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# COST OF HEPATOCELLULAR CARCINOMA FROM THE PAYER'S PERSPECTIVE IN TÜRKIYE: RESULTS OF A DELPHI PANEL ANALYSIS

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## ABSTRACT

**Background:** Liver cancer is the sixth most frequently diagnosed cancer in the world ranking third in cancer related deaths. Hepatocellular carcinoma (HCC) accounts for 75-80% of liver cancers. Despite a decrease in cases of Hepatitis B (HBV) and Hepatitis C (HCV) in recent years, it is predicted that HCC will continue to increase primarily due to the burden imposed by other risk factors such as obesity, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). Financial data is essential for a reimbursement agency to understand the cost burden of a disease and predict its impact on the healthcare budget.

**Aim:** This study aims to estimate the financial burden of HCC on the Social Security Institution (SSI) of Türkiye.

**Methodology:** The data needed to estimate the cost of HCC was gathered through expert opinions. The Modified Delphi Method was used to reach a consensus among experts. A Healthcare Resource Utilization (HRU) form was designed and sent to experts to be filled out independently. Twelve experts were selected through purposeful sampling (one general surgeon, one hepatologist and ten medical oncologists). The answers from the first round were consolidated as averages, and a consensus document was prepared. This document was then discussed in a face-to-face meeting with the experts to finalize the consensus-building process. The costs were estimated using the rules and reimbursement prices set by the SSI.

**Results:** The annual cost per patient for unresectable HCC was estimated as 1,056,396TRY (US$32,937) for the first line treatment and 495,342TRY (US$15,144) for the second line treatment. The annual cost per patient for resectable HCC was estimated as 18,614TRY (US$580). The total cost of HCC to the SSI was estimated as 2,178,840,160TRY (US$67,933,569) for unresectable cases and 37,082,609TRY (US$1,156,190) for resectable cases. This accounted for 0.4% of total SSI expenditures.

**Conclusion:** Increasing risk factors such as obesity, type 2 diabetes and NAFLD in Türkiye may result in an increase in HCC cases. Our findings indicate the need to consider the potential burden of HCC on the SSI budget in the future.

## KEYWORDS

**Hepatocellular Carcinoma, Türkiye, Cost, Social Security Institution, Delphi Panel.**

## INTRODUCTION

Liver cancer is the sixth most commonly diagnosed cancer in the world and ranks third in terms of cancer related deaths. Hepatocellular carcinoma (HCC), accounts for 75-80% of liver cancers(1). According to GLOBOCAN data, there were 905,677cases of liver cancer in 2022(1). In Türkiye, GLOBOCAN data shows that 5,469 new cases of liver cancer are diagnosed annually accounting for 2.4% of all new cancer cases(2).

Cirrhosis is the main risk factor for chronic liver disease and HCC. Two different sources have stated that 74%(3) and 87%(4) of HCC cases in Türkiye are related to cirrhosis. Around 20% of cirrhosis patients develop HCC within 10 years of being exposed to the disease(5). Hepatitis B (HBV) and hepatitis C (HCV) infections are among the main causes of chronic liver disease and cirrhosis(4–6). In two studies, HBV and HCV were found to be the

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main risk factors for HCC in Türkiye followed by alcohol consumption(4,7). Türkiye has achieved a decrease in HBV incidence in the young population with the introduction of HBV immunization for newborns in 1998 and immunization programs for the young population between 2005-2009(8,9). As a result of these policies, the HBV incidence has decreased from 8.26/100,000 in 2002 to 4.26 in 2010(9). There is no vaccine for HCV, but new generation antiviral drugs have contributed positively to the treatment of the disease. HCV prevalence in Türkiye is stated to be between 0.5% and 0.96%(10).

The decline in HBV and treatment of HCV may have a positive impact on preventing chronic liver disease and cirrhosis. However, other risk factors for HCC such as consuming aflatoxin contaminated food, excessive alcohol consumption, obesity, type 2 diabetes, smoking and non-alcoholic fatty liver disease (NAFLD)(1,11,12) have become more prevalent recently. NAFLD affects almost one-third of the world's population and is considered as the main cause of mortality and morbidity from liver related diseases(11,13). Obesity and type 2 diabetes are the major public health problems in Türkiye and NAFLD has emerged as a new concern. A recent study found that the prevalence of NAFLD in Türkiye is 30%, placing the country among those with the highest prevalence rates(13).

