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