Caucasian and Hispanic patients with HCC; longer survival at 1 year was observed in the subset of patients with localized disease (i.e., tumor confined to 1 liver lobe) or disease within Milan Criteria [83] (i.e., a single lesion measuring <5 cm, or no more than 3 lesions measuring <3 cm each), which is typically used to determine eligibility for liver transplantation.

Figure 5. Payers among inpatients with hepatocellular carcinoma. Each stacked bar represents a cohort from a given year or timeframe, as indicated.

HCC: Hepatocellular carcinoma; NIS: National Inpatient Sample; UHC: University Health Consortium.

Cauble (2013) [55]; Jinjuvadia (2017) [59]; Mishra (2013) [66]; Sobotka (2019) [72].
transplant (Figure 7). Although disparities were observed in survival data based only on race, the authors reported that multivariate analyses that adjusted for age, sex, race, disease stage, year of diagnosis and treatment received determined that Asian and African-American patients had higher 5-year survival rates than Caucasian patients [24].

Only 1 citation was identified that provided median overall survival based on BCLC disease stage at diagnosis (Figure 7) [79]. The authors reported that the survival of Veterans Affairs patients was 3.2 years for those diagnosed in BCLC 0, 2.4 years for BCLC A, 1.2 years for BCLC B, 0.4 years for BCLC C and 0.3 years for BCLC D [79].

**Humanistic burden**

A total of 15 studies described humanistic burden among patients with HCC (Supplementary Table 4) [84–98]. These studies tended to be small and performed in one to two centers. The most commonly used instruments were the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) and 36-Item Short Form Survey (SF-36).

**Symptom burden**

Seven studies assessed symptom burden on patients with HCC or their caregivers [84–89,91]. The major symptom assessed was pain, although the evidence regarding pain prevalence varied across studies. Patients with HCC at end of life experienced lack of energy, pain, feeling drowsy, difficulty sleeping, problems with sexual interest, itching, lack of appetite, difficulty concentrating, worrying and feeling irritable [86]. Diarrhoea, fatigue, skin toxicities and appetite loss had the most impact on patients’ quality of life [89].
1, 3, and 5-year survival rates, all payers

**Figure 7. Survival.**

*Localized* refers to tumors involving a single lobe of the liver.

*Milan Criteria* refers to a single lesion measuring <5 cm, or no more than 3 lesions measuring <3 cm each [83].

AJCC: American Joint Committee on Cancer; BCLC: Barcelona Clinic Liver Cancer; SEER: Surveillance, Epidemiology and End Results.

Ha (2016) [24]; Serper (2017) [79].

**Quality of life & survival**

Two studies assessed the association between quality of life and survival in patients with HCC [90,93]. One found that overall health-related quality of life and some subscales on the FACT-Hep were significantly associated with survival. The second study found significant correlations between advanced BCLC stage and reduced global quality of life and individual components of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30).
Treatment on quality of life

Six studies assessed the impact of HCC treatment on quality of life [92,94–98]. Quality of life was higher at baseline than after 3 months of treatment. In one study describing a comparison of patients receiving TARE versus patients receiving TACE, TARE patients had better quality of life than TACE patients 4 weeks after treatment [92]. Other studies not comparing different locoregional modalities found mixed results of TARE, TACE and DEB-TACE on quality of life [94–98]. No studies were identified describing the impact of systemic treatment on quality of life.

Economic burden

Direct costs or charges per admission

A total of six studies reported admission-related payer costs [63,75,76,99–101]; however, all of these were in selected populations, including patients with malnutrition [100], patients born 1945–1965 [99], patients who underwent radiofrequency ablation [101], patients who received palliative care [63] or patients with HCC combined with patients with hepatobiliary diseases [75]. Admission-related hospital charges were described in five publications [41,59,66,67,102]; in the most recent data in a nonselected population (year 2011), mean charges per admission were US$59,686 [59].

Direct costs per month

A total of seven studies reported mean per month direct medical costs [52,57,65,68,71,74,103]; two of these studies described only patients receiving systemic treatment [52,57] and one compared costs among patients with HCV and cirrhosis, HCC or transplant [103]. The remaining four studies described monthly costs among nonselected cohorts (Supplementary Table 5) [65,68,71,74]. These studies described the difference in monthly payer costs before and after diagnosis [74], compared HCC and non-HCC cohorts [68], described costs based on treatment used [71] and described costs based on disease stage [65].