Global and Türkiye based studies show that HCC is more frequently diagnosed in males(1,14,15). According to Ministry of Health statistics, the age standardized frequency of liver cancer is 3.9/100,000 for males and 1.6/100,000 for females(16). A recent study aimed to elaborate on the characteristics of HCC patients in Türkiye by analyzing data from 547 patients treated in 25 gastroenterology and oncology clinics(15). The mean age at diagnosis was 62.6 years (range, 19 to 92 years, with 72.5% aged 40-69 years) and 81.6% of patients were male. 68.2% of the patients had HBV and 17.2% had HCV. The findings of this study are similar to those of an earlier one(4).

Türkiye has a social security based health care system with the Social Security Institution (SSI) covering over 90% of the population as the primary purchaser of health care services from both public and private sectors. The SSI holds significant power in determining rules and reimbursement conditions for all health care products and services, making it a key player in financing. Given the extensive coverage of the population and the comprehensive health benefits package there is a growing need for financial information regarding all reimbursement issues. We did not come across any studies about the cost of treating HCC in Türkiye from the SSI perspective. Since HCC is one of the diseases frequently seen in Türkiye as well, this study aims to estimate the financial burden of HCC on the SSI of Türkiye.

## MATERIALS AND METHODS

The SSI has a financial information system (called MEDULA), but the data collected in this system is not shared with the public. Therefore, any study aiming to estimate the financial burden of a disease must use alternative methodologies for these estimations. One commonly preferred method is using expert opinions. However, reaching a consensus among selected experts can be a challenge for researchers. The Delphi Method defined as 'a scientific method to organize and manage structured group communication processes with the aim of generating insights on current or prospective challenges; especially in situations with limited availability of information'(17), is widely used in the healthcare sector. This method has also been utilized in several studies in Türkiye (18–25). In the absence of data, we turned to expert opinions and used the Delphi method to reach a consensus among the experts. The classical Delphi Method typically involves multiple rounds of consensus-building phases with pre-designed and distributed statements. Participants are usually anonymous. In this study, we utilized the Modified Delphi Method which includes a face-to-face meeting with the experts to finalize the consensus-building process(26).

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Purposeful sampling(27) was used to identify twelve experts (one general surgeon, one hepatologist and ten medical oncologists) to participate in the study. Typically 5-10 experts are considered acceptable in the Delphi Method to ensure content validity(26). A Healthcare Resource Use (HRU) form was developed based on the treatment algorithms for HCC for both resectable and unresectable cases. The form included questions about the type, patient ratio and frequency of resources used for outpatient, inpatient, intensive care and emergency care. Participants were asked to independently fill out the form. Following this initial round, researchers analyzed all responses, calculated averages and created a draft consensus document for discussion during a face-to-face meeting. Healthcare resources were priced according to the SSI's reimbursement rules and guidelines. After identifying the unit costs of all tests, procedures and drugs, these unit costs were multiplied by the percentage of patients and frequency of the resource use. During the face-to-face meeting all responses were reviewed, and a final consensus was reached. Once the form was finalized, annual per patient costs for treating of resectable and unresectable HCC were calculated. The total cost of HCC to the SSI was estimated using epidemiological data provided by the experts.

## RESULTS

We asked general questions about HCC in Türkiye in order to understand the overall outlook of the disease and gather the necessary data for nationwide estimates. Tables 1 and 2 display a summary of the consensus reached on these questions.

**Table 1: Overview of HCC in Türkiye**

| | |
|---|---|
| HCC prevalence in Türkiye | 7/100,000 |
| HCC incidence in Türkiye | 3/100,000 |
| Distribution of HCC patients by BCLC criteria at diagnosis | |
| A | 25% |
| B | 40% |
| C | 27% |
| D | 8% |

**BCLC: Barcelona Clinic Liver Cancer, HCC: Hepatocellular Carcinoma**

**Table 2: HCC treatments used according to BCLC criteria**

| | A | B | C | D |
|---|---|---|---|---|
| Resection | %41 | %12 | %2 | %0 |
| Ablation | %29 | %14 | %4 | %0 |
| Liver transplantation | %13 | %15 | %9 | %0 |

