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# Hepatocellular carcinoma: what are the differential costs compared to the general population?

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## ABSTRACT

**Introduction:** Hepatocellular carcinoma (HCC), which accounts for about 90% of all primary liver cancer cases, is the fifth most common malignancy and the second leading cause of cancer-related mortality worldwide. This study aims to analyse the differential costs of HCC-related hospital admissions compared to the general population in Spain.

**Methods:** A retrospective multicenter study analyzed inpatient admissions from a Spanish national discharge database, covering 90% of hospitals between 2010 and 2022. HCC-related admissions were identified using ICD-9 and ICD-10 codes, while control admissions were selected from the general population in the same database without an HCC diagnosis. The direct hospitalization cost was included, covering medical examinations, procedures, medications, surgeries, personnel and equipment. Statistical methods, including nearest-neighbor matching, propensity score matching, and a generalized linear model, were used to estimate differential costs and to ensure comparability based on age, gender, and Charlson Comorbidity Index (CCI).

**Results:** A total of 199,670 HCC-related hospital admissions and 200,000 control admissions were analyzed. Most HCC-related admissions involved male patients (78%) aged 66–85 years, with an average CCI of 5.18. HCC-related admissions incurred significantly higher costs, with an estimated differential cost of €1,303.68 using GLM, €1,804.25 *via* propensity score matching, and €1,767.77 using nearest-neighbor matching. Total costs per HCC admission ranged between €1,000 and €31,000.

**Conclusions:** HCC-related hospital admissions impose a significantly higher economic burden due to the complexity of care. Given the high mortality and resource utilization, advancements in early detection, treatment, and cost-effective interventions are needed to improve patient outcomes and reduce healthcare costs.

## 1. Introduction

Liver cancer is a major health problem, with more than 850,000 new cases diagnosed annually worldwide[1]. Hepatocellular carcinoma (HCC), which accounts for about 90% of all primary liver cancer cases[1], is the fifth most common malignancy and the second leading cause of cancer-related mortality worldwide[2]. Unlike many other malignancies, the risk factors for HCC are well established[1]. The risk factors for HCC include chronic hepatitis B (HBV) and C (HCV) infections, alcohol addiction, metabolic liver diseases (notably nonalcoholic fatty liver disease), and exposure to dietary toxins like aflatoxins and aristolochic acid[3]. Regarding age, in most populations, HCC incidence rates increase directly with age until around 75 years[4]. However, the median age at diagnosis is typically somewhat younger[4]. Regarding gender, it is roughly twice as prevalent in men compared to women and is more common in individuals over the age of 40[5].

Despite prevention efforts, the incidence and cancer-specific mortality of HCC continue to rise in many countries[6], largely due to the increasing prevalence of major risk factors such as chronic hepatitis B and C infections, alcohol related liver disease, and metabolic-associated fatty liver disease[4,7]. Additionally, due to the complex clinical course of HCC, most patients are still diagnosed at an advanced stage in many parts of the world[6]. The disease is often diagnosed at an advanced stage due to the absence of specific early symptoms, the lack of early diagnostic markers, and the fact that only 10–20% of HCC cases are eligible for radical resection at diagnosis[8]. Consequently, most HCC patients face a poor prognosis[8], resulting in a significant healthcare burden, requiring intensive hospital-based management, including advanced imaging, surgical interventions, systemic therapies, and palliative care. It urgently requires advancements in pathogenetic understanding, therapeutic approaches, diagnostics, prevention, and personalized medicine[9]. Even so, prevention is possible[1]. Vaccination against HBV has been shown to reduce the incidence of HCC in populations with a high prevalence of HBV[1].

While the clinical burden of HCC is well-documented, its economic impact on healthcare systems remains less explored, particularly regarding hospital admission costs[9,10]. Hospitalization is a major cost driver in cancer care, as patients with HCC often require prolonged inpatient stays, management of disease-related complications, and high-cost interventions[11]. Understanding the financial impact of HCC-related hospitalizations is essential for policymakers and healthcare providers to optimize resource allocation, assess the cost-effectiveness of treatments, and implement strategies for early detection and prevention[12,13].

The main contribution of this study is to provide estimate of the differential costs for HCC patients in Spain by providing average annual costs of this patients compared to the costs of the general population admitted in Spain. This study aims to analyze the differential costs of HCC-related hospital admissions compared to the general population in Spain, providing insight into the financial burden associated with HCC hospitalization and highlighting potential areas for cost reduction and healthcare system improvements.

## 2. Methods

### 2.1. Study design

A retrospective multicenter study was conducted to analyze the differential costs of hospital admissions for HCC compared to the general Spanish hospital-admitted population. The analysis was conducted from the payer perspective, specifically considering the costs incurred by public healthcare payers in Spain. The study used a national hospital discharge database, which collects data codified at the hospital level using the International Statistical Classification of Diseases and Related Health Problems, incorporating both the 9th and 10th versions (ICD-9 and ICD-10). The data inclusion period spanned from 1 January 2010 to 31 December 2022, with data from hospitals across all Spanish regions.

