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Adhering to the Barcelona Clinic Liver Cancer Disease Staging and Treatment Algorithm: Disease Burden and Cost of Illness of Hepatocellular Carcinoma in Portugal

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Keywords
Hepatocellular carcinoma · Burden of disease · Cost of illness

Abstract

Objectives: The aim of this study was to assess disease burden and cost of illness of hepatocellular carcinoma (HCC) in Portugal, assuming full adherence to the treatment algorithm associated to the Barcelona Clinic Liver Cancer (BCLC) system. ***Methods:*** An individual-level, continuous-time, state-transition model was used to simulate the progression of HCC patients through the BCLC disease stages. Health state transition rates were derived from the published literature. An expert panel provided further information on Portuguese epidemiology and clinical practice, including treatments and other healthcare resources utilization at each disease stage. Unit costs for health resources were collected from national public sources. HCC associated costs and outcomes were estimated over a 5-year time horizon. ***Results:*** Over the 5-year horizon of this study, the projections of HCC annual prevalence (including patients in remission) show an increasing trend, rising from 4,151 in 2023 to 4,851 in 2027. Despite the slight reduction in the predicted annual mortality rate (from 29.8% to 28.7%), we estimated that HCC could still lead to a total of 120,314 years of life lost due to premature mortality in the Portuguese population. Costs attributed to HCC were predicted to rise from around EUR 70 million in 2023 up to around EUR 77 million in 2027. Around 44.3% of these costs are related to HCC systemic treatment and 29.0% related to liver transplantation costs. ***Conclusion:*** HCC's increasing prevalence trend will continue to impose substantial disease burden in terms of premature mortality, with more than 20,000 years of life lost per year in the Portuguese population. Consequently, costs attributed to HCC are expected to rise despite the reduction on mortality by full adherence to the BCLC treatment algorithm. Continuing high disease burden and substantial

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cost of illness urge for a need of a comprehensive and effective healthcare interventions, as well as adequate resource allocation for HCC.

Adesão ao Algoritmo de Estadiamento e Tratamento Barcelona Clinic Liver Cancer: Carga e Custo do Carcinoma Hepatocelular em Portugal

Palavras Chave
Encargos com doença · Custo da doença · Carcinoma hepatocelular

Resumo
Objetivos: Avaliar o custo e carga do carcinoma hepatocelular (CHC) em Portugal, assumindo uma adesão total aos algoritmos de tratamento associados ao sistema de estadiamento de acordo com a classificação Barcelona Clinic Liver Cancer (BCLC). ***Métodos:*** A progressão dos doentes com CHC através dos estágios BCLC e os correspondentes algoritmos de tratamento foram simulados usando um modelo de transições entre estados de saúde em tempo contínuo e ao nível individual. As taxas de transição entre os estados de saúde do modelo foram estimadas através da literatura publicada. Um painel de peritos forneceu informação adicional sobre a epidemiologia e prática clínica portuguesas, incluindo a utilização de tratamentos e outros recursos de saúde em cada estado da doença. Os custos unitários dos recursos de saúde foram recolhidos de fontes públicas nacionais. Os custos e resultados em saúde associados ao CHC foram estimados para um horizonte de 5 anos. ***Resultados:*** Ao longo do horizonte de cinco anos deste estudo, as projeções da prevalência anual do CHC (incluindo doentes em remissão) mostram uma tendência crescente, evoluindo de 4.151 em 2023 para 4.851 em 2027. Apesar da ligeira redução na taxa de mortalidade anual prevista (de 29,8% para 28,7%), estimámos que, num período de 5 anos, o CHC ainda poderá levar a um total de 120.314 anos de vida perdidos por mortalidade prematura na população portuguesa. Em termos de impacto económico, previu-se que os custos atribuídos ao CHC aumentariam de cerca de 70 milhões de euros em 2023 para cerca de 77 milhões de euros em 2027. Cerca de 44,3% destes custos estão relacionados com o tratamento sistémico e 29,0% relacionados com os custos de transplante hepático. ***Conclusões:*** A tendência para o aumento da prevalência do CHC continuará a representar um impacto substancial em termos de mortalidade prematura, com mais de 20.000 anos de vida perdidos por ano na população portuguesa. Consequentemente, prevê-se que os custos atribuídos ao CHC aumentem, apesar da redução na mortalidade decorrente da plena adesão ao sistema de estadiamento e algoritmo de tratamento da classificação BCLC. A carga elevada e os custos substanciais do CHC exigem intervenções de saúde abrangentes e eficazes, bem como uma adequada alocação de recursos.

Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary hepatic cancer, representing 90% of cases [1]. Worldwide, HCC is the third main cause of death by oncologic disease, accounting for more than 830 thousand deaths in 2020 [2]. Consequently, it is vital to diagnose HCC while in early stages [1, 3]. However, due to the asymptomatic form of disease in most stages (including the early ones) along with surveillance program design's flaws, diagnosis usually occurs in more advanced stages of the disease. In fact, more than 50% of patients are in advanced stage at diagnosis [4].

The costs related to HCC have been increasing due to the rise in its incidence. Marinho et al. [5] concluded that between 1993 and 2005, the costs of hospital admissions due to HCC increased by 8.7 times, reaching over EUR 4.5 million, showing the substantial and increasing economic impact of HCC in National Health System [5].

Choice of the best treatment is the first step to reduce the socioeconomic impact of HCC and the staging of the HCC is crucial to attain it [6]. Out of all of the staging systems, the guidelines from the European Association for the Study of the Liver (EASL) recommend to classify HCC based on the Barcelona Clinic Liver Cancer (BCLC) staging system [1, 3, 7], which embodies information related to the tumoral stage, hepatic function, and performance status, classifying patients in one of 5 stages (0, A, B, C, or D) [1]. These are grouped by the therapeutic guidelines from EASL, which define the best treatment for each patient according to the disease status, in four main stages of disease: Initial stage (BCLC 0 and A); Intermediate stage (BCLC B); Advanced stage (BCLC C); Terminal stage (BCLC D) [1].

Despite the availability of evidence-based guidelines like BCLC, variations in clinical practice and health resource allocation can lead to suboptimal care delivery. Thus, a thorough evaluation of the current practices and