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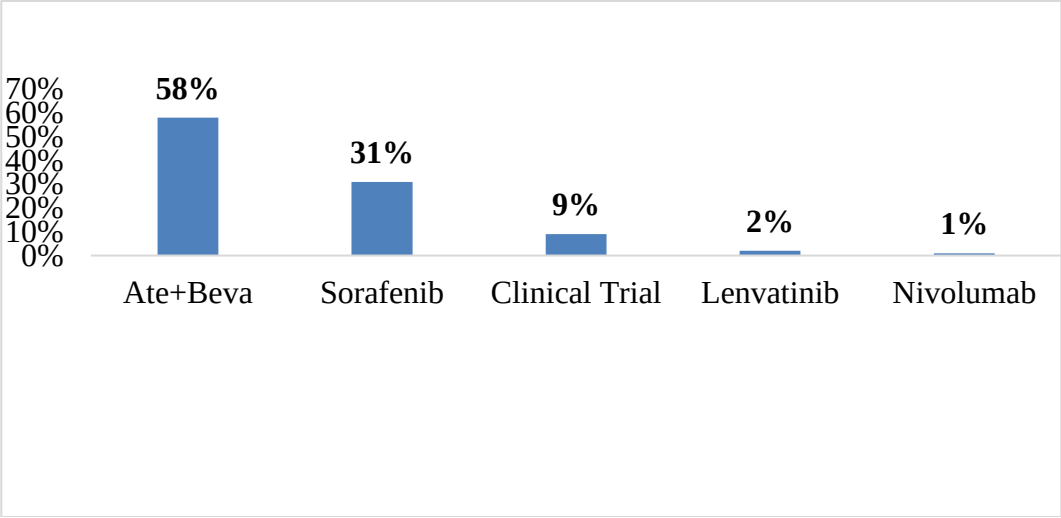
| | | | | |
|---|---|---|---|---|
| Locoregional treatment (TACE) | %5 | %20 | %8 | %1 |
| Locoregional treatment (TARE) | %5 | %20 | %8 | %1 |
| Locoregional treatment + systemic treatment | %4 | %16 | %17 | %4 |
| Systemic treatment (Atezo+Beva, TKI, clinical trial) | %1 | %7 | %33 | %5 |
| Monitoring without treatment | %6 | %1 | %11 | %18 |
| Best supportive care | %0 | %4 | %11 | %61 |

**Atezo: Atezolizumab, Beva: Bevacizumab, BCLC:Barcelona Clinic Liver Cancer, HCC: Hepatocellular Carcinoma, TACE: Transarterial Chemoembolization, TARE: Transarterial Radioembolization, TKI: Tyrosine Kinase Inhibitor**

HCC prevalence and incidence were reported as 7 per 100,000 and 3 per 100,000 respectively. The Turkish Statistics Institute has estimated the population for 2024 to be 87,886,000. Therefore, it is estimated that there are 6.152 HCC patients in Türkiye. Our experts have reached a consensus that 63% of these cases are unresectable, totaling 3,876 patients. Figures 1 and 2 illustrate the systemic treatments used for these patients. The combination of atezolizumab and bevacizumab was the most commonly used option for first line treatment, while sorafenib was preferred choice for second line treatment.