The national discharge database, Registro de Actividad de Atención Especializada - Conjunto Mínimo Básico de Datos (RAE-CMBD), managed under the supervision of the Spanish Ministry of Health[14], covers 90% of hospitals in Spain from all regions, including public and private facilities. Specifically, it includes data from both general hospitals and specialized centers; however, it is important to note that data from certain specialized cancer centers may be underrepresented, depending on their participation in the database. Additionally, although the database predominantly captures inpatient hospitalizations, it does not comprehensively include pharmacy claims, or laboratory results outside of the hospitalization setting. Therefore, the analysis is focused on inpatient care and does not capture the full spectrum of healthcare utilization, such as outpatient treatments or prescriptions.

The national database undergoes internal validation and periodic audits to ensure data reliability and accuracy. During these audits, errors and unreliable data are eliminated, ensuring that the information used in the analysis is of high quality. Each participating center is responsible for codification, evaluation, and confidentiality of the records submitted to the database.

The index date for this study was defined as the date of the first recorded HCC diagnosis (either primary or secondary diagnosis) during the observation period. This allows for the analysis of healthcare utilization and associated costs before and after the HCC diagnosis. For patients with multiple admissions, the first recorded admission with a confirmatory ICD code for HCC was used to determine the index date.

The observation window for each patient covered a minimum of one year before the index date and continued for at least one year after the diagnosis of HCC. This period allowed for the assessment of healthcare resource utilization and costs associated with both the diagnosis and treatment of HCC, as well as the comparison of pre- and post-diagnosis costs.

Hospital readmissions were defined as any subsequent hospital admission for the same patient within 30 days of discharge. Readmission for the same patient were considered as unique cases unless specifically stated otherwise. Each hospital admission was treated independently for the purpose of cost calculations, which allowed for a comprehensive assessment of healthcare resource utilization per admission. However, readmissions were tracked and considered in the analysis to account for any recurring healthcare needs associated with HCC. When analysing costs, readmissions were factored in separately, ensuring that the cumulative healthcare burden of HCC was accurately represented without inflating the utilization estimates. This approach minimized the potential for bias while allowing for the assessment of the broader impact of HCC-related admissions, including any subsequent hospitalizations.

### 2.2. Data extraction

Inclusion criteria for the HCC cohort were patients with at least one inpatient admission with a primary or secondary diagnosis of HCC, identified using ICD-9 codes 155, 155.0, 155.1, 155.2 and ICD-10 codes C22.0, C22.2, C22.3, C22.4, C22.7, C22.8, and C22.9. To ensure the validity of the HCC diagnosis, only patients with at least one confirmatory ICD code for HCC were included, reducing the risk of misclassification bias.

Exclusion criteria included patients with incomplete or missing data, those diagnosed with other primary malignancies that might have confounded the results, and those whose hospital admission records were not linked to the national discharge database. Additionally, patients with prior or concurrent conditions that could significantly affect healthcare resource utilization (e.g. end-stage liver disease, advanced metastatic cancer, etc.) were excluded from the study to ensure that the comparison group was comparable.

The database includes anonymized information; therefore, no direct access to patient identifiers was available. Since this research did not involve human participants and there was no access to identifying information, patient consent and ethics committee approval were not required according to Spanish legislation. No healthcare centers or medical histories were identified, and to maintain anonymity in

compliance with the Good Clinical Practice principles and the Declaration of Helsinki, all records were recoded.

## 2.3. Control group selection and matching

To compare the differential costs of HCC-related hospital admissions, a control group was selected from the same national discharge database. The control group consisted of hospital admissions unrelated to HCC, ensuring that all comparisons were conducted within the same healthcare system and time frame.

To minimize bias and enhance comparability between HCC-related admissions and general hospitals admissions, statistical matching techniques were applied. The control admissions were matched to HCC-related admissions based on age, gender and Charlson Comorbidity Index (CCI), as these variables significantly influence healthcare costs and resource utilization.

Two matching methodologies were employed: nearest-neighbor matching and propensity score matching (PSM). Nearest-neighbor matching was performed using multiple distance metrics, including Mahalanobis, inverse variance, and Euclidean distances. This method allowed for the identification of control admissions that closely resembled HCC-related admissions in terms of demographic and clinical characteristics. Propensity score matching was conducted using a logistic regression model, where HCC diagnosis was the dependent variable, and age, gender, and CCI were included as covariates. Control and HCC admissions were then paired based on their propensity scores to achieve balance between groups.

The success of the matching process was assessed using balance diagnostics, ensuring that no statistically significant differences remained between the groups after matching. This approach enhanced the robustness of the cost comparisons, allowing for a more accurate estimation of the differential costs associated with HCC-related hospital admissions.