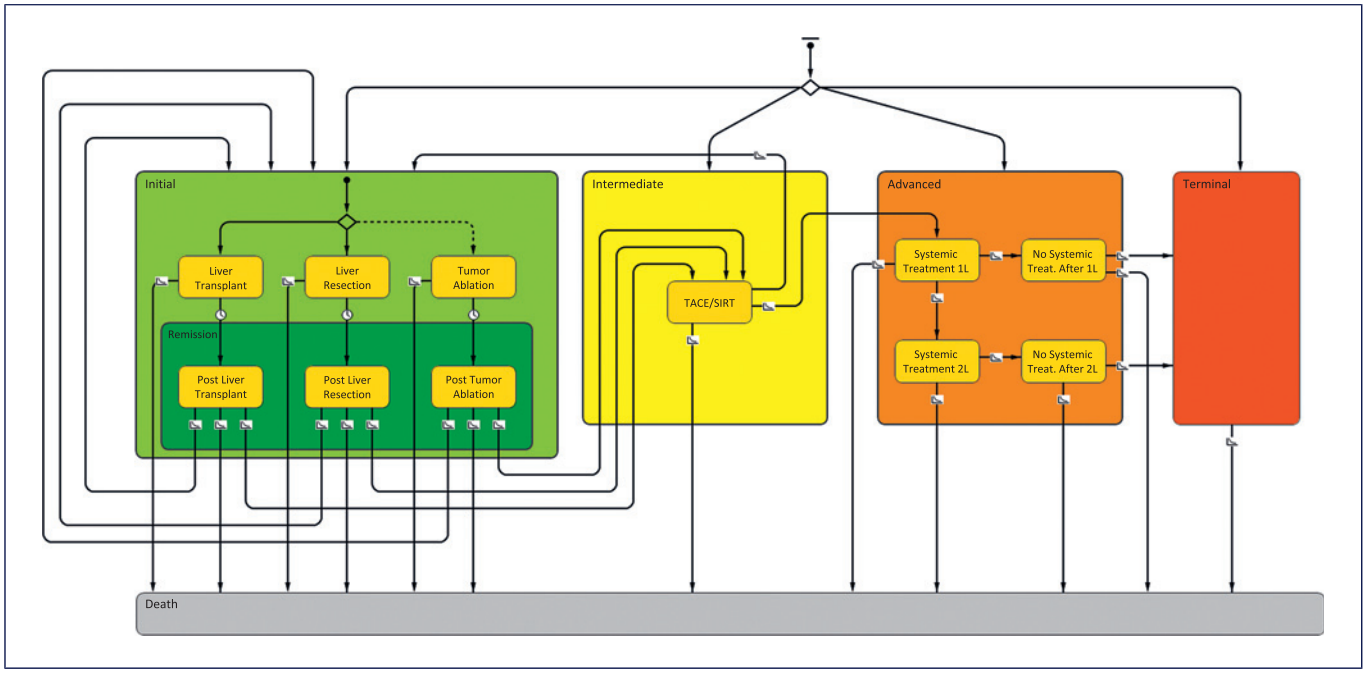

Fig. 1. Conceptual model for HCC natural history based on the BCLC staging system. TACE, transarterial chemoembolization; SIRT, selective internal radiation therapy; 1L, 1st line; 2L, 2nd line.

adherence to guidelines is crucial to identify gaps, inform targeted interventions, and ultimately enhance the quality of care for patients battling this challenging disease in Portugal. The present study aimed to estimate the burden and costs of HCC in Portugal for 5 years (from 2023 to 2027), from the perspective of the Portuguese Health System, assuming that all the new cases of HCC could be treated according to the algorithm provided by the guidelines from EASL [1] and that all the treatments are readily available whenever needed.

Materials and Methods

Model Development

An epidemiologic model was developed to derive estimates for the total number of patients who go through each disease stage and treatment, as well as the time spent in each disease stage, using the software Anylogic v7.3.7. Transitions between health states in continuous time at an individual level are simulated for a hypothetical cohort of HCC patients. Conceptually, the model was comprised by five main health states that represent disease staging according to the BCLC system: "Initial" (BCLC stages 0 and A), "Intermediate" (BCLC B), "Advanced" (BCLC C), "Terminal" (BCLC D), and "Death." The "Initial" and "Advanced" states are divided into substates related to treatment options in that disease stage to incorporate the treatment algorithm underlying the BCLC staging system. The Initial stage if further disaggregated into is divided into "Liver Transplant," "Liver Resection," "Tumor Ablation," "Post Liver Transplant," "Post Liver Resection," and "Post Tumor Ablation." Advanced stage is divided into "Systemic Treatment 1L" (first line of systemic treatment), "Systemic Treatment 2L" (second line of systemic treatment), "No Systemic Treatment after 1L" (for patients that only receive one line of treatment), and "No Systemic Treatment after 2L" meaning no systemic second-line treatments (shown in Fig. 1).

In the "Initial" health state, for the substates "Liver Transplant," "Liver Resection," and "Tumor Ablation," it is assumed that patients remain for a maximum period of 90 days, during which the death probability reflects the short-term increase in mortality post procedure. Patients who survive this period subsequently transition to one of the "Remission" substates, in which they remain until death or disease relapse. In the latter case, patients can transition to the "Intermediate" health state or remain in the "Initial" health state and undergo new treatment in this state (with the exception of a second liver transplant). In the "Intermediate" health state, patients can undergo treatment with transarterial chemoembolization (TACE) or selective internal radiation

therapy (SIRT). It is assumed that patients in the "TACE/SIRT" substate can transition to the "Initial" health state (downstaging) or progress to the "Systemic Treatment 1L" substate of the "Advanced" health state. The "Advanced" health state contains two substates to account for advanced disease in patients who are not eligible for subsequent systemic treatment (Fig. 1).