**Figure 1: Systemic treatments used in the first line treatment for HCC**




**Ate: Atezolizumab; Beva: Bevacizumab; HCC: Hepatocellular Carcinoma**

**Figure 2: Systemic treatments used in the second line treatment for HCC**

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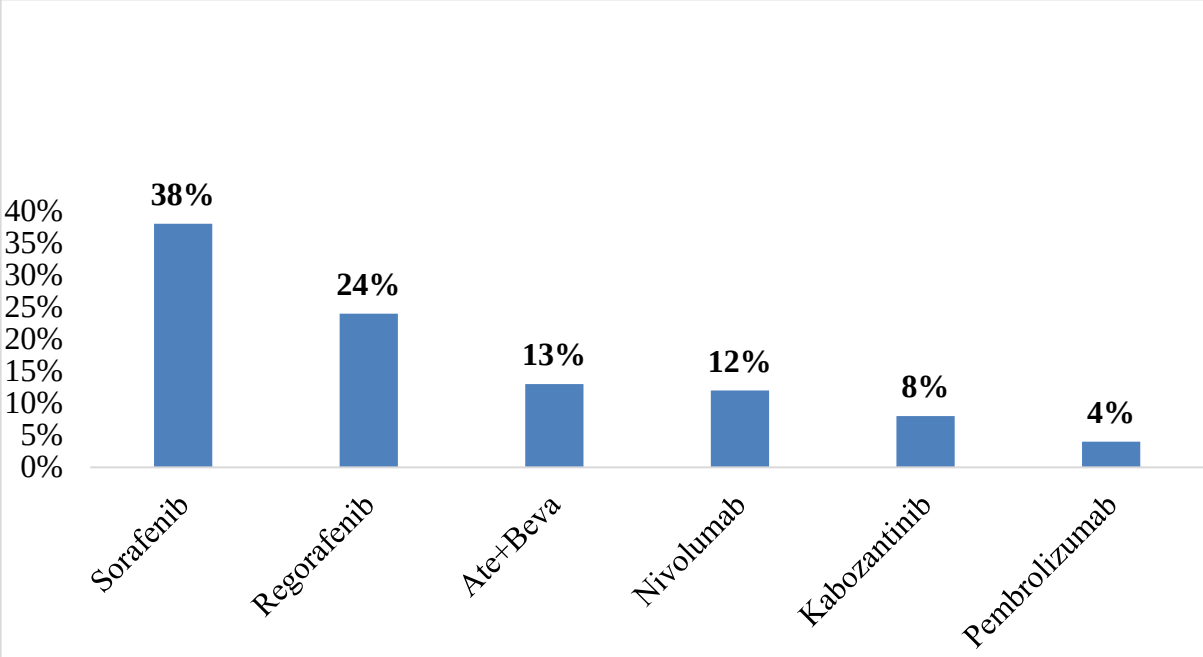


**Ate: Atezolizumab; Beva: Bevacizumab, HCC: Hepatocellular Carcinoma**

Table 3 presents the annual cost per patient for unresectable HCC cases followed by Table 4 which presents the costs for resectable HCC cases.

**Table 3: Annual cost per patient for unresectable HCC in Türkiye**

| | **Cost (TRY)** |
|---|---|
| **Outpatient Care** | |
| Healthcare services | 11,239 |
| First line oncologic drugs | 962,863 |
| Second line oncologic drugs | 401,809 |
| Other drugs | 16,519 |
| Total outpatient care first line | 990,621 |
| Total outpatient care second line | 429,567 |
| **Inpatient Care** | |
| Healthcare services | 11,810 |
| Drugs | 26,719 |

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| | |
|---|---|
| Total inpatient care | 38,529 |
| **Emergency Care** | |
| Healthcare services | 9,839 |
| Drugs | 1,619 |
| Total emergency care | 11,458 |
| **Intensive care** | 15,788 |
| **Total annual cost per patient for first line treatment** | **1,056,396** |
| **Total annual cost per patient for second line treatment** | **495,342** |

**HCC: Hepatocellular Carcinoma; TRY: Turkish Lira**

**Table 4: Annual cost per patient for resectable HCC in Türkiye**

| | **Cost (TRY)** |
|---|---|
| **Outpatient Care** | |
| Healthcare services | 2,600 |
| Drugs | 12,629 |
| Total outpatient care | 15,230 |
| **Inpatient Care** | |
| Healthcare services | 976 |
| Drugs | 755 |
| Total inpatient care | 1,732 |
| **Emergency Care** | |
| Healthcare services | 1,072 |
| Drugs | 580 |
| Total emergency care | 1,652 |
| **Total annual cost per patient** | **18,614** |

**HCC: Hepatocellular Carcinoma; TRY: Turkish Lira**

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The annual cost per patient for first line treatment of unresectable HCC was 1,056,396TRY (US$32,937) and 495,342 TRY (US$15,444) for second line treatment. For resectable HCC, the annual cost per patient after resection was 18,614TRY (US$580).

Based on the experts' opinions and population statistics, it is projected that there will be 6,152 patients with HCC in Türkiye in 2024. Of these, 3,876 will be unresectable cases, while 2,276 will be resectable cases. The experts have determined that 70% of unresectable patients receive outpatient treatment as first line treatment (2,713 patients) while 30% receive second line treatment (1,163 patients). Additionally, it was found that 40% of patients receive inpatient care, 20% receive intensive care and 80% receive emergency care. These percentages were used to estimate the number of patients in each state. Table 5 outlines the total costs of HCC to the SSI in Türkiye.

**Table 5: Annual Total Cost of Unresectable HCC Patients to the SSI in Türkiye**

| | Number of Patients | Cost per Patient (TRY) | Total Cost (TRY) |
|---|---|---|---|
| Diagnosis | 3,876 | 801 | 3,103,910 |
| Outpatient first line | 2,713 | 693,434 | 1,881,315,897 |
| Outpatient second line | 1,163 | 128,870 | 149,841,116 |
| Inpatient | 1,550 | 38,529 | 59,731,914 |
| Intensive care | 775 | 5,788 | 12,238,348 |
| Emergency | 3,101 | 11,458 | 35,526,366 |
| | | **Total** | **2,141,757,551** |

**HCC: Hepatocellular Carcinoma; TRY: Turkish Lira**

The annual total cost of unresectable HCC patients was estimated to be over 2 billion TRY (US$ 66,777,379 ).

The experts have concluded that 10% of resectable patients receive inpatient care and 15% visit emergency care after resection. Table 6 presents the annual cost of resectable HCC cases to the SSI after resection.

**Table 6: Annual Total Cost of Resectable HCC Patients to the SSI in Türkiye**

| | Number of Patients | Cost per Patient (TRY) | Total Cost (TRY) |
|---|---|---|---|
| Diagnosis | 2,276 | 801 | 1,822,932 |
| Outpatient | 2,276 | 15,230 | 34,667,430 |

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| | | | |
|---|---|---|---|
| Inpatient | 228 | 1,732 | 394,322 |
| Emergency | 341 | 580 | 197,925 |
| | | **Total** | **37,082,609** |

**HCC: Hepatocellular Carcinoma; SSI: Social Security Institution; TRY: Turkish Lira**

The annual total cost for resectable HCC patients after resection was estimated at 37,082,609 TRY (US$1,156,190) These results indicate that the total annual cost of HCC to the SSI is 2.178,840,160TRY (US$67,933,569). In 2023, the total healthcare spending of the SSI was 553,143,000,000TRY(28). The share of HCC spending in the SSI's healthcare budget is 0.4%.

## DISCUSSION

This study aimed to estimate the total cost of HCC to the SSI of Türkiye. Cost of disease studies in Turkey are not frequently conducted, mainly due to barriers in accessing data. The Delphi method is commonly used to determine the type, amount and frequency of resources used in the treatment of a disease(18,18–21,23–25). We utilized the modified Delphi method in this study.

There is an increasing trend in the incidence and prevalence of HCC globally(29–33). Cost of disease studies for HCC are also rare in the literature, especially after the inclusion of atezolizumab+bevacizumab as a preferred option for first line therapy. Cullen et al estimated the cost of HCC to the UK's National Health Service (NHS) using the National Cancer Registration Dataset. They found that there were 2,971 patients with HCC and the cost of treatment was £44 million for the two years post-diagnosis(29). In another study in Taiwan, the direct costs of HCC patients were estimated for the Taiwan National Health Insurance program using the program's database between 1997 and 2012. The program spent US$92 million on 5,522 patients, with a mean cost of US$16,711 per patient(34). It is difficult to compare the results of cost of disease studies due to different methodologies and approaches used to estimate costs. Therefore, all studies should be assessed based on their own results and limitations.

## CONCLUSION

Our results have shown that the cost of HCC to the SSI is over 2 billion TRY (US$ 68 million) accounting for 0.4% of the organization's overall spending. The main limitation of this study is that it relies on expert opinions rather than social health insurance data. However, since SSI data is not accessible, this methodology provides a viable option to estimate the cost of any disease. With obesity, type 2 diabetes and NAFLD on the rise in Turkey, despite successes in controlling HBV and HCV, the incidence and prevalence of HCC may increase in the coming years as seen in other countries. Preventive measures and screening could help alleviate the strain on the SSI's budget.

**Conflict of Interest: This study was supported by Roche Türkiye.**

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