## 2.4. Study variables

The study analyzed multiple variables related to hospital admissions to comprehensively assess the economic burden of HCC. Demographic variables included patient age, gender, and national region. These factors were critical in matching the control group to the HCC cohort and were included in statistical models as potential confounders. Clinical characteristics encompassed primary and secondary diagnoses, intensive care unit (ICU) admission, medical procedures, readmission status and CCI. These variables were essential for understanding the clinical complexity of the HCC cohort and their potential impact on healthcare resource utilization and costs. Hospitalization details included type of admission, length of hospital stay, and discharge status, including death. These variables provided a detailed picture of the healthcare services utilized during hospitalization.

The primary outcome variable was direct medical costs per hospital admission, which were extracted from the database. These costs were based on standardized cost structures established by the Spanish Ministry of Health and covered a broad range of healthcare services. The cost components included medical procedures, diagnostic tests, medications, surgical interventions, hospitalization costs, medical personnel, equipment, and other healthcare resources.

## 2.5. Data analysis

The cost analyses were conducted from the public healthcare payer perspective. All costs analyses were conducted using standardized cost data applied to each hospital admission. Direct medical costs were calculated based on hospital records and according to the admission cost reported on the database.

The differential cost is defined as the additional annual healthcare cost per admission for HCC-related cases compared to general hospital admissions. To estimate these costs, several statistical methods were applied. A Generalized Linear Model (GLM) was used to adjust for patient characteristics and account for variations in hospital costs. Nearest-neighbor matching was employed to compare costs between matched HCC-related and control admissions using multiple distance metrics. Propensity score matching was used to further refine comparisons and control for potential confounders, ensuring that cost differences were not driven by baseline disparities between groups.

The nearest-neighbor matching approach has been widely used in various fields, including ecology and biology. In epidemiology, it has been employed in cross-sectional and quasi-experimental studies, though it is less commonly applied in case-control studies[9]. This method has been hypothesized to improve case-control matching and covariate adjustment compared with other techniques[15]. Nearest-neighbor matching calculates a selected distance metric between cases and controls using all possible exposures except the one under active consideration[15]. Each case is then matched with its nearest neighbors to achieve better comparability across all measured covariates[15]. The different distance metrics used in this study included Mahalanobis, inverse variance, and Euclidean distances.

Matching techniques are essential for equating treatment groups with respect to baseline characteristics[16]. PSM is particularly effective in achieving balanced treatment groups, thereby reducing bias when assessing the treatment effect on outcomes[16]. The PSM process involved several steps. First, feasibility was assessed to evaluate the suitability of PSM with the available data, ensuring that data on potential confounders were accessible[16]. Propensity scores were then calculated using a logistic regression model, where HCC diagnosis was the outcome variable and age, gender, and CCI were included as predictors. Next, hospital admissions in both groups were matched based on similar propensity scores to ensure balance across these variables. The success of the matching process was evaluated using balance diagnostics, either graphically or analytically, before proceeding with statistical comparisons.

The GLM was used as an additional analytical approach due to its flexibility in accommodating a wide range of outcome distributions[17]. GLMs allow for a function of the outcome variable to vary linearly with respect to covariates,

**Table 1.** Patient baseline characteristics.

| | Hepatocarcinoma patients (N = 199,670) | Control group (N = 200,000) | p-value |
|---|---|---|---|
| Admissions, N | 199,670 | 200,000 | |
| Unique patients, N | 149,210 | 150,100 | |
| Age (years), N (%) | | | |
| 0–17 years, N (%) | 2,080 (1.04) | 18,940 (9.47) | <0.0001 |
| 18–30 years, N (%) | 626 (0.31) | 13,384 (6.70) | <0.0001 |
| 31–50 years, N (%) | 11,523 (5.77) | 36,868 (18.43) | <0.0001 |
| 51–65 years, N (%) | 66,233 (33.16) | 36,488 (18.24) | <0.0001 |
| 66–85 years, N (%) | 109,391 (54.79) | 72,448 (36.22) | <0.0001 |
| >85 years, N (%) | 9,827 (4.92) | 21,872 (10.94) | <0.0001 |
| Average age | 67.55 | 57.56 | <0.0001 |
| Gender, N (%) | | | |
| Males | 155,039 (77.65) | 98,772 (49.39) | <0.0001 |
| Females | 44,625 (22.35) | 101,200 (50.60) | <0.0001 |
| N/A | 6 (0.003) | 28 (0.01) | <0.0001 |
| Charlson Comorbidity Index (CCI), N (%) | | | |
| Mean CCI | 5.18 | 1.45 | <0.0001 |
| Median CCI | 5 | 1 | <0.0001 |
| CCI 0, N (%) | 0 (0) | 94,084(47.04) | <0.0001 |
| CCI 1, N (%) | 0 (0) | 32,776(16.39) | <0.0001 |
| CCI 2, N (%) | 24,360 (12.20) | 28,740 (14.37) | <0.0001 |
| CCI > 3, N (%) | 175,310 (87.80) | 44,400 (22.2) | <0.0001 |
| Updated CCI, N (%) | | | |
| Mean updated CCI | 5.39 | 1.21 | <0.0001 |
| Median updated CCI | 6 | 0 | <0.0001 |
| CCI 0 | 0 (0) | 110,776 (55.39) | <0.0001 |
| CCI 1 | 0 (0) | 22,188 (11.09) | <0.0001 |
| CCI 2 | 32,436 (16.24) | 31,248 (15.63) | <0.0001 |
| CCI > 3 | 167,234 (83.76) | 35,788 (17.89) | <0.0001 |
| Type of admission, N (%) | | | |
| Emergency | 145,081 (72.66) | 120,575 (60.29) | <0.0001 |
| Elective | 54,589 (27.34) | 79,425 (39.71) | <0.0001 |
| Discharge type, N (%) | | | |
| Home | 153,317 (76.79) | 181,608 (90.80) | <0.0001 |
| To other hospital | 16,752 (8.39) | 11,680 (5.84) | <0.0001 |
| Death | 29,601 (14.82) | 6,712 (3.36) | <0.0001 |
| Funding scheme, N (%) | | | |
| Public | 195,038 (97.68) | 193,920 (96.96) | <0.0001 |
| Private | 4,632 (2.32) | 6,080 (3,04) | <0.0001 |

