HEALTH-RELATED QUALITY OF LIFE OF PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA AND COST-EFFECTIVENESS OF THE FIRST-LINE TREATMENTS IN A MEDICAL UNIVERSITY HOSPITAL IN YUNNAN, CHINA

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by

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ABC	activity-based costing
AIC	Akaike information criterion
ASR	Age-standardized incidence rate
BCLC	Barcelona clinic liver cancer
BIA	Budget impact analysis
BIC	Bayesian information criterion
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CMA	Cost-minimization analysis
CSCO	Chinese Society of Clinical Oncology
CUA	Cost-utility analysis
EASL	European Association for the Study of the Liver
EORTC	The European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EORTC QLQ-HCC18	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module
EVPI	Expected value of perfect information
FACT-Hep	Functional Assessment of Cancer Therapy-Hepatobiliary
FV	Future value
GDP	Gross domestic product
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HFSR	Hand and foot skin reactions
HICs	High-income countries
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment

iCCA	Intrahepatic cholangiocarcinoma
ICER	Incremental cost-effectiveness ratio
INMB	Incremental net monetary benefit
IQR	Interquartile range
LMICs	Low- and middle-income countries
MWA	Microwave ablation
NCDs	Noncommunicable Diseases
NHI	National Health Insurance
NHSA	National Healthcare Security Administration
NICE	National institute for health and care excellence
NMB	Net-monetary benefit
NRCMS	New Rural Cooperative Medical Scheme
NRDL	National Reimbursement Drug List
OS	Overall survival
PartSA	Partitioned survival analysis
PD	Progression disease
PD-1	Programmed death 1
PDGFR	Platelet-derived growth factor receptor
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PV	Present value
QALY	The quality-adjusted life year
RFA	Radiofrequency ablation
SBRT	Stereotactic body radiation therapy
SD	Standard deviation
SDOH	Social determinants of health
SES	Socioeconomic status
TA	Technology appraisal
TACE	Transarterial chemoembolisation
TKI	Tyrosine kinase inhibitor
UEBMI	Urban Employee Basic Medical Insurance
uHCC	Unresectable hepatocellular carcinoma

UICC	Union for International Cancer Control
URBMI	Urban Resident Basic Medical Insurance
US	The United States
USM	Universiti Sains Malaysia
VEGFR	Vascular endothelial growth factor receptors
WHO	World Health Organization
WTP	Willingness-to-pay

LIST OF APPENDICES

KUALITI HIDUP BERKAITAN KESIHATAN PESAKIT DENGAN KANSER HEPATOSELULAR TAK BOLEH DIOPERASI DAN KEBERKESANAN KOS BAGI RAWATAN BARIS PERTAMA DI HOSPITAL UNIVERSITI PERUBATAN DI YUNNAN, CHINA

ABSTRAK

Di China, karsinoma hepatoselular yang tidak dapat dibedah (uHCC) merupakan cabaran klinikal yang signifikan, menekankan keperluan untuk menilai keberkesanan kos dan aksesibiliti rawatan lini pertama. Kajian ini meneliti keberkesanan kos sorafenib, lenvatinib, dan donafenib untuk uHCC di China, dengan tumpuan kepada perbezaan dalam Kualiti Hidup Disesuaikan Mengikut Tahun (QALY). Kami menggunakan model kelangsungan hidup yang dibahagikan untuk analisis, mengambil data klinikal daripada rekod perubatan, hasil laporan pesakit, literatur, dan konsensus pakar. Hasil utama termasuk kos dalam dolar Amerika Syarikat, hasil kesihatan dalam QALY, dan nisbah keberkesanan kos tambahan (ICER) berdasarkan ambang kesediaan membayar sebanyak US $37,128 (tiga kali ganda KDNK per kapita China) untuk setiap QALY yang diperoleh. Analisis sensitiviti dijalankan untuk menilai keteguhan hasil ini. Kami juga menjalankan model regresi linear untuk meneroka hubungan antara QALY dan pemboleh ubah seperti rawatan, umur, jantina, berat badan, status pekerjaan, pendidikan, pendapatan, etnik, dan penyakit hati kronik. Nilai Shapley digunakan untuk menentukan kepentingan relatif faktor-faktor ini. Sorafenib memberikan tambahan 0.024 QALY berbanding lenvatinib, dengan ICER sebanyak US $-176,876.12/QALY (berat >60 kg) dan US $-562,151.20/QALY (berat <60 kg). Nilai ICER negatif menunjukkan bahawa sorafenib bukan sahaja lebih berkesan tetapi juga lebih murah berbanding

lenvatinib, menjadikannya pilihan rawatan yang dominan untuk kedua-dua kategori berat badan. Lenvatinib memberikan tambahan 0.03 QALY berbanding donafenib, dengan ICER sebanyak US $566,714.90/QALY (berat >60 kg) dan US $254,502.90/QALY (berat <60 kg), kedua-duanya melebihi ambang kesediaan membayar. Analisis sensitiviti mengesahkan kebolehpercayaan hasil ini. QALY dikaitkan dengan penyakit hati kronik atau tidak, pendapatan, dan rejimen rawatan. Analisis Shapley menunjukkan bahawa penyakit hati kronik atau tidak dan pendapatan memberi kesan paling besar terhadap QALY. Bagi keluarga yang mempunyai bajet terhad, sorafenib dan lenvatinib mungkin tidak berkesan dari segi kos. Kami juga memerhati ketidaksamaan dalam QALY di kalangan pesakit uHCC.