Long-term direct costs or charges

A total of 16 studies reported long-term direct medical costs [17,39,43,44,46,49,50,53,56,57,60,61,70,71,81,104]; three of these studies described charges [17,56,104], four described costs related to specific interventions [53,57,61,81] and five described costs among specific etiologies [39,43,44,46,49]. The remaining four studies described long-term costs among nonselected cohorts (Supplementary Table 6) [50,60,70,71]. One study described cumulative payer costs for patients with HCC that ranged US$87,556 for best supportive care to US$208,595 for liver-directed treatment + sorafenib (sorafenib alone, US$79,212; liver-directed treatment alone, US$203,502) [71]. A second study described inpatient costs of US$71,937, with different costs based on age and payer [50]. A third study described costs based on disease stage, with lowest costs for no treatment and highest cost for liver transplant [70]. Finally, a fourth study described 3-year Veterans Affairs payer costs of US$154,688 in cirrhosis and HCC versus US$69,010 in noncancer patients with cirrhosis; 3-year payer costs based on BCLC stage were the following: 0, US$221,046; A, US$193,859; B, US$149,177; C, US$96,838; D, 137,771 [60].

Indirect costs

One study provided costs due to sick leave, workers compensation and disability among employees with HCV and no cirrhosis, cirrhosis, HCC, liver transplant or non-HCV in the 6-month period following the most severe claim (Figure 8) [39]. The costs of work loss and numbers of days missed over a 6-month period were the following: no HCV/no HCC, US$652 (3.4 days); noncirrhotic HCV with no HCC, US$1003 (5.1 days); compensated cirrhosis HCV with no HCC, US$732 (3.1 days); decompensated cirrhosis HCV with no HCC, US$1354 (9.3 days); any HCV who have HCC, US$3594 (22.1 days); liver transplant, US$2800 (31.3 days) [39].

Healthcare resource use

A total of 13 studies reported inpatient length of stay [17,41,50,57,59,63,66,67,73,76,99,100,102], of which four studies described nonselected cohorts and reported trends over time [59,66], by etiology [102], and by age or payer [50]. The typical inpatient length of stay was approximately 6 days.

A total of six studies reported specialist visits [17,52,56,58,79,105]; four of these studies described nonselected cohorts (Supplementary Table 7) [17,58,79,105]. Nearly all patients in the Veterans Affairs cohort visited a specialist within 30 days of diagnosis; specialist visit rates were lower in the two Medicare cohorts, which suggests that the likelihood of visiting a specialist may be related to the payer involved.
Indirect costs (US$)

| Condition                  | Indirect costs (US$) |
|----------------------------|----------------------|
| No HCV, no HCC             | 10000                |
| Non-cirrhotic HCV          | 2000                 |
| Compensated cirrhosis      | 3000                 |
| Decompensated cirrhosis    | 4000                 |
| HCV + HCC                  | 652                  |
| Liver transplant           | 1003                 |
| Total indirect costs       | 732                  |
| Absence days               | 1354                 |
| Total absence days         | 3594                 |
|                            | 31.3                 |

Figure 8. Indirect costs. Data source: Human Capital Management Services integrated databases; 2001–2013. Patients with HCV, n = 1,386; non-HCV patients, n = 727,588. Each stacked bar represents data from one patient group, as indicated. HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus. Baran (2015) [39].

Absence days

| Condition                  | Absence days |
|----------------------------|--------------|
| No HCV, no HCC             | 652          |
| Non-cirrhotic HCV          | 1003         |
| Compensated cirrhosis      | 732          |
| Decompensated cirrhosis    | 1354         |
| HCV + HCC                  | 3594         |
| Liver transplant           | 31.3         |

Figure 9. Treatment. Each bar represents treatment utilization within a given study cohort. Text adjacent to each bar notes the specific liver-direct treatment used, as described by study authors.

Treatments not mutually exclusive.
NIS: National Inpatient Sample; SEER: Surveillance, Epidemiology and End Results; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; UHC: University Health Consortium; UNOS: United Network on Organ Sharing.