making them well-suited for cost analysis[17]. The GLM equation follows the structure:

$$f(E(Y))) = \hat{\beta}_0 + \hat{\beta}_1 X_1 + \ldots + \hat{\beta}_n X_n$$

where $E(Y)$ represents the expected cost, and $X_1, X_2, \ldots X_n$ correspond to the independent covariates used in the model.

All statistical analyses were conducted using Microsoft Excel Professional Plus 2016 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP, College Station, TX, USA). These software programs enabled efficient data processing, statistical modeling, and comparative cost analyses.

## 3. Results

The study analyzed a total of 199,670 HCC-related admissions and 200,000 control admissions from the general Spanish hospital-admitted population. The baseline characteristics of the two groups studied are presented in Table 1. HCC-related admissions were predominantly male (78%) and primarily occurred in patients aged 66–85 years, with an average CCI of 5.18, indicating high burden of comorbidities.

### 3.1. Comorbidities associated with HCC-related admissions

As shown in Table 2, a large proportion of HCC-related hospital admissions were associated with chronic liver disease and metabolic conditions. Liver cell carcinoma was the most commonly recorded secondary diagnosis, present in 92% of cases, confirming the primary disease in nearly all admissions. Cirrhosis was also prevalent, with 35.2% of patients diagnosed with unspecified cirrhosis of the liver and 22.3% diagnosed with alcoholic cirrhosis without ascites. Other commonly observed conditions included essential hypertension (33.8%), type 2 diabetes mellitus (26.0%), and chronic hepatitis C virus (HCV) infection (24.3%). Additional complications of liver disease were noted, such as secondary esophageal varices without hemorrhage (15.4%), a condition linked to portal hypertension and advanced cirrhosis. A significant proportion of HCC patients (14.5%) had a personal history of smoking, which may contribute to the overall disease burden.

### 3.2. Medical procedures and healthcare utilization

HCC-related admissions required a higher frequency of specialized medical procedures and interventions compared to control admissions. As presented in Table 3, abdominal ultrasound was performed in 18% of HCC-related admissions, serving as a common imaging modality for liver evaluation. Additionally, 14% of patients underwent abdominal computed tomography

**Table 2.** Patient comorbidity profile.

| | Hepatocarcinoma patients ($N = 199,670$) | Control group ($N = 200,000$) | $p$-value |
|---|---|---|---|
| Liver cell carcinoma | 183,106 (91.70%) | – | < 0.0001 |
| Unspecified cirrhosis of the liver | 70,301 (35.21%) | – | < 0.0001 |
| Essential hypertension | 67,435 (33.77%) | 61,692 (30.85%) | < 0.0001 |
| Diabetes mellitus type 2 | 51,935 (26.01%) | 27,440 (13.72%) | < 0.0001 |
| Chronic viral hepatitis type C | 48,492 (24.29%) | – | |
| Alcoholic cirrhosis without ascites | 44,567 (22.32%) | – | < 0.0001 |
| Secondary esophageal varices without hemorrhage | 30,819 (15.43%) | – | < 0.0001 |
| Personal history of smoking | 28,980 (14.51%) | 20,284 (10.14%) | < 0.0001 |
| Current smoking (cigarettes, without complications) | 26,982 (13.51%) | – | < 0.0001 |
| Hyperlipidemia | – | 40,096 (20.05%) | < 0.0001 |
| Unspecified atrial fibrillation | – | 21,780 (10.89%) | < 0.0001 |