The outcomes from this study were obtained by combining the estimates for the number of treatments, mortality, and time spent in each health state for the average incident patient at each BCLC stage (derived through the epidemiological model) with estimates of the incidence and related costs. The estimates were obtained through the Monte Carlo simulation method. Computer simulated cohorts were generated at a rate of 500 patients per day during 366 days, summing to 183,000 yearly individual patients. Initial age and health substate are also computer-generated ("Liver Transplant," "Liver Resection," "Tumor Ablation," "Intermediate," "Systemic Treatment 1L," and "Terminal"). Events simulation through patients' life (0–100 years) is modeled according to the expected incidence distribution of HCC by age-groups in the Portuguese population (see online suppl. material Table C; for all online suppl. material, see https://doi.org/10.1159/000542884). In total, these procedures accounted for 110.9 million individual simulations.

The average results for each age and initial status were then weighted by the initial age and initial model health state distributions for the incident population to obtain results for an average incident patient. The age distribution used includes few very young and very old patients, as presented in online supplementary material Table C. Subsequently, these per-patient auxiliar results were combined with incidence estimates at a national level to derive the results at the population level. With this modeling approach, there was no counterfactual, and hence, no comparator was specified.

Data Sources

Health state transition annual rates for the epidemiological model are presented in Table 1. These were derived from information in the literature identified via a targeted literature review (see online suppl. material Table A for the information collected in the literature), transforming from a probability in a certain time horizon to an annual rate using the formula $r = -\frac{\ln(1-p)}{t}$.

For example, for the transition from "Liver Transplant" to "Death," Meyerovich et al. [8] reported a probability of death of 9.8% in the first 90 days after transplant. Using the formula above, we obtain an annual rate of $r = -\frac{\ln(1-9.8\%)}{90\ days} = 0.419$. The annual rate values indicate the speed of transition.

Given the scarcity of recent information in the literature regarding the Portuguese clinical practice in the treatment of HCC, Portuguese-specific parameters required by the model were obtained through an expert panel. This panel was comprised by a multidisciplinary team of 11 clinicians with extensive experience in the treatment of HCC in the Portuguese National Health Service (NHS). The composition of the panel sought to be not only representative of the different medical specialties involved in the treatment and monitoring of patients with HCC during the course of the disease but also of the various institutions, geographically dispersed, where these patients receive specialized medical care.

The panel was conducted by Exigo Consultores, consisting of two main phases. The first phase consisted in the collection of independently and individually responses to a structured questionnaire, available online using Sawtooth Software®'s Lighthouse studio® between June 27, 2022, and July 10, 2022, which addressed all the parameters for which published information was scarce or even inexistent. The second phase consisted of a scientific meeting that took place on July 15, 2022, with all the experts included in the panel, where descriptive statistics of responses to the questionnaire collected in the first phase were presented and discussed.

Results of the elicitation process carried out through this expert panel can be found in the (online suppl. material Tables B–H). Note that relative to systemic treatments, the included drugs were not restricted to the ones mentioned in the EASL guidelines. The distributions of treatments in each state of the model are reported in Table 2.

Unit costs for all the health resources identified in the expert panel were retrieved from public sources perspective regarding the costs for the Portuguese National Health System in 2022. Only direct medical costs were included [9–13]. Briefly, drugs unit costs for treatments in the BCLC advanced stage were collected from the Public Contract 2021/6 for supply of oncology medicines and immunomodulators to NHS institutions and services [10], while the majority of other health resources unit costs were obtained from the Government ordinance No. 207/2017 [9].