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ABSTRACT

In China, unresectable hepatocellular carcinoma (uHCC) poses a significant clinical challenge, highlighting the need to assess the cost-effectiveness and accessibility of first-line treatments. This study examined the cost-effectiveness of sorafenib, lenvatinib, and donafenib for uHCC in China, with a focus on disparities in Quality-Adjusted Life Years (QALYs). We used a partitioned survival model for the analysis, drawing clinical data from medical records, patient-reported outcomes, literature, and expert consensus. Key outcomes included costs in US dollars, health outcomes in QALYs, and the incremental cost-effectiveness ratio (ICER) based on a willingness-to-pay threshold of US $37,128 (three times China's per capita GDP) per QALY gained. Sensitivity analyses were conducted to assess robustness. We also ran linear regression models to explore the relationship between QALYs and variables such as treatment, age, gender, weight, job status, education, income, ethnicity, and chronic liver disease. Shapley values were used to determine the relative importance of these factors. Sorafenib provided an additional 0.024 QALYs compared to lenvatinib, with ICERs of US $-176,876.12/QALY (weight >60 kg) and US $-562,151.20/QALY (weight <60 kg). Negative ICER values indicate that sorafenib is not only more effective but also less costly compared to lenvatinib, making it a dominant treatment option for both weight categories. Lenvatinib provided an

additional 0.03 QALYs compared to donafenib, with ICERs of US $566,714.90/QALY (weight >60 kg) and US $254,502.90/QALY (weight <60 kg), both exceeding the willingness-to-pay threshold. Sensitivity analyses confirmed the reliability of these results. QALYs were strongly linked to chronic liver disease or not, income, and treatment regimen. Shapley analysis showed chronic liver disease or not and income had the most significant impact on QALYs. For families with limited budgets, sorafenib and lenvatinib may not be cost-effective. We also observed inequities in QALYs among uHCC patients.

CHAPTER 1 INTRODUCTION

Liver cancer is the seventh most common cancer in terms of incidence worldwide (Figure 1.1) and the third most common cause of cancer-related mortality globally (Figure 1.2) (Sung et al., 2021). The two most common histological subtypes of primary liver cancer are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) (Sung et al., 2021). Most HCC patients have a background of chronic liver disease, such as hepatitis B virus (HBV) or hepatitis C virus (HCV). Obesity, diabetes, and nicotine use are also associated with an increase in the incidence rate of HCC (Petrick et al., 2020). iCCA occurs in the hepatic bile ducts, mainly caused by foodborne flukes and Clonorchis sinensis (Chuang et al., 2009). HCC accounts for approximately 80% of liver cancer cases worldwide (Josep M. Llovet et al., 2021; Sung et al., 2021). Although in the early stages, the disease can be cured through resection, liver transplantation, or ablation, most patients present as unresectable hepatocellular carcinoma (uHCC) with a poor prognosis. The treatment of uHCC imposes a massive economic burden to patients' families, health systems, and society as a whole (Qin et al., 2021).

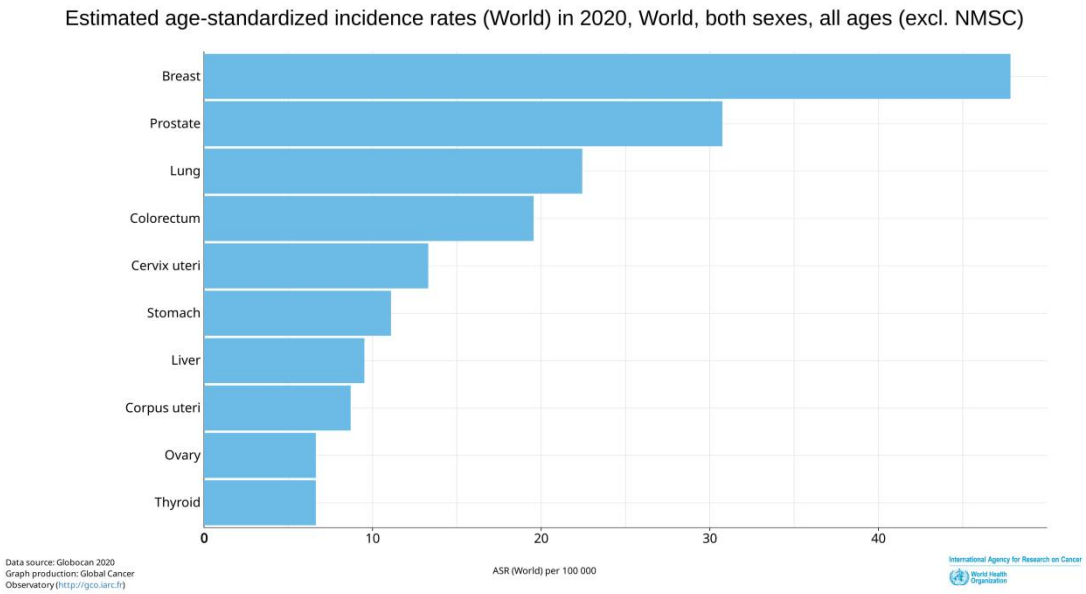

Figure 1.1 Estimated age-standardized incidence rates of cancer in 2020. (Sung et al., 2021)

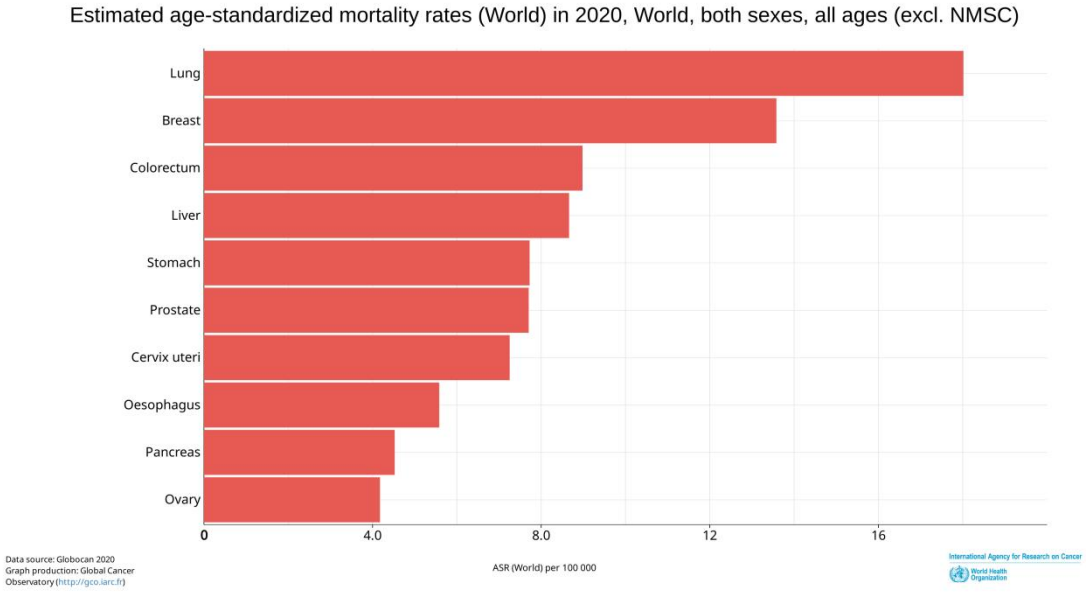

Figure 1.2 Estimated age-standardized mortality rates of cancer in 2020. (Sung et al., 2021)