**Table 3.** Medical procedures.

| | Hepatocarcinoma patients ($N = 199,670$) | Control group ($N = 200,000$) | $p$-value |
|---|---|---|---|
| Diagnostic ultrasounds of abdomen and retroperitoneum, $N$ (%) | 36,164 (18.11%) | – | < 0.0001 |
| Computerized axial tomography of abdomen, $N$ (%) | 28,641 (14.34%) | – | < 0.0001 |
| Injection or infusion of chemotherapy substance against cancer, $N$ (%) | 25,318 (12.68%) | – | < 0.0001 |
| Antibiotic injection, $N$ (%) | 20,277 (10.16%) | 23,336 (11.67%) | < 0.0001 |
| Simple chest x-ray, $N$ (%) | – | 16,376 (8.19%) | < 0.0001 |
| Measurement of electrical activity, cardiac, external approach, $N$ (%) | – | 12,524 (6.26%) | < 0.0001 |
| CT scan of the head, $N$ (%) | – | 11,564 (5.78) | < 0.0001 |
| Manually assisted birth, $N$ (%) | – | 11,384 (5.69) | < 0.0001 |



**Figure 1.** Cost distribution: Control group vs HCC.

(CT) scans, which play a crucial role in the detection, staging, and treatment planning for HCC.

Beyond imaging, cancer treatment-related procedures were also frequently recorded. Injection or infusion of chemotherapy substances was administered in 13% of admissions, indicating a substantial proportion of patients receiving systematic therapy during hospitalization. The use of antibiotic injections was noted in 10% of cases, likely due to increased susceptibility to infections in patients with cirrhosis, liver dysfunction, and immunosuppression.

### 3.3. Differential costs

Using a GLM, the estimated cost difference per admission was 1,303.68 euros after adjusting for patient characteristics. PSM produced a higher differential cost estimate of 1,804.25 euros, while nearest-neighbor matching yielded an average difference of 1,767.77 euros per admission. These findings

indicate that HCC-related hospitalizations impose a substantially higher economic burden on the healthcare system compared to non-HCC admissions.

The distribution of total hospital costs per admission is illustrated in Figure 1. In the control group, the majority of admissions had costs ranging between 1,000 and 17,000 euros, whereas for HCC-related admissions, costs were higher, ranging between 1,000 and 31,000 euros per admission. The peak cost density was observed at around 5,000 euros for control admissions and 7,000 euros for HCC-related admissions, aligning with the estimated differential costs reported in Table 4.

### 3.5. Mortality

Among HCC-related admissions, 15% of patients were discharged due to death, a significantly higher rate compared to 3.36% in the control group ($p < 0.0001$). The markedly higher

**Table 4.** Differential annual costs.

| Method | Estimation |
|---|---|
| Nearest neighbor matching (distance: mahalanobis) | 1818.184 (35.62)* |
| Nearest neighbor matching (distance: ivariance) | 1818.184 (36.54)* |
| Nearest neighbor matching (distance: Euclidean) | 1717.360 (29.21)* |
| Propensity score matching | 1804.251 (30.08)* |
| Generalized linear model | 1303.679 (27.39)* |

*P-value < 0.0001. Standard errors are in parenthesis.

mortality rate suggests that a large proportion of HCC hospitalizations occur at an advanced disease stage, requiring intensive medical care, prolonged hospital stays, and costly interventions. This aligns with the high resource utilization observed among HCC-related admissions, including the increased use of imaging, chemotherapy, and critical care services.

# 4. Discussion

This study is the first to assess the economic impact of HCC using longitudinal administrative data from Spain, providing important into the direct healthcare costs associated with the disease. Although there have been several studies worldwide assessing the healthcare costs of HCC using claims data[18–20], this study is the first to focus specifically on Spain. The findings offer valuable contributions to the literature by highlighting the cost burden of HCC on the Spanish healthcare system and shedding light on specific cost drivers related to hospital admissions and treatment.

HCC, as a leading cause of liver cancer, poses significant challenges for healthcare systems globally. While liver disease in general is on the rise due to factors like aging populations and the obesity epidemic, it is crucial to focus specifically on HCC due to its distinct clinical progression and poor prognosis[21]. Unlike many other liver diseases, HCC is often diagnosed at advanced stages due to the lack of specific early symptoms, resulting in a higher burden on healthcare systems[22]. The rising incidence of liver disease is a well-documented phenomenon[23], but it is the escalating prevalence of HCC, which remains the most aggressive form of liver cancer, that is of particular concern[24]. HCC is associated with high hospitalization costs[25], and this study aims to quantify the direct economic impact of this disease on the healthcare system.