Model Validation

Throughout the study development process, the methodology (including the conceptual structure of the epidemiological model and sources of information for transition rates between health states) and results were presented and discussed with a group of national clinical experts. Following expert comments, some adjustments were incorporated into the conceptual structure of the epidemiological model and sources of information for

Table 1. Annual transition rates from departure to arrival health state

Departure health state	Arrival health state	Annual rate
Liver transplant	Remission post liver transplant	Nonapplicable (fixed at 90 days)
Liver transplant	Death	0.419
Remission post liver transplant	Initial	0.007
Remission post liver transplant	Intermediate	0.046
Remission post liver transplant	Death	0.182
Liver resection	Remission post liver resection	Nonapplicable (fixed at 90 days)
Liver resection	Death	0.136
Remission post liver resection	Initial	0.123
Remission post liver resection	Intermediate	0.178
Remission post liver resection	Death	0.132
Tumor ablation	Remission post tumor ablation	Nonapplicable (fixed at 90 days)
Tumor ablation	Death	0.136
Remission post tumor ablation	Initial	0.071
Remission post tumor ablation	Intermediate	0.148
Remission post tumor ablation	Death	0.074
Intermediate	Initial	1.996
Intermediate	Advanced	0.561
Intermediate	Death	0.429
Systemic treatment 1L	No systemic treatment after 1L	1.346
Systemic treatment 1L	Systemic treatment 2L	0.202
Systemic treatment 1L	Death	0.021
No systemic treatment after 1L	Terminal	1.914
No systemic treatment after 1L	Death	0.026
Systemic treatment 2L	No systemic treatment after 2L	2.273
Systemic treatment 2L	Death	0.037
No systemic treatment after 2L	Terminal	1.379
No systemic treatment after 2L	Death	0.023
Terminal	Death	6.931

transition rates. The results of the study were also assessed in light of the study objective and underlying limitations.

Economic models rely on conceptual and process of simulation assumptions and depend on the evidence used to parametrize the model. All of these are subject to uncertainty which is amplified further when extrapolating events distant in the future. However, procedures from our model validation have shown that results obtained are solely affected by changes in the variables being modeled (internal validity, Table R of online suppl. material) and that in terms of HCC incidence, one of the main drivers of future disease burden and cost, the model's outcomes were predominantly consistent with the real-world data (external validity, online suppl. material Figure T).

Outcomes

The outcomes of this study are the following:

- prevalence
- mortality rate and total number of deaths
- years of life lost
- number of treatments
- costs (outpatient and inpatient care, lab tests, examination, and treatments)

Table 2. Distribution of treatments in each state of the model

Treatment	Initial	Intermediate	Advanced – 1st line	Advanced – 2nd line
Liver transplant	29.3%	–	–	–
Liver resection	26.8%	–	–	–
Tumor ablation	43.9%	–	–	–
TACE	–	93.9%	–	–
SIRT	–	6.1%	–	–
Sorafenib	–	–	67.0%	2.5%
Lenvatinib	–	–	20.8%	0.5%
Atezolizumab + bevacizumab	–	–	10.5%	–
Nivolumab	–	–	1.7%	19.7%
Regorafenib	–	–	–	64.7%
Cabozantinib	–	–	–	6.0%
Ramucirumab	–	–	–	1.5%
Pembrolizumab	–	–	–	3.0%
Nivolumab + ipilimumab	–	–	–	2.2%

The years of life lost due to HCC are calculated according to the definition of the World Health Organization, where each death is associated with a number of years of life lost due to premature mortality, based on the life expectancy in the general population at the age of death [14] – life expectancy estimates were obtained from the "Complete Mortality Table for Portugal 2017–2019" published by the Portuguese National Institute of Statistics [15]). Disease burden and cost of illness of HCC in Portugal were estimated over a 5-year time horizon. No discount rate was applied, and therefore, estimated costs or outcomes reflect their present value.

This study was conducted according to the Consolidated Health Economic Evaluation Reporting Standards – CHEERS [16]. The checklist on the reporting of methods and results is shown in the online supplementary material Table S.

Results

Demographic and Clinical Characteristics

The distribution of patients between the different model health states were taken from Park et al. [4], a study including 18,031 HCC patients from 14 countries between 2005 and 2012. The values used were the ones reported for the European cohort of patients, in order to be as close to the Portuguese reality as possible.