A total of 15 studies reported treatments and procedures [20,52,53,55,57,64,69–72,77,79,106,107]. Of these, four studies described subpopulations based on intervention (i.e., systemic treatment [52,57] or liver-directed treatment [53,64]), two described likelihood of treatment (but not specific treatments received) based on insurance status [106] and race [107], and one did not report proportions receiving potentially curative treatments [71]. The remaining seven studies described nonselected populations (Figure 9) [20,55,69,70,72,77,79]. Data collection dates and treatment setting...
must be considered in interpreting these results, since some treatments (i.e., sorafenib) were not available within some studies’ data collection dates, and treatments requiring hospital admission (i.e., transplant or resection) may be overrepresented in the inpatient study data. Across all studies, most patients did not undergo liver transplant or resection, and a large proportion of patients did not undergo any locoregional or systemic treatment [20,55,69,70,72,77,79]. Notably, in the three studies providing treatment based on disease stage, a substantial proportion did not receive treatment in even the earliest disease stages (patients not receiving treatment: 52–67% of patients within Milan criteria [range based on race] vs 77% overall [77], 43% of patients in AJCC stage I vs 68% overall [70], and 14% of patients in BCLC 0 vs 25% overall [79]).

Economic models

Eleven studies described economic models for various aspects of HCC (Supplementary Table 8) [60,70,78,108–115]. Two of these studies are described in the sections above [60,70]. Four involved a comparison against TACE [70,110,113,114], four involved a comparison against a systemic treatment (sorafenib, two; cabozantinib, one; regorafenib, one) [78,108,111,115], one involved stereotactic body radiation therapy versus radiofrequency ablation [112], one involved independent factors affecting cost and survival [60] and one was treatment-agnostic and evaluated the cost to society [109].

Discussion

This review provides a comprehensive understanding of the epidemiology, patient characteristics, and economic burden (including healthcare resource use) of HCC in the USA. The data presented here indicate that many patients with HCC are diagnosed in intermediate or advanced stage disease; as such, it may not be surprising that few patients are eligible for liver transplant or resection. However, many patients also do not receive locoregional or systemic treatment. It is unclear from this research whether the high proportion of patients not receiving treatment is due to patient choice, ineligibility based on disease stage, or other factors (e.g., healthcare access, cost). It is unlikely that disease stage accounts entirely for the lack of treatment, as a substantial proportion of patients did not receive treatment in the earliest disease stages. All treatments for HCC, including supportive care, are associated with a substantial economic burden to payers and patients. Limited information suggests that patients with HCC experience a significant quality of life burden; however, little information was found comparing different locoregional modalities, and no information was found regarding quality of life or preferences associated with systemic treatment. In addition to the quality of life and economic burden associated with HCC, patients experience poor clinical outcomes, with approximately three-quarters of patients with HCC dying within 5 years of diagnosis.

This study provides a broad perspective on the epidemiology of HCC in the USA in recent years, but changing population demographics are anticipated to affect HCC incidence generally and within demographic subgroups in the near future. Using existing HCC incidence data from SEER and projected population data from the US Census Bureau, a study published in 2016 forecasted that HCC incidence will be 21.1 per 100,000 PY in 2030, but incidence will increase more quickly in men versus women and in Hispanic and Caucasian populations versus African-American and Asian populations due to shifts in projected populations in the USA [7]. This study also forecasted that HCC patients (both men and women) diagnosed in 2020–2030 will be older on average than patients diagnosed 2000–2013 [7]. However, this study does not take changes in prevalence of HCC risk factors into account, such as hepatitis infection, NASH, and NAFLD, and possible prevention of subsequent HCC. Both HBV and HCV prevalence may diminish in coming years due to HBV vaccination [116] and increased use of direct-acting antiviral therapies in HCV [117]. Conversely, prevalence of NASH and NAFLD in the USA are expected to rise 44 and 8%, respectively, by 2030 [118].

This study also describes the costs and healthcare resource use associated with HCC in recent years; these costs will likely rise in the near future. The US Centers for Medicare and Medicaid Services estimated that healthcare spending will grow 5.4% per year from 2019 to 2028 [119]. This projected increase in healthcare spending will likely be reflected in increased costs per HCC patient, while the anticipated rise in HCC incidence by 2030 will certainly drive total healthcare-related societal costs (currently estimated at US$405 million annually [109]) higher in the coming years.

