REVIEW ARTICLE

Improving Health Care for Patients with Hepatocellular Carcinoma in the Federation of Bosnia and Herzegovina

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most common cancer globally and the third leading cause of cancer-related deaths. It remains especially lethal among patients with cirrhosis and chronic liver diseases like hepatitis B and C, alcohol abuse and non-alcoholic fatty liver disease. A retrospective, multicenter study was conducted across five oncology centers in the Federation of Bosnia and Herzegovina, with the aim of gaining a better insight into the current state of healthcare for patients with HCC in this region. The study reveals several regional disparities in the etiology, treatment, and outcomes of HCC, but it also indicates that the diagnostic approach varies significantly from one city to another. One of the highlights of the study is the late-stage diagnosis of most patients, due to the limited healthcare access, diagnostic delays and, especially, lack of screening programs. Implementation of targeted screening methods, regular monitoring of high-risk patients and enhanced use of biomarkers could lead to a significant improvement in the diagnostic accuracy. The limited use of innovative treatments recommended by the global guidelines was also identified as an issue, which directly leads to limited surgical and other treatment options. This study signals the need for a standardized patient pathway in the Federation of Bosnia and Herzegovina, implementation of national registry and targeted HCC database, which could reduce mortality, improve overall care and patient outcomes.

Keywords: hepatocellular carcinoma, healthcare, standardized patient pathway.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed cancer globally, with 900,000 new cases recorded in 2020 (1). It is also the third leading cause of death among cancer patients, with over 830,000 deaths (2). With a five-year survival rate of 21%, HCC remains one of the most lethal gastrointestinal malignancies (3).

The main risk factors for HCC development are cirrhosis and chronic liver diseases, irrespective of etiology. Specific risk factors include viral infections such as hepatitis B and C, chronic alcohol abuse, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hemochromatosis, and coinfections with HBV/HCV and HIV (4).

HEPATOCELLULAR CARCINOMA IN THE FEDERATION OF BOSNIA AND HERZEGOVINA

To analyze the current state of healthcare for patients with HCC in the Federation of Bosnia and Herzegovina (FBiH), a retrospective, multicenter collection of epidemiological, demographic, and clinical data was conducted across five oncology centers: the Clinical Center of the University of Sarajevo, University Clinical Center Tuzla, University Clinical Hospital Mostar, Cantonal Hospital Zenica, and Cantonal Hospital Bihać. The data covered patients diagnosed and/or treated for HCC between 1 January 2022 and 31 December 2023 in these centers.

The analysis revealed that Tuzla has the highest number of cases, while Zenica has the lowest. Sarajevo and Mostar fall in between, possibly reflecting differences in healthcare access, diagnostic capabilities, and demographic factors across these regions. In terms of age, Sarajevo and Mostar have older patient populations, while Zenica has a younger demographic. Zenica also has the highest proportion of male patients, potentially indicating specific regional risk factors.

Regarding etiology, HBV infection is predominant in Tuzla, while alcoholic cirrhosis is more common in Mostar, suggesting varied risk factors and habits across the country. A high percentage of undetermined causes underscores the need for enhanced diagnostics and more detailed patient monitoring.

Diagnosis in Sarajevo was largely based on biopsy, whereas non-invasive methods like ultrasound (US), CT, or MRI were more commonly used in Tuzla. This trend highlights significant disparities in diagnostic approaches and capacities between cities.

Most patients across cities are diagnosed at later stages of the disease (BCLC stage C), indicating a lack of early detection. Compared with global data, where approximately 50% of cases are diagnosed at an advanced stage, 61% of patients in FBiH receive a late-stage diagnosis, limiting surgical and other curative treatment options. Furthermore, only 10% are diagnosed in the early stage (BCLC A) compared to up to 33% globally, as observed in Italy (5). This reflects significant diagnostic delays likely due to limited healthcare access, lack of effective early screening programs, and lower health awareness among the population. Additionally, 10% of patients in FBiH are diagnosed at terminal stage (BCLC D), compared to a lower global average, indicating that patients often present with advanced disease, further highlighting the urgent need for improved early detection programs.

Innovative therapies like the Atezolizumab-Bevacizumab combination are limited in FBiH, diverging from leading global guidelines (BCLC, ESMO, NCCN), which recommend this combination as a first-line systemic therapy. Such discrepancies underscore the need for standardization in HCC treatment across Bosnia and Herzegovina to align with neighboring countries where these treatments are already standard (6-8).