The study by Park et al. [4] reported that 29.5% of patients are diagnosed with HCC on the Initial stage (BCLC 0 and A), 11.2% for the Intermediate stage, 51.2% for the Advanced, and 8.1% are diagnosed as Terminal patients. This distribution is aligned with the experts' perception that around 50% of patients are diagnosed in the advanced or terminal stages.

Disease Burden

Over a 5-year time horizon, the projections of HCC annual prevalence point to an increase in the number of patients from 4,151 in 2023 up to 4,851 in 2027, as it is shown in the last line of. Alternatively, considering the prevalence of patients alive at the end of each year, we denote the same increasing trend but with lower absolute values (Table 3). For example, at the end of 2023, the projections point to 1,433 patients with active disease (i.e., not in remission), rising to 1,556 at the end of 2027.

Fully adhering to the BCLC system, the predicted annual mortality rate could slightly decrease from 29.8% in 2023 to 28.7% in 2027, however still leading to a total of 120,314 years of life lost due to premature mortality, by increasing from 22,760 in 2023 up to 25,191 in 2027. This increment in years of life lost results mainly because of the increase in prevalent patients shown in Table 3.

Cost of Illness

Overall, the costs attributed to HCC are predicted to rise from around EUR 70 million in 2023 up to around EUR 77 million in 2027, adding up to around EUR 370

Table 3. HCC prevalence evolution (2023–2027) at the end of the year

Health state	2023	2024	2025	2026	2027
Initial (under treatment)	162	167	171	175	179
Intermediate	167	178	186	194	200
Advanced	978	996	1,013	1,028	1,042
Terminal	126	128	131	132	134
Subtotal	**1,433**	**1,469**	**1,501**	**1,530**	**1,556**
Initial (in remission)	1,480	1,613	1,726	1,821	1,902
Total	**2,914**	**3,083**	**3,227**	**3,350**	**3,457**
Annual prevalence	4,151	4,367	4,552	4,711	4,851

million in the 5-year period (shown in the last line of Table 4). These costs are mainly due to patients under systemic treatment (44.3%) and liver transplantation (29.0%).

In the first case, the costs (related to treatments, outpatient and inpatient care, lab tests, and examinations) add up to between EUR 34.0 million in 2023 and EUR 36.2 million in 2027, where 82.4% of these are treatment related costs. In the case of liver transplants, the costs rise from EUR 18.3 million to EUR 20.2 million throughout the 5 years in study, 80.5% of these being due to inpatient care and 17.4% due to the surgeries costs (191 transplants in 2023 up to 210 in 2027).

Average cost per patient throughout the disease, reported in Table 4, is the ratio of total costs by the number of prevalent patients during each year. With the exception of the costs related to the remission health states, average per patient costs are expected to decrease each year after 2023. This is driven by the accumulation of patients in remission health states, causing the proportion of patients on each non-remission state to decrease. The low cost of these remission health states also imply a reduction on the total costs per prevalent patient. Additional results of disease burden and cost of illness of HCC in Portugal (prevalence, mortality, number of treatments, costs stratified by type, and total costs) can be found in the (online suppl. material Tables I–Q).

Discussion

In this study, we estimated a potentially high burden and cost of illness in Portugal associated with HCC in a hypothetical scenario where all treatments are readily available and all patients are effectively treated with complete adherence to the treatment algorithm associated to the BCLC staging system. Our results show a point prevalence over 1,400 individual with HCC in Portugal, with an increasing trend over time. We estimated more than 1,200 deaths per year, also increasing over time, representing more than 120,000 years of life lost in the Portuguese population in a time horizon of 5 years due to HCC. This burden is also associated with a potentially high economic impact on the Portuguese NHS, equally increasing over time, mostly driven by the high costs associated with hospitalization for liver transplantation and the costs of HCC first-line systemic treatment. We estimated that the total expenditure for the NHS associated with HCC could, with full adherence to the BCLC treatment algorithm, amount to almost EUR 70 million in 2023.