The prevalence of HCC-related risk factors varies substantially globally; the average cohort of patients with HCC in the USA likely has a different risk factor profile than patients with HCC in other parts of the world. For example, cases attributable to HBV, smoking and obesity vary substantially across high-income regions globally [120]. The
payer and healthcare system in the USA is different than other countries with high HCC incidence. Therefore, this study's emphasis on patients from USA provides a unique perspective, but further analyses and comparisons with global data are warranted [121–123].

Our review has some limitations. First, relative to the number of studies describing epidemiology, patient characteristics and economic burden, few studies describing humanistic burden were identified. More humanistic burden information may be available from randomized controlled trials; however, the scope of this review included only observational studies to capture a real-world understanding of patients with HCC. Second, this review does not fully capture emerging additions in the treatment landscape for advanced HCC. In addition to sorafenib, some options recently added to NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) [9] for the first-line setting include lenvatinib, nivolumab for patients ineligible for tyrosine kinase inhibitors or other anti-angiogenic agents, and atezolizumab + bevacizumab, which is undergoing review for an indication in HCC from the US Food and Drug Administration [124]. The changing treatment landscape in advanced HCC is likely to impact survival and costs, but real-world data describing systemic treatments other than sorafenib was not readily available for this review. Third, this review did not include citations describing epidemiology, patient characteristics, or economic burden based on data sources representing a single state/region. We also note that there are regional differences in the treatment pathways and clinical outcomes of HCC within the USA [125]. However, we believe that including studies requiring national sampling for these outcomes provides the most generalizable data.

Conclusion

The incidence and costs of HCC represent a major burden to patients, caregivers, and the healthcare system in the USA. Patients with intermediate or advanced HCC may elect to forgo treatment due to high costs and limited survival benefits of existing treatments. More efficacious, accessible treatment options are necessary to extend survival and improve patient quality of life.

Summary points

- Using the most recent data available, the incidence of hepatocellular carcinoma (HCC) in the USA among all payers was 9.5 per 100,000 person-years; the most recent incidence was higher in Medicare and Veterans Affairs patients.
- The incidence of HCC in patients with HCV, HBV or cirrhosis was approximately 100-times higher than incidence of HCC in the overall population (i.e., populations not selected based on these etiologies).
- HCC etiologies varied widely between studies, ranging 1–14% with HBV, 17–68% with HCV, 5–55% with alcoholism/alcoholic cirrhosis and 13–56% with other cirrhosis.
- Using the most recent data available, payers of inpatients with HCC included Medicare (44%), commercial (27%), Medicaid (19%) and self-pay/other (10%).
- Approximately two-thirds of patients had early or intermediate disease at diagnosis, while a third had advanced disease.
- Patients with HCC at end of life experienced lack of energy, pain, feeling drowsy, difficulty sleeping, problems with sexual interest, itching, lack of appetite, difficulty concentrating, worrying and feeling irritable. Diarrhoea, fatigue, skin toxicities and appetite loss had the most impact on patients’ quality of life.
- Most patients with early stage HCC did not receive transplant or resection. A large proportion of patients with intermediate or advanced HCC did not undergo any locoregional or systemic treatment.
- The incidence and costs of HCC represent a major burden to patients and to the healthcare system in the USA. Patients not eligible for transplant or resection may elect to forgo treatment due to high costs and limited survival benefits of existing therapies.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/hep-2020-0024

Author contributions

A Aly, Y Doleh and F Benavente contributed to study conception, design and revisions to the manuscript; S Ronnebaum and D Patel contributed to study design, data analysis, drafting and revision of the manuscript.
Acknowledgments

Manuscript editorial support was provided by Catherine Mirvis of Pharmerit - an OPEN Health Company.

Financial & competing interests disclosure

Funding for this study was provided by AstraZeneca. A Aly, Y Doleh and F Benavente are employees and stockholders of AstraZeneca. S Ronnebaum and D Patel are employees of Pharmerit - an OPEN Health Company. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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