1.1 Global prevalence of hepatocellular carcinoma

According to Globocan 2020 estimates, primary liver cancer is the seventh most common cancer and the third leading cause of cancer death worldwide, with

approximately 906,000 new cases and 830,000 deaths annually (Sung et al., 2021). The incidence age-standardized rate (ASR) for males is 14.1 per 100,000, while the incidence ASR for females is 5.2 per 100,000. In addition, the mortality ASR for males is 12.9 per 100,000 individuals, with 4.8 per 100,000 individuals for females. Region-specific incidence and mortality ASR by sex shows that East Asia ranks first, Micronesia ranks second, and then Southeast Asia (Figure 1.3) (Sung et al., 2021). Primary liver cancer includes HCC (comprising 75%–85% of cases) and iCCA (10%–15%), in addition to other rare types (Chimed et al., 2017). Patients diagnosed with HCC are mainly males aged 60 to 70 years old (Petrick et al., 2020). HCC is usually caused by chronic hepatitis B or C virus (HBV or HCV) infection, aflatoxin exposure, excessive drinking, obesity, diabetes, and smoking. Approximately 72% of HCC occurs in Asia, with HCC cases in China accounting for 47% (Ozakyol, 2017).

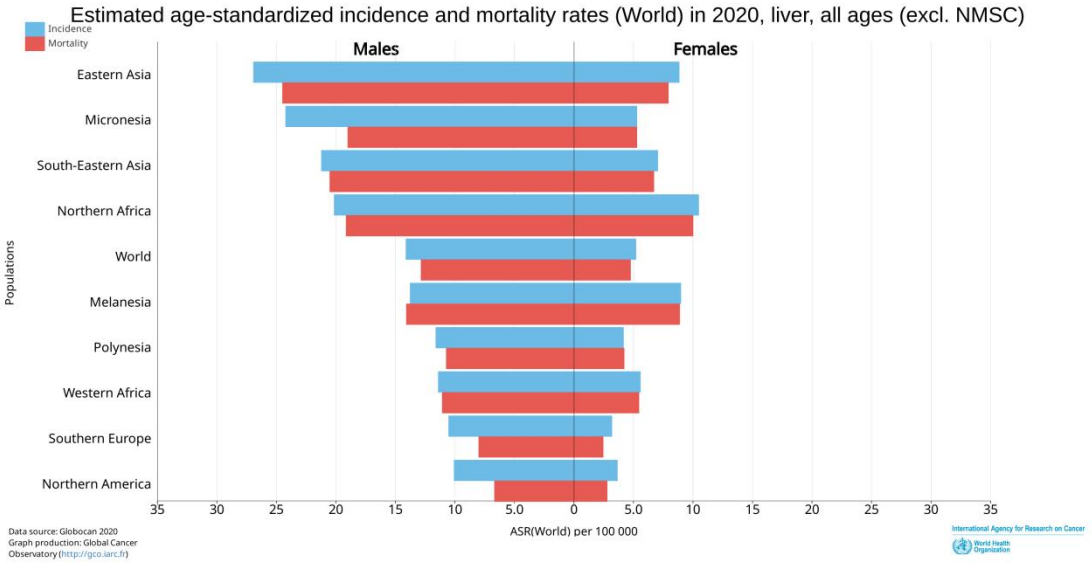

Figure 1.3 Estimated age-standardized incidence and mortality rates of cancer's area in 2020. (Sung et al., 2021)

1.2Prevalence of hepatocellular carcinoma in China

As the number of people suffering from HCC in China accounts for half of the global total, the Chinese government has implemented a series of intervention measures in the past two decades, including universal HBV vaccination, regional dietary aflatoxin control, and the establishment of primary and secondary prevention measures, such as screening and early detection (Shi et al., 2021). Although this series of measures can significantly reduce the future HBV infection rate, the current number of patients who progress to HCC due to HBV or HCV is still huge (Cao et al., 2020). In 2020, the China incidence and mortality rates for liver cancer were estimated to be 18.2 and 17.2 per 100,000 individuals, respectively. The five-year survival rate of HCC was much lower than the average of all cancers in 2020 (29.4% vs. 40.5%) (Yu et al., 2022), and patients with uHCC had a five-year survival rate of 18% (Siegel et al., 2017). The only way for HCC to achieve long-term survival or cure is through surgical resection. However, in China, most patients are already in the middle-to-advanced stage when diagnosed with HCC, and they no longer have the chance to undergo surgical resection (Park et al., 2015; Zhou & Song, 2021).

1.3Treatment for early-stage hepatocellular carcinoma

Figure 1.4 depicts the treatment options for HCC based on tumor stages and expected benefits of major intervention measures. Hepatectomy or liver transplantation is the main treatment for early HCC. Hepatectomy is generally used in patients with a single lesion and normal liver function, while liver transplantation is used in patients with

multiple lesions and cirrhosis. Generally, only a few liver cancer patients do not have cirrhosis. However, if the patient meets the criteria for liver resection surgery, hepatectomy is the first choice (Lang et al., 2005; Viganò et al., 2015). Traditional hepatectomy tries to preserve the liver parenchyma with better function in the patient (Ivanics et al., 2022; Kabir et al., 2021). With the implementation of minimally invasive techniques in liver resection, the recurrence and mortality rates of patients after surgery have been effectively reduced (Berzigotti et al., 2015). Liver transplantation can solve both the patients' tumor and cirrhosis. Meanwhile, patients have a better five-year survival rate and a lower recurrence rate of HCC. However, there is a major limitation that patients need to wait for good liver tissue, where the waiting time often ranges from 6 to 9 months (Berzigotti et al., 2015; Meirelles Júnior et al., 2015). During the waiting process, patients need to undergo some treatment to avoid the progression of HCC. This treatment is referred to as bridging therapy. Transarterial chemoembolization, ablation, and radiation belong to bridging therapy (Mazzaferro et al., 2020). Studies have demonstrated that living donor liver tissue transplantation results are better than liver transplantation from deceased donors (Goldaracena et al., 2019; Lai et al., 2021).