Geographic disparities in diagnostic and treatment approaches across FBiH, coupled with inequalities compared to neighboring countries, signal the need for immediate healthcare system improvements focused on prevention, early diagnosis, and access to modern therapies. Comprehensive screening programs and education for both healthcare professionals and patients could significantly reduce incidence and improve HCC treatment outcomes.

According to GLOBOCAN, HCC is not among the top five cancers in Bosnia and Herzegovina. However, it ranks eighth in incidence, with 492 new cases, and sixth in mortality, with 462 deaths annually (9). These figures reflect high mortality associated with liver cancer, consistent with our analysis showing late-stage diagnoses (BCLC C) in most patients, limiting treatment options. Alarmingly, only 135 HCC patients were diagnosed/treated by oncologists in FBiH over two years, far below GLOBOCAN's expected rate. This highlights the critical need for increased awareness, early detection, and regular

monitoring of at-risk populations, as well as establishing a unified population-based and clinical registry.

OPTIMIZATION OF SCREENING AND MONITORING PROGRAMS

HCC poses a significant clinical challenge, particularly among patients with cirrhosis or chronic hepatitis B infection. Regular ultrasound and AFP screening are recommended for early detection of liver changes that may indicate HCC. For patients without nodules or with nodules less than 10 mm on ultrasound, biannual follow-ups are advised. For those with positive AFP or nodules larger than 10 mm, additional imaging (CT or MRI) is necessary to precisely define lesion characteristics (8).

Biomarkers and Diagnostic Advancements

While AFP has traditionally been used in HCC screening and diagnosis, its sensitivity and specificity limitations necessitate additional biomarkers. PIVKA-II, discovered to be elevated in HCC patients, can complement AFP, enhancing diagnostic accuracy when used together, with combined detection sensitivity reaching up to 92% compared to 52% with AFP alone (10-14).

OPTIMAL MULTIDISCIPLINARY THERAPEUTIC APPROACH

For potentially resectable or transplantable HCC patients, evaluating liver function and overall condition is critical. Resection is preferred for patients with good liver function and no portal hypertension. However, transplant remains optimal for eligible patients. Multidisciplinary team assessments should guide therapeutic decisions, incorporating ablative or arterial therapies as bridges to transplant when applicable, along with regular radiological evaluations and AFP measurement to monitor recurrence (8).

SYSTEMIC ONCOLOGICAL TREATMENT

Systemic therapy is reserved for advanced HCC patients ineligible for curative or locoregional treatments and with adequate liver function. The Atezolizumab-Bevacizumab combination is suggested for patients with good functional status, while Tremelimumab-Durvalumab is an alternative for those who cannot tolerate Bevacizumab. For patients in poor condition or post-transplant recurrence, monotherapy with Sorafenib or Lenvatinib is preferred over conventional cytotoxic chemotherapy (15).

EXPERT PANEL RECOMMENDATIONS

1. **Early Detection of HCC**: Introduce regular monitoring of high-risk patients (e.g., ultrasound and serum AFP every six months) to detect HCC in early stages, alongside patient and healthcare provider education for improved screening cooperation.
2. **Enhanced Monitoring of High-Risk Patients**: Establish routine follow-up programs for high-risk patients, supported by multidisciplinary teams for timely diagnosis.
3. **Utilization of New Biomarkers**: Introduce PIVKA II in combination with AFP and ultrasound for early HCC detection, with gastroenterologists and infectious disease specialists selecting appropriate patients.
4. **HCC Diagnosis**: Increase reliance on biochemical markers and digital radiology (CT, MRI) for early detection, reducing the need for invasive biopsy.
5. **Timely Systemic Oncological Treatment**: Ensure timely access to systemic oncological treatment with drugs established as the standard of care for HCC to improve outcomes and survival.

IMPLEMENTATION STRATEGIES

To optimize HCC care, a standardized patient pathway across FBiH is essential, covering diagnosis, multidisciplinary assessment, personalized treatment, and follow-up. This pathway should align with international guidelines, fostering equal access to healthcare and improving patient outcomes.

Developing a targeted HCC database to track clinical parameters will enhance resource planning, intervention optimization, and contribute to research initiatives. Finally, the establishment of multidisciplinary team meetings for interventional oncology procedures will ensure thorough and timely assessment of candidates for interventions such as embolization, ablation, or resection.

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