This burden may not be fully visible to society, due to the underdiagnosis, as identified by Machado et al. [17]. Our study identified a heavy burden for this disease, which corroborates the need for timely diagnosis and contribute to change the current statistics on HCC [17].

Our study considers that 67% of patients take sorafenib as first-line systemic treatment with average duration of 5.3 months, as observed in Llovet et al. [18]. The study by Presa Ramos et al. [19] with a follow-up of 10 years concluded that in Portugal, the average duration of sorafenib treatment is 5 months. Hence, Portuguese clinical practice reported in the literature agrees with our parametrization, supporting the external validity of the model.

Our model assumes that patients in the "TACE/SIRT" substate can regress to the "Initial" health state or progress to the "Systemic Treatment 1L" substate of the "Advanced" health state. Ferreira-Silva et al. [20] assessed possible predictors of overall and 6-month survival free of

Table 4. Average total costs per prevalent patient (treatments, outpatient and inpatient care, lab tests, and examinations)

Health state	2023	2024	2025	2026	2027
Per prevalent patient					
Liver transplant	EUR 4,410	EUR 4,321	EUR 4,254	EUR 4,201	EUR 4,159
Remission after liver transplant	EUR 403	EUR 428	EUR 447	EUR 462	EUR 473
Liver resection	EUR 1,396	EUR 1,374	EUR 1,357	EUR 1,345	EUR 1,335
Remission after liver resection	EUR 243	EUR 250	EUR 254	EUR 257	EUR 259
Tumor ablation	EUR 1,130	EUR 1,111	EUR 1,098	EUR 1,088	EUR 1,080
Remission after tumor ablation	EUR 385	EUR 405	EUR 420	EUR 431	EUR 440
Intermediate	EUR 273	EUR 276	EUR 279	EUR 281	EUR 282
Systemic treatment 1L	EUR 7,074	EUR 6,850	EUR 6,682	EUR 6,555	EUR 6,457
Systemic treatment 2L	EUR 505	EUR 490	EUR 478	EUR 469	EUR 462
No systemic treatment after 1L	EUR 496	EUR 481	EUR 469	EUR 461	EUR 454
No systemic treatment after 2L	EUR 105	EUR 102	EUR 100	EUR 99	EUR 97
Terminal	EUR 361	EUR 350	EUR 342	EUR 335	EUR 330
Total	EUR 16,780	EUR 16,438	EUR 16,179	EUR 15,983	EUR 15,830
Population (all patients)					
Total	EUR 69,660,611	EUR 71,791,397	EUR 73,648,957	EUR 75,301,580	EUR 76,785,137

liver decompensation before TACE refractoriness in a cohort of Portuguese patients with intermediate-stage HCC submitted to TACE. These authors' findings suggest that albumin <35 mg/dL and the absence of objective response rate to initial TACE are predictors of early liver decompensation before TACE. This evidence may be useful for fine tuning progression to HCC advanced health state in future versions of our model.

To our knowledge, no other study aimed at estimating the (either real or hypothetical) burden and cost of illness of HCC at a national level in Portugal. However, we compared the results of our study with those of Athanasakis et al. [21], reporting a total average cost of HCC per patient of EUR 12,119.10, which is lower than our estimate. This difference can be related to among countries with different clinical practices or healthcare system settings.

Notwithstanding, the large and growing economic impact of HCC estimated for Portugal is in line with the reported trend for hospitalization costs by HCC in the studies by Marinho et al. [5] and Vítor et al. [22]. On the other hand, some of the estimates obtained in this study should constitute upper limits for to the current Portuguese reality (where the treatment algorithm based on the BCLC staging system is not always followed). For example, in this study, we estimated that more than 190 liver transplants would be performed annually. This could represent more than 70% of the total number of liver transplants at the national level if we take as a reference the total number of liver transplants performed in Portugal over the last years before the COVID-19 pandemic, which varied between 188 (for 2012) and 272 (for 2016) [23]. Such a high proportion of liver transplants is admissible considering that we modeled an ideal reality where all patients are effectively treated and with no access limitations. In the particular case of transplantation, organs are not always available in a short run and patients on the waiting list may progress or even die, ending up not receiving a transplant (for example, 13 deaths were observed on the waiting list for liver transplants in 2021, in Portugal [23]). Such aspects were disregarded in the modeling applied in this study.