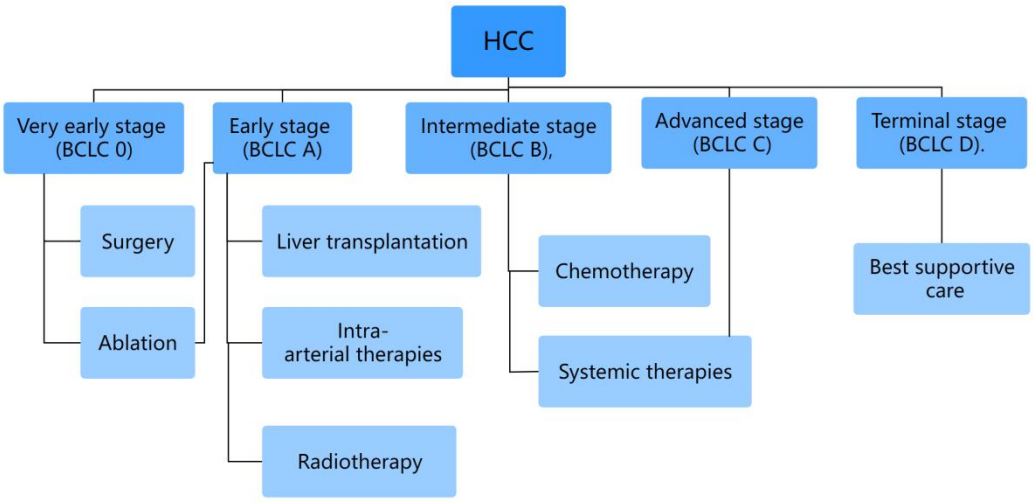

Figure 1.4 Treatment strategy in the management of HCC. (Renne et al., 2021)

Tumor ablation is a minimally invasive treatment approach. For patients with liver cancer tissue less than 2 cm or those with liver cancer tissue between 2 and 4 cm but unable to undergo surgery, radiofrequency ablation (RFA) is the foremost choice. Its principle is to cause thermal damage to tumor tissue through electromagnetic energy. The RFA probe around the tumor tissue forms a closed loop circuit, causing damage to the tumor through 4–6 min of 50–100°C (Izzo et al., 2019). Microwave ablation (MWA) has the advantage of achieving a larger ablation zone than RFA as several needles can be used simultaneously (J. M. Llovet et al., 2021). However, no difference exists in progression and disease key indicators between the treatment of RFA and MWA in comparative studies (Cheng et al., 2015; Hu et al., 2019).

Due to the abundance of blood vessels surrounding HCC tissue and the fact that most of the blood coming from the hepatic artery, intra-arterial therapies are the main treatment method for mid-term HCC (Llovet et al., 2002). In general, intra-arterial therapy is categorized into bland particle embolization, chemoembolization (conventional

trans-arterial chemoembolization or drug-eluting bead), or radioembolization. In all cases, the hepatic artery is accessed with microcatheters via groin access (Lammer et al., 2010; Llovet et al., 2002).

HCC radiotherapy is a local treatment that includes stereotactic body radiation therapy (SBRT), proton therapy, and interstitial brachytherapy. In the report on the outcome of SBRT treatment, the control rate of patients after one year of treatment is between 75% and 95% (Wong et al., 2021). Compared with SBRT, proton therapy is reported to have a longer overall survival (OS). This is ascribable to the fact that proton therapy can reduce the decompensated function of liver tissue (Sanford et al., 2019). Research has shown that compared with SBRT, interstitial brachytherapy is better at preserving normal liver tissue while providing an excellent target for HCC (Walter et al., 2021).

1.4Treatment for advanced-stage hepatocellular carcinoma

The systematic treatment of HCC is primarily used for middle or advanced-stage patients and uHCC patients. At this stage, the main purpose of treatment is to prolong the patient's survival as much as possible, and there is no way to eradicate the HCC.

1.4.1 First-line treatment

The first-line treatment options for uHCC are guided by several international protocols and guidelines, including the European Association for the Study of the Liver (EASL) (European Association For The Study Of The, 2023), the American Association for the Study of Liver Diseases (AASLD) (Chalasani et al., 2018), and the Chinese Society of Clinical Oncology (CSCO) (Wang et al., 2021) guidelines. These guidelines

recommend a range of first-line systemic therapies, including targeted tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors, based on the patient's overall health, liver function, and disease stage.

Sorafenib is the first TKI for the treatment of uHCC. It is a multitargeted TKI that blocks the activity of Raf serine/threonine kinase isoforms, as well as the receptor tyrosine kinases vascular endothelial growth factor receptors (VEGFR)-2 and VEGFR-3, platelet-derived growth factor receptor (PDGFR) β, c-KIT, FLT-3, and RET to inhibit tumor angiogenesis and tumor cell proliferation (Wilhelm et al., 2006; Wilhelm et al., 2004). The results of phase III of SHARP trial have demonstrated a survival benefit for sorafenib versus placebo with median PFS was 5.5 and 2.8 months, respectively (hazard ratio [HR] 0.58, 95% CI 0.45–0.74). Median OS in the sorafenib and placebo groups was 10.7 and 7.9 months, respectively (HR 0.69, 95% CI 0.55–0.87) (Llovet et al., 2008).