In our findings, the average admission costs for HCC admission ranged from €3,000 to €7,000, aligning with previous research in other settings. For instance, a population-based study in Ontario, Canada, reported that the net costs of HCC care per 30 patient-days were $3,204 in the initial phase, $2,055 in the continuing care phase, and $7,776 in the terminal phase, with a mean 5-year net cost of care reaching $77,509[18]. These findings underscore the significant economic burden of HCC hospital admissions. Our study contributes further by employing a comprehensive longitudinal approach, offering detailed insights into the cost dynamics of HCC treatment over an extended period.

It is important to note that this study did not include liver transplantation costs, which are highly relevant in the treatment of advanced liver disease but were not within the scope of this analysis. Liver transplantation remains the only curative option for selected patients with HCC within

transplant criteria, yet its accessibility is constrained by the high costs and limited availability of donor organs[26]. Given that the average cost of a liver transplant in the United States can exceed $800,000, these procedures add a substantial economic burden to healthcare expenditures for patients with advanced liver disease[27]. The exclusion of liver transplantation in this study's cost analysis means that the results focus solely on inpatient costs related to diagnosis, treatment, and complications of HCC, rather than the full range of costs associated with end-stage liver disease.

The higher hospitalization costs observed in HCC patients compared to control admissions are driven by several key factors. HCC is a clinically complex disease requiring advanced imaging techniques, frequent monitoring, and a combination of surgical, locoregional, and systemic therapies. Procedures such as liver biopsies, contrast-enhanced imaging, transarterial chemoembolization, and radiofrequency ablation contribute significantly to inpatient costs[28]. Additionally, the need for intensive care admissions, management of cirrhosis-related complications, and supportive therapies further increases overall healthcare expenditures[29].

The economic burden of HCC is further compounded by high readmission rates, as patients frequently require hospitalization due to disease progression, treatment complications, or liver failure. Previous studies have highlighted that patients with advanced liver disease experience multiple hospitalizations, with costs rising significantly in the final stages of the disease[30,31]. Our findings suggest that the severity of comorbid conditions, particularly cirrhosis, portal hypertension, and hepatic decompensation, plays a major role in increasing healthcare utilization and costs[32].

The findings of this study emphasize the urgent need for cost-effective strategies to manage HCC within the Spanish healthcare system. Early detection programs through improved surveillance and screening of high-risk populations, particularly those with cirrhosis or chronic viral hepatitis, could lead to earlier-stage diagnosis and reduce hospital admissions for late-stage disease[33,34]. Cost-effectiveness studies have demonstrated that HCC screening using ultrasound and alpha-fetoprotein testing is associated with improved survival outcomes and reduced long-term healthcare costs[35,36].

Additionally, increasing access to curative-intent treatments, such as surgical resection and liver transplantation for eligible patients, may improve survival rates and potentially lower costs associated with late-stage complications[37,38]. Further research should focus on evaluating the long-term economic impact of different treatment strategies and identifying interventions that can optimize resource allocation while maintaining high-quality care[39–41].

Despite its strengths, this study has several limitations. First, the analysis was based on administrative hospital discharge data, which does not provide granular details on specific cost components, such as medications, imaging studies, or specific procedures performed during admission. Additionally, medication information is not detailed in the database; however, any medications administered during hospitalization are included in the total admission cost. The total admission costs reported in this study encompass all medical services provided during

hospitalization but do not differentiate between the cost drivers individually.

Second, the study does not capture outpatient costs, including expenses related to ambulatory treatments, chemotherapy, follow-up care, or surveillance programs. Given that HCC management often includes significant outpatient components, future research should integrate inpatient and outpatient data to provide a more comprehensive understanding of the total cost burden.

Finally, this study focused solely on direct medical costs from the perspective of public healthcare payers in Spain. Indirect costs, such as loss of productivity, caregiver burden, and societal economic impact, were not considered. Including these factors in future analyses could provide a broader understanding of the full economic consequences of HCC.

Future research should aim to address these limitations by incorporating detailed cost breakdowns, outpatient care expenses, and long-term follow-up data to better capture the total economic impact of HCC. Additionally, studies evaluating the cost-effectiveness of early detection strategies and innovative treatment approaches, such as immunotherapy, targeted therapies, and combination treatments, are needed to guide healthcare decision-making and resource allocation.

## 5. Conclusion

The findings emphasize the significant economic burden that HCC imposes on the healthcare system, particularly in terms of hospital admission costs. Patients diagnosed with HCC had higher admission costs compared to those without HCC, highlighting the substantial impact of this condition on hospital resources.

Given the focus on inpatient care, the results underscore the need for further research into the economic burden of HCC, specifically looking at trends in healthcare utilization and how these costs evolve over time. While the study does not present data on incidence or prevalence, it provides valuable information on the direct costs of HCC management, which can inform resource allocation and policy decisions aimed at improving disease management.