While the findings of this study are based on hypothetical scenarios, they hold significant value for policymakers. The insights derived from the study can guide decisions related to the allocation of resources. By understanding the potential disease burden and cost implications, policymakers can strategize more effectively, ensuring that resources are directed where they are most needed. This could potentially lead to more efficient management of HCC and, ultimately, improved health outcomes for patients. The study thus serves as a valuable tool for informing policy and shaping future strategies in healthcare.

This study has some limitations which should be taken into account. Perhaps the most evident and relevant is the fact that we had to rely on the opinion of experts to characterize many of the parameters related to the Portuguese context in the treatment of HCC. This primarily stems from the fact that published information at a national level regarding HCC is quite scarce and data requests to NHS public institutions did not succeed.

Given that an expert panel was one of the main sources of data of this study, the results can be regarded as fairly uncertain.

Challenges in getting full adherence to the BCLC treatment algorithm in real life and the lack of external validation of the model are also limitations that apply to our study, particularly in the elderly population because elderly patients often present comorbidities and in clinical practice, comorbidities contribute to poor adherence to BCLC guidelines, despite some conflicting evidence [24]. Another limitation is that given the lack of available information on a national level, it was considered unfeasible by the authors to quantify the real burden and cost of HCC in Portugal, against which we could compare the results presented in this study to ascertain to what extent the hypothetical scenario model deviates from current clinical practice. Future studies may try to address these limitations, either by diminishing the extent to which expert opinion is used or by aiming at estimating the actual burden and cost of HCC in Portugal, based on registries or datasets from the Ministry of Health.

Despite the limitations, in this study, we showed a high and growing burden associated with HCC, with more than 1,200 deaths per year at a national level. We also showed that by fully adhering to the algorithm proposed by the EASL guidelines [1] and assuming no restrictions in the patients' access to treatments, the costs to the NHS resulting from this disease could amount to more of EUR 70 million per year, following the expected increasing trend in the burden of HCC in Portugal.

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Statement of Ethics

As there were no inclusion or identification of patients, no experimental drugs administration, no additional costs or procedures for the patients, and no consultation of medical records, this is not applicable.

Conflict of Interest Statement

Nuno Picado and Jorge Félix were Exigo Consultores employees at the time of manuscript development. The study sponsor contracted Exigo Consultores to plan and develop this research project. Exigo Consultores provided support in the form of salaries for authors. Guilherme Macedo had no conflicts of interest to declare that are relevant to the content of this article. José Presa received speaker and consultant honoraria from Roche, Eisai, and AstraZeneca. Mário Jorge Silva received speaker and consultant honoraria from Roche; speaker honoraria from Eisai. Filipe Veloso Gomes has received research grants from Terumo; educational grants from Terumo, Medtronic, Guerbet; speaker or advisory honoraria from Bayer, Guerbet, Medtronic, and Roche. Joana Alarcão and Isabel Monteiro are employees of Roche Farmacêutica e Química, Lda., Portugal.

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Author Contributions

Nuno Picado: study design, data collection, analytical calculations, interpretation of results, drafting, and critical revision of the manuscript; Jorge Félix: interpretation of results, drafting, and critical revision of the manuscript; Guilherme Macedo, José Presa, Mário Jorge Silva, and Filipe Veloso Gomes: content expertise, interpretation of results, and critical revision of the manuscript; Joana Alarcão and Isabel Monteiro: study conception, study design, interpretation of results, and critical revision of the manuscript.

Data Availability Statement

All data and material relevant to the analysis are presented in the outlined publication or supplementary material.

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