Lenvatinib, an inhibitor of VEGFR 1–3, fibroblast growth factor receptor 1–4, PDGFR α, RET, and KIT, shows activity in HCC. The analysis results of the REFLECT trial on the Chinese population showed that compared with sorafenib, lenvatinib significantly improved the median PFS (7.4 vs. 3.7 months, HR 0.66, 95% CI 0.57–0.77) and median OS (13.6 vs. 12.3 months, HR 0.92, 95% CI 0.79–1.06) of patients and increased the objective response rate by 18% (Kudo et al., 2018). Therefore, it is currently the preferred choice for an increasing number of clinical experts.

Donafenib is a derivative of sorafenib, which adds trimethoxyN-methyl to enhance molecular stability and improve pharmacokinetic characteristics (Walter et al., 2021). The results of the Phase II/III ZGDH3 trial studying the first-line treatment of uHCC with donafenib and sorafenib in the Chinese population revealed that the PFS (3.7 vs. 3.6

months, HR 0.909, 95% CI 0.763–1.082) of patients receiving donafenib regimen was non-inferior to those receiving sorafenib regimen (R. Chen et al., 2023; Qin et al., 2021).

The data from the 2019 IMbrave150 trial revealed that the combination of the programmed death-ligand 1 (PD-L1) inhibitor atezolizumab and VEGF inhibitor bevacizumab could significantly improve the objective response rate, with a median PFS (6.9 vs. 4.3 months, HR 0.65, 95% CI 0.53–0.81) and median OS (19.2 vs. 13.4 months, HR 0.66, 95% CI 0.52–0.85) than that of sorafenib (Finn et al., 2020). The IMbrave150 trial in 2023 supplemented some previously immature data, and the results showed that the regimen of atezolizumab plus bevacizumab could significantly prolong the survival of uHCC than that corresponding to sorafenib (Cheng et al., 2022).

Programmed death 1 (PD-1) inhibitor sintilimab plus bevacizumab has been approved by the National Medical Products Administration (NMPA) of China as the first-line treatment for patients with uHCC. According to the published 14-month clinical trial data of Phase II/III ORIENT-32 in Chinese patients with uHCC, the objective response rate of sintilimab plus bevacizumab was 25.0% higher than that of the sorafenib, with a median PFS (4.6 vs. 2.8 months, HR 0.56, 95% CI 0.46–0.70) and median OS (not reached vs. 10.4 months, HR 0.57, 95% CI 0.43–0.75) (Ren et al., 2021).

Combination treatments involving dual anti-PD-1/VEGFR-2 therapy have been documented to reshape the immune microenvironment (Shigeta et al., 2020). The blockade of anti-VEGFR-2 has been proven to trigger the expression of PD-L1 in both endothelial cells and CD4+ cells, which infiltrate tumors. Consequently, the co-administration of anti-PD-1 inhibitors and antiangiogenic agents has garnered significant attention. Nevertheless, the aforementioned combination strategies were assessed or applied exclusively in the first-line setting, and there is a dearth of available data in a

broader population, particularly with a substantial prevalence of concurrent HBV infection. The RESCUE trial stands out as the most extensive study conducted in a population with a significant prevalence of HBV infection, aiming to evaluate the effectiveness and safety of camrelizumab in combination with apatinib for uHCC. The median PFS was 5.7 months (95% CI 5.4–7.4), and the 12-month survival rate reached 74.7% (95% CI 62.5–83.5) (Xu et al., 2021). The objective response rate was 34.3%. It was approved as the first-line treatment in January 2023.

The RATIONALE-301 trial demonstrated compared tislelizumab with sorafenib as the first-line treatment for uHCC (Qin et al., 2023). Median OS was 15.9 months vs 14.1 months, respectively (HR 0.85, 95% CI 0.71–1.02). Median PFS was 2.1 months vs 3.4 months with tislelizumab vs sorafenib (HR 1.11, 95% CI 0.92–1.33). The objective response rate reached 14.3% with tislelizumab compared with 5.4% with sorafenib.

1.4.2 Second-line treatment

Regorafenib has been proven by multiple countries to be a continuous treatment regimen for advanced first-line treatment of sorafenib (Komiyama et al., 2020; Llovet et al., 2022). Regorafenib is an oral diphenylurea multi-kinase inhibitor that targets VEGFR1-3, PDGFR-β, FGFR, and oncogenic receptor tyrosine kinases.

Cabozantinib, a TKI with activity against multiple targets including MET, VEGFR, and the Tyro3, Axl, and Mer (TAM) kinase family, is endorsed by the Chinese Food and Drug Administration, European Medicines Agency, and the Food and Drug Administration as a second-line treatment for patients with uHCC (Abou-Alfa et al., 2018; Maeda & Ando, 2018).

Ramucirumab is a monoclonal antibody that targets the VEGFR-2, inhibiting angiogenesis and impacting the growth of blood vessels that supply tumors. The REACH-2 trial, focusing on ramucirumab, specifically included patients with baseline α-fetoprotein levels of ⩾400 ng/dL (Zhu et al., 2019). The results of the trial revealed enhanced overall survival associated with the use of ramucirumab.

1.5Impact on patients' quality of life

In addition to extremely high mortality rates, the quality of life of uHCC patients is severely affected by comorbidities. The comorbidities of uHCC include liver failure, ascites (fluid accumulation in the abdominal cavity), hepatic encephalopathy (abnormal brain function due to impaired liver function), weight loss, anemia, bleeding tendency, and hepatorenal syndrome, among others (Hobeika et al., 2022; Hsu et al., 2010; Saito et al., 2023; Smith et al., 2019). These comorbidities can affect the quality of life of patients and even affect their daily behavioral abilities.

The adverse reactions of regimens for uHCC also impact patients' quality of life. The incidence rate of treatment-related grade 3 or 4 adverse reactions with sorafenib was reported to be 46.0% (Llovet et al., 2008). The incidence rates of diarrhea (8.0%), weight loss (2.0%), hand and foot skin reactions (HFSR, 8.0%), hypertension (2.0%), and abdominal pain (2.0%) in the sorafenib group were higher than those in the placebo group ($P<0.001$). Among patients receiving lenvatinib treatment, 75.0% experienced grade 3 or higher adverse events (Kudo et al., 2018). Hypertension (42.2%), diarrhea (38.7%), decreased appetite (34.0%), and weight loss (30.9%) were found to be common among patients. The incidence rate of grade 3 or 4 adverse reactions related to donafenib was

7.0%. The most common drug-related adverse events were HFSR (50.0%) and diarrhea (30.0%) (Qin et al., 2021). Treatment-related adverse events occurred in 43.0% of patients treated with atezolizumab plus bevacizumab (Cheng et al., 2022). The most common treatment-related adverse events with atezolizumab plus bevacizumab were proteinuria (29.0%), hypertension (28.0%), increased aspartate aminotransferase (16.0%), and fatigue (16.0%). Reportedly, 32.0% of patients in the sintilimab–bevacizumab biosimilar group had serious adverse events (Ren et al., 2021). The most common grade 3 or worse adverse events were a decrease in neutrophil count (30.0%), a decrease in white blood cell count (17.0%), anemia (13.0%), and hypokalemia (5.0%). In camrelizumab in combination with apatinib, adverse events related to the treatment of grade $\geqslant$3 were observed in 147 (77.4%) out of 190 patients, with hypertension (34.2%) being the most prevalent. Serious treatment-related adverse events were noted in 28.9% of patients, and 1.1% of treatment-related deaths occurred (Xu et al., 2021). Grade $\geqslant$3 treatment-related adverse events were documented in 75 (22.2%) patients treated with tislelizumab (Qin et al., 2023). The most prevalent treatment-related adverse events in patients included elevated levels of aspartate aminotransferase (23.1%), alanine aminotransferase (16.6%), and blood bilirubin (12.4%).

Due to the complex relationship between tumor burden and potential liver function, HCC specific health-related quality of life (HRQoL) assessment is necessary for clinical management and evaluation of the safety and effectiveness of new therapies (Llovet et al., 2008; Zhu et al., 2014).

The EuroQol 5-dimension scale (EQ-5D) is a popular health-related quality of life instrument used in the clinical and economic evaluation of health care (Augustovski et al.,

2009). For the description component, patients self-rate their health in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using either a three-level (EQ-5D-3L and EQ-5D-Y) or a five-level (EQ-5D-5L) scale (Kreimeier & Greiner, 2019; van Hout & Shaw, 2021). The sample of EQ-5D-5L questionnaire is shown in APPENDIX A. Following assessment, the scores from the descriptive component can be reported as a five-digit number ranging from 11111 (full health) to 55555 (worst health). A number of methods exist for analyzing these five-digit profiles. However, frequently they are converted to a single utility index using country-specific value sets, which can be used in the clinical and economic evaluation of health care as well as in population health surveys. An EQ-5D-5L value set reflecting the health preferences of the Malaysian adult population was developed in 2019 (Shafie et al., 2019), and an EQ-5D-5L value set for China of residents living in the urban areas was estimated in 2017 (Luo et al., 2017).

In addition to generic scales that can be used for both normal individuals and patients, there are some scales specifically designed for HCC that can assess the disease burden and HRQoL of patients. The most common instrument used to assess HRQoL in patients with HCC are the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) and its HCC-specific module, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module (EORTC QLQ-HCC18) (Blazeby et al., 2004). The EORTC QLQ-C30 (APPENDIX B) is a questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC) to assess the HRQoL in cancer patients. It covers a diverse range of aspects such as physical functioning, emotional functioning, pain, fatigue, and overall health status

(Aaronson et al., 1993). Additionally, it includes specific questions related to common cancer symptoms and side effects of treatment. The questionnaire is widely used in clinical trials and research to gather information directly from cancer patients about their well-being and functioning. Furthermore, the EORTC QLQ-HCC18 (APPENDIX C) is another questionnaire developed by the EORTC to specifically assess the HRQoL with HCC, the most common type of primary liver cancer. It includes questions related to symptoms and side effects specifically relevant to individuals with HCC (Li et al., 2017). It covers various aspects such as pain, fatigue, nutritional aspects, and other concerns related to liver cancer and its treatment. The physical health status and overall HRQoL of HCC patients are significantly lower than those of normal individuals and patients with chronic liver disease (Fan et al., 2010). Serious symptoms of HCC or side effects of treatment will result in pain, loss of appetite, digestive difficulties, and fatigue. Although HRQoL may decrease in the first three months of treatment, it will increase from 3 to 6 months of treatment (Fan et al., 2010).

1.6Economic burden of hepatocellular carcinoma

The global economic burden of uHCC on public health care is a significant and growing concern. This burden encompasses the direct and indirect costs associated with the diagnosis, treatment, and management of uHCC patients within public healthcare systems worldwide. Direct costs involve expenses related to medical interventions, hospitalization, medications, diagnostic procedures, and other healthcare services directly associated with the diagnosis and treatment of uHCC (Tan et al., 2012). These costs can place a substantial strain on public healthcare budgets, particularly considering the often complex and prolonged nature of uHCC treatment. Indirect costs encompass the broader

economic impact of uHCC on society, including productivity losses due to disability, premature mortality, and the impact on caregivers. The global prevalence of uHCC contributes to a heightened economic burden, as the disease requires long-term management and often affects individuals in their working years (Jallon et al., 2011).

The economic burden is exacerbated by the need for advanced and expensive treatments, such as targeted therapies and immunotherapies, which are frequently part of the standard of care for uHCC. Additionally, the burden is influenced by factors such as the availability and accessibility of healthcare resources, the prevalence of risk factors contributing to uHCC (such as viral hepatitis), and the overall efficiency of healthcare systems (Valgus, 2017).

The global burden of liver cancer continues to rise, with the greatest impact on East Asia and the high burden and early onset of disease in some low-income countries such as Mongolia, Lao PDR, and Vietnam (Are et al., 2017). In the United States, direct cost with uHCC had the highest mean total per patient per month costs (US $9,585 / person) followed by regional (US $8,072 / person) and localized disease (US $7,265 / person) (White et al., 2012). Furthermore, the annual productivity loss caused by cancer for each patient was US $3,553 (Lang et al., 2009). In 2017, the United States' Gross Domestic Product (GDP) per capita reached US $59,484. In Greece, the average cost per patient was estimated at US $21,375.1 per year (Athanasakis et al., 2020), while Greece's per capita GDP in 2018 was US $19,747.5.

In 2012, the highest proportion of productivity losses among all cancers in China resulted from premature death due to HCC (US $8.15 billion) (Pearce et al., 2018). The overall economic burden of HCC was estimated at US $11.1 billion in China in 2019 (0.047% of the local GDP). At the same time, experts have predicted that if there is no

effective control, the overall cost will reach US $34.0 billion by 2030 (0.192% of China's GDP) (Cao et al., 2022). Obviously, HCC represents a heavy toll, both from the clinical as well as from the economic perspective.

Efforts to mitigate the economic burden of uHCC on public healthcare systems may involve strategies such as prevention and early detection programs, optimizing treatment pathways for cost-effectiveness, and implementing measures to reduce risk factors associated with uHCC development. Public health policies aimed at addressing the socioeconomic impact of uHCC can contribute to more sustainable and equitable healthcare delivery globally.

1.7Cost-effectiveness for first-line treatments of unresectable hepatocellular carcinoma

In recent years, a large number of TKIs and immunotherapies have been approved as first-line treatment guidelines for uHCC in various countries. The increasing number of choices has created a dilemma in seeking and recommending the best alternative. However, the most critical factor in preventing this dilemma is uncertainties surrounding their cost-effectiveness (Anwanwan et al., 2020). Due to nearly half of the world's HCC patients being in China, the Chinese health ministry needs to pay a large number of fees annually for the treatment of uHCC. Any treatment regimen that requires payment from national basic medical insurance requires a real-world health technology evaluation.

In a setting with limited resources, it becomes essential to conduct an "economic evaluation" to assess and enhance health outcomes. This involves a comparative analysis of alternatives, considering both their costs and consequences. On the one hand, cost components are consistently quantified in monetary units, determined by the chosen

perspective for calculation and the scope of expenditures considered. For instance, a societal cost perspective encompasses all relevant elements, including expenses for healthcare service provision, patient spending, and other societal costs. This perspective often covers both “direct costs”, associated with service provision and utilization, and “indirect costs”, reflecting productivity losses to society due to illness-related time off from work and treatment (Raftery & Powell, 2013). On the other hand, the evaluation of strategies involves measuring the outcomes in various ways, and the chosen method shapes the type of evaluation conducted. In healthcare, four main types of analysis are commonly utilized: (1) cost-minimization analysis (CMA), comparing only cost components when outcomes are assumed to be equal; (2) cost-effectiveness analysis (CEA), where outcomes are measured in natural or physical units; (3) cost-utility analysis (CUA), employing a generic measure like the quality-adjusted life years (QALYs); and (4) cost-benefit analysis (CBA), expressing benefits in monetary terms (Ahuja et al., 2004; Shiragami, 2003). While the study's objective ultimately guides the analysis type chosen, contemporary guidelines and health technology agencies recommend opting for CUA in decision-making owing to its ease of interpretation and comparability across different service provisions (Ahuja et al., 2004).

CUA on uHCC has already been conducted by some researchers in China (Liu et al., 2022; Sun et al., 2022; Zhao et al., 2022; T. Zhou et al., 2022). Research perspectives include the healthcare system, payer, and the third-party payment (Table 1.1). However, some data in the models (such as clinical data and utility values) were not collected entirely based on the actual situation. Thus, the results should be interpreted with caution. All studies used indirect comparisons because there were no direct randomized controlled trials between/among the drug groups (Liu et al., 2022; Sun et al., 2022; Zhao et al., 2022;

T. Zhou et al., 2022). Most studies used a common control drug as a bridge and used the constant HR hypothesis. Most of the utility values were derived from the phase III clinical trials (Finn et al., 2020), other literature data (Rabin & de Charro, 2001; Shlomai et al., 2018), or the National Institute for Health and Care Excellence technology appraisal guidance (Roberts et al., 2020; Tosh et al., 2011). This underscores the need to appraise the cost-effectiveness of first-line treatments of uHCC based on real-world data. Only research on real-world data can have a useful impact on medical decision-making.

Table 1.1 Economic evaluations on first-line treatments of uHCC in China

First author, year (country)	Clinical data from Phase III clinical trials	The number of clinical trials	A head-to-head trial comparison	Utility from other literature
Zhao, M, 2022 (China)	Yes	IMbrave150, REFLECT, ORIENT-32, and ZGDH3	No	Yes
Zhou, T, 2022 (China)	Yes	ORIENT-32 and REFLECT	No	Yes
Sun, K. X, 2022 (China)	Yes	NR	No	Yes
Li, L, 2022 (China)	Yes	ORIENT-32 and IMbrave 150	No	Yes
Wen, F, 2021 (China)	Yes	IMbrave150	Yes	Yes
Zhou, T, 2022 (China)	Yes	ORIENT 32	Yes	Yes
Liu, K. 2023 (China)	Yes	RATIONALE-301; SHR-1210-III-310; and LEAP-002	No	Yes

NR: Not reported

1.8Inequities in the quality of life and health

Inequities in the HRQoL are observed among individuals affected by cancer. These disparities are ascribable to various factors: (1) Access to health care, disparities in access to cancer screening, diagnosis, and treatment services can impact health outcomes.

Individuals with limited access to healthcare facilities or resources may experience delays in diagnosis and receiving optimal care (Rouëssé, 2013). (2) Socioeconomic factors, economic disparities can affect the ability of individuals to afford cancer treatments, medications, and supportive care services (Morriscey & Hajizadeh, 2021). Financial challenges may lead to differences in the overall quality of life during and after cancer treatment. (3) Geographical disparities, rural or underserved areas may have limited access to specialized cancer care centers, leading to disparities in the availability and quality of healthcare services (Gilbert et al., 2016). (4) Educational disparities, differences in educational attainment can influence health literacy and the ability to understand and navigate complex healthcare information. Lower educational levels may result in less proactive health-seeking behaviors and adherence to treatment plans (Morriscey & Hajizadeh, 2021). (5) Cultural and ethnic factors, cultural beliefs, language barriers, and differences in healthcare-seeking behaviors can contribute to disparities in cancer outcomes (Harvey et al., 2023). Tailoring healthcare approaches to diverse cultural backgrounds is essential for achieving equitable outcomes. (6) Health insurance coverage, disparities in health insurance coverage may impact access to preventive measures, early detection, and timely cancer treatments (Arroyave et al., 2013).

Despite the proven effectiveness of treatment approaches such as targeted drugs and immunosuppressive agents in extending the OS of cancer patients in recent years, health disparities persist in cancer treatment among populations. Health disparities are defined as preventable differences in disease burden, treatment outcomes, and opportunities for achieving optimal health compared with the overall population. Research by Kassandra and others demonstrates significant differences in HRQoL post-

cancer diagnosis between individuals with low and high socioeconomic status (Starkweather et al., 2023).

The American National Academies of Sciences, Engineering, and Medicine has acknowledged that structural inequities exacerbate the health status of vulnerable populations, leading to unfair and unjust outcomes. A 60-year study revealed higher cancer mortality and incidence rates in socioeconomically impoverished areas compared with those in affluent regions, particularly for colorectal cancer, liver cancer, stomach cancer, lung cancer, and cervical cancer (de Souza et al., 2016).

The study by Ani and colleagues reveals that individuals from minority groups without insurance or inadequate insurance coverage face unfavorable opportunities for viral hepatitis screening and treatment (Alcaraz et al., 2020). This situation leads to higher liver-related mortality and a greater proportion of liver cancer being diagnosed at advanced stages. Simultaneously, there are significant differences in HRQoL among patients with uHCC.

1.9Problem statement

In China, a variety of drugs are included in the first-line treatment regimens for uHCC, as recommended by the CSCO and international guidelines. However, the healthcare system faces significant challenges in managing its limited resources while ensuring equitable access to effective treatments. With rising healthcare costs and the increasing prevalence of uHCC, there is an urgent need to evaluate the cost-effectiveness of these first-line treatments. This evaluation is critical to help balance treatment efficacy with the financial sustainability of the healthcare system. Without a clear understanding of the economic impact of these treatments, policymakers and clinicians may struggle to

make informed decisions regarding resource allocation and treatment accessibility, potentially exacerbating existing disparities in cancer care.

1.10 Study significance

Evaluating the cost-effectiveness of first-line treatments for uHCC is not only crucial for clinical decision-making but also for informing health policy and resource allocation. From a healthcare system perspective, understanding the economic impact of different treatment options is essential for managing healthcare budgets and optimizing resource use. Economic evaluations, such as cost-effectiveness analyses, allow health authorities to determine which therapies provide the most benefit relative to the investment. This research is particularly important in the context of rising healthcare costs, where it is critical to ensure that patients receive high-quality treatments within budgetary constraints.

Furthermore, this study aims to comprehensively examine the differences and influencing factors in the HRQoL of patients with uHCC to promote health equity in cancer care. Equity refers to providing care that is fair and just, ensuring all patients receive the resources and treatment tailored to their specific needs, which may differ depending on their individual circumstances. This differs from equality, which focuses on providing the same resources to everyone regardless of their needs. By focusing on equity, this research seeks to address disparities in cancer care and provide actionable recommendations for clinical practice, research, and health policy, ultimately contributing to the elimination of cancer-related health inequities.

1.11 Research objectives

This study aimed to address the following objectives in the context of uHCC:

a. To calculate the cost of treatments from the healthcare system perspective.

b. To measure the real-world survival data of patients with uHCC who receive systemic therapy.

c. To evaluate changes in HRQoL throughout the treatment stages of uHCC patients.

d. To identify the most cost-effective first-line treatment option for uHCC patients based on real-world data and assess the key factors driving cost-effectiveness in the treatment of uHCC.

e. To explore the factors influencing QALYs in uHCC patients, with a focus on potential health inequities.

CHAPTER 2 LITERATURE REVIEW

2.1China's healthcare system and health technology assessment

2.1.1 Overview of china’s healthcare system

China’s healthcare system has undergone significant transformation over the past few decades, evolving from a system primarily dependent on public hospitals to a more integrated healthcare model. The introduction of three major insurance schemes-Urban Employee Basic Medical Insurance (UEBMI), New Rural Cooperative Medical Scheme (NRCMS), and Urban Resident Basic Medical Insurance (URBMI)-has improved the healthcare coverage rate, ensuring a broad spectrum of the population has access to basic healthcare services (Cai et al., 2023). Despite these advances, disparities in healthcare resource allocation remain a challenge, with rural areas and less developed regions often facing shortages in medical personnel, technology, and facilities.

The government's efforts in healthcare reform, such as the Healthy China 2030 initiative, aim to address these inequities by expanding coverage, improving service quality, and encouraging health equity. The reforms emphasize the importance of universal health coverage, particularly in the areas of chronic disease management, elderly care, and basic medical services (Kang et al., 2023). These changes are intended to align China's healthcare system with international standards while controlling costs and improving population health outcomes.

2.1.2 The introduction and evolution of health technology assessment

Health Technology Assessment (HTA) has become a pivotal tool in China's healthcare system, particularly as the country shifts towards evidence-based healthcare decision-making (Yao et al., 2022). HTA is used to evaluate the clinical efficacy, safety, and economic impact of medical technologies, drugs, and interventions. Although HTA originated in Europe and North America, its integration into China's healthcare policies began more recently, gaining momentum in the past decade. The development of HTA in China is closely tied to the growing demand for cost-effective healthcare solutions, especially as the country's population ages and the prevalence of chronic diseases rises (W. Chen, L. Y. Zhang, et al., 2023).

Historically, drug approvals and medical technology assessments in China focused primarily on clinical outcomes, such as safety and efficacy. However, in the last decade, the rising healthcare costs prompted policymakers to consider the economic implications of new treatments, particularly in oncology and other high-cost disease areas like cardiovascular diseases. The integration of HTA into China's National Health Insurance (NHI) decision-making process represents a significant shift towards balancing clinical benefit with economic value. This shift has been essential in ensuring sustainable healthcare spending (Zhou, Lu, et al., 2024).

2.1.3 The Role of the National Healthcare Security Administration in health technology assessment

The establishment of the National Healthcare Security Administration (NHSA) in 2018 marked a critical turning point in the institutionalization of HTA in China. The