The poor prognosis for many HCC patients, often diagnosed at advanced stages, is reflected in the high healthcare costs associated with their hospital admissions. These findings further highlight the urgency of developing more effective diagnostic methods and treatment strategies to improve early detection, which could potentially reduce the economic burden by preventing the need for costly late-stage interventions.

In conclusion, the study's findings demonstrate the significant economic impact of HCC inpatient care, providing a foundation for future research aimed at improving patient outcomes and optimizing healthcare resources. Addressing the high costs of HCC management is crucial, and further investigations into both the clinical and economic aspects of the disease are needed to improve patient care and reduce the strain on healthcare systems.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

The database used is the Registro de Actividad de Atención Especializada - Conjunto Mínimo Básico de Datos (RAE-CMBD), available from https://www.sanidad.gob.es/estadEstudios/estadisticas/cmbdhome.htm.

### Ethics approval and consent to participate

This research did not involve human participants and there was no access to identifying information, so in this case Spanish legislation does not require patient consent and ethics committee approval. There was no identification of healthcare centers or medical history, and to maintain anonymity in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, recoding was performed on all records.

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## References

[1] Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6. doi:10.1038/s41572-020-00240-3.

[2] Wen N, Cai Y, Li F, et al. The clinical management of hepatocellular carcinoma worldwide: a concise review and comparison of current guidelines: 2022 update. Biosci Trends. 2022;16(1):20–30. doi:10.5582/bst.2022.01061.

[3] Yang JD, Hainaut P, Gores GJ, et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019;16(10):589–604. doi:10.1038/s41575-019-0186-y.

[4] McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. Hepatology. 2021;73(Suppl 1):4–13. doi:10.1002/hep.31288.

[5] Thompson Coon J, Rogers G, Hewson P, et al. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. Health Technol Assess. 2007;11(34):1–206. doi:10.3310/hta11340.

[6] Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived

with disability, and disability-adjusted life-years for 29 Cancer Groups, 1990 to 2017: a Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2019;5(12):1749–1768. doi:10.1001/jamaoncol.2019.2996.

[7] Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease – Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84. doi:10.1002/hep.28431.

[8] Ren Z, Ma X, Duan Z, et al. Diagnosis, therapy, and prognosis for hepatocellular carcinoma. Anal Cell Pathol. 2020;2020:8157406. doi:10.1155/2020/8157406.

[9] Foglia B, Turato C, Cannito S. Hepatocellular carcinoma: latest research in pathogenesis, detection and treatment. Int J Mol Sci. 2023;24(15):24. doi:10.3390/ijms241512224.

[10] Aly A, Malangone-Monaco E, Noxon V, et al. Treatment patterns and direct medical costs among patients with advanced hepatocellular carcinoma. Curr Med Res Opin. 2020;36(11):1813–1823. doi:10.1080/03007995.2020.1824899.

[11] Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: observational study. BMJ. 2018; 362:k2817. doi:10.1136/bmj.k2817.

[12] Kim DD, Hutton DW, Raouf AA, et al. Cost-effectiveness model for hepatitis B screening and vaccination among Asian and Pacific Islander adults in the United States. Hepatology. 2011;53(2):416–424. doi:10.1002/hep.24035.

[13] Kanwal F, Singal AG. Surveillance for hepatocellular carcinoma: current best practice and future direction. Gastroenterol. 2019; 157(1):54–64. doi:10.1053/j.gastro.2019.02.049.

[14] Ministry of Health. Specialised Care Activity Register. RAE-CMBD. Register of Discharges from National Health System Hospitals; [cited 2024 May 1]. Available from: https://www.sanidad.gob.es/estadEstudios/estadisticas/cmbdhome.htm.

[15] Cui Z, Marder EP, Click ES, et al. Nearest-neighbors matching for case-control study analyses: better risk factor identification from a study of sporadic campylobacteriosis in the United States. Epidemiology. 2022; 33(5):633–641. doi:10.1097/EDE.0000000000001504.

[16] Staffa SJ, Zurakowski D. Five steps to successfully implement and evaluate propensity score matching in clinical research studies. Anesth Analg. 2018;127(4):1066–1073. doi:10.1213/ANE.0000000000002787.

[17] Arnold KF, Davies V, de Kamps M, et al. Reflection on modern methods: generalized linear models for prognosis and intervention-theory, practice and implications for machine learning. Int J Epidemiol. 2021;49(6):2074–2082. doi:10.1093/ije/dyaa049.

[18] Thein HH, Isaranuwatchai W, Campitelli MA, et al. Health care costs associated with hepatocellular carcinoma: a population-based study. Hepatology. 2013;58(4):1375–1384. doi:10.1002/hep.26231.

[19] Karim MA, Ramezani M, Leroux T, et al. Healthcare costs for medicare patients with hepatocellular carcinoma in the United States. Clin Gastroenterol Hepatol. 2023;21(9):2327–2337.e9. doi:10.1016/j.cgh.2022.11.015.

[20] Lang K, Danchenko N, Gondek K, et al. The burden of illness associated with hepatocellular carcinoma in the United States. J Hepatol. 2009;50(1):89–99. doi:10.1016/j.jhep.2008.07.029.

[21] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–249. doi:10.3322/caac.21660.

[22] Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology. 2019;156(2):477–491.e1. doi:10.1053/j.gastro.2018.08.065.

[23] Estes C, Razavi H, Loomba R, et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;67(1):123–133. doi:10.1002/hep.29466.

[24] Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016;2(1):16018. doi:10.1038/nrdp.2016.18.

[25] Jinjuvadia R, Salami A, Lenhart A, et al. Hepatocellular Carcinoma: a decade of hospitalizations and financial burden in the United States. Am J Med Sci. 2017;354(4):362–369. doi:10.1016/j.amjms.2017.05.016.

[26] Moon AM, Singal AG, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. Clin Gastroenterol Hepatol. 2020;18(12):2650–2666. doi:10.1016/j.cgh.2019.07.060.

[27] Bentley TS, Phillips SJ. 2017 U.S. organ and tissue transplant cost estimates and discussion; 2017. Milliman Research Report; [cited 2024 May 1]. Available from: https://www.milliman.com/en/insight/2017-us-organ-and-tissue-transplant-cost-estimates-and-discussion.

[28] Lima PH, Fan B, Bérubé J, et al. Cost-utility analysis of imaging for surveillance and diagnosis of hepatocellular Carcinoma. AJR Am J Roentgenol. 2019;213(1):17–25. doi:10.2214/AJR.18.20341.

[29] Nguang SH, Wu CK, Liang CM, et al. Treatment and cost of hepatocellular carcinoma: a population-based cohort study in Taiwan. Int J Environ Res Public Health. 2018;15(12):2655. doi:10.3390/ijerph15122655.

[30] Romero-Gomez M, Kachru N, Zamorano MA, et al. Disease severity predicts higher healthcare costs among hospitalized nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) patients in Spain. Medicine. 2020;99(50):e23506. doi:10.1097/MD.0000000000023506.

[31] Petta S, Ting J, Saragoni S, a LHUs group., et al. Healthcare resource utilization and costs of nonalcoholic steatohepatitis patients with advanced liver disease in Italy. Nutr Metab Cardiovasc Dis. 2020; 30(6):1014–1022. doi:10.1016/j.numecd.2020.02.016.

[32] Kim WR, Gross JB, Jr, Poterucha JJ, et al. Outcome of hospital care of liver disease associated with hepatitis C in the United States. Hepatology. 2001;33(1):201–206. doi:10.1053/jhep.2001.20798.

[33] Melendez-Torres J, Singal AG. Early detection of hepatocellular carcinoma: roadmap for improvement. Expert Rev Anticancer Ther. 2022;22(6):621–632. doi:10.1080/14737140.2022.2074404.

[34] Pascual S, Miralles C, Bernabé JM, et al. Surveillance and diagnosis of hepatocellular carcinoma: a systematic review. World J Clin Cases. 2019;7(16):2269–2286. doi:10.12998/wjcc.v7.i16.2269.

[35] Kao SZ, Sangha K, Fujiwara N, et al. Cost-effectiveness of a precision hepatocellular carcinoma surveillance strategy in patients with cirrhosis. EClinicalMedicine. 2024;75:102755. doi:10.1016/j.eclinm.2024.102755.

[36] Ruggeri M. Hepatocellular carcinoma: cost-effectiveness of screening. A systematic review. Risk Manag Healthc Policy. 2012;5:49–54. doi:10.2147/RMHP.S18677.

[37] Akoad ME, Pomfret EA. Surgical resection and liver transplantation for hepatocellular carcinoma. Clin Liver Dis. 2015;19(2):381–399. doi:10.1016/j.cld.2015.01.007.

[38] Sapisochin G, Bruix J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. Nat Rev Gastroenterol Hepatol. 2017;14(4):203–217. doi:10.1038/nrgastro.2016.193.

[39] Sherrow C, Attwood K, Zhou K, et al. Sequencing systemic therapy pathways for advanced hepatocellular Carcinoma: a cost effectiveness analysis. Liver Cancer. 2020;9(5):549–562. doi:10.1159/000508485.

[40] Patel MV, Davies H, Williams AO, et al. Transarterial therapies in patients with hepatocellular carcinoma eligible for transarterial embolization: a US cost-effectiveness analysis. J Med Econ. 2023; 26(1):1061–1071. doi:10.1080/13696998.2023.2248840.

[41] Likhitsup A, Parikh ND. Economic implications of hepatocellular carcinoma surveillance and treatment: a guide for clinicians. Pharmacoeconomics. 2020;38(1):5–24. doi:10.1007/s40273-019-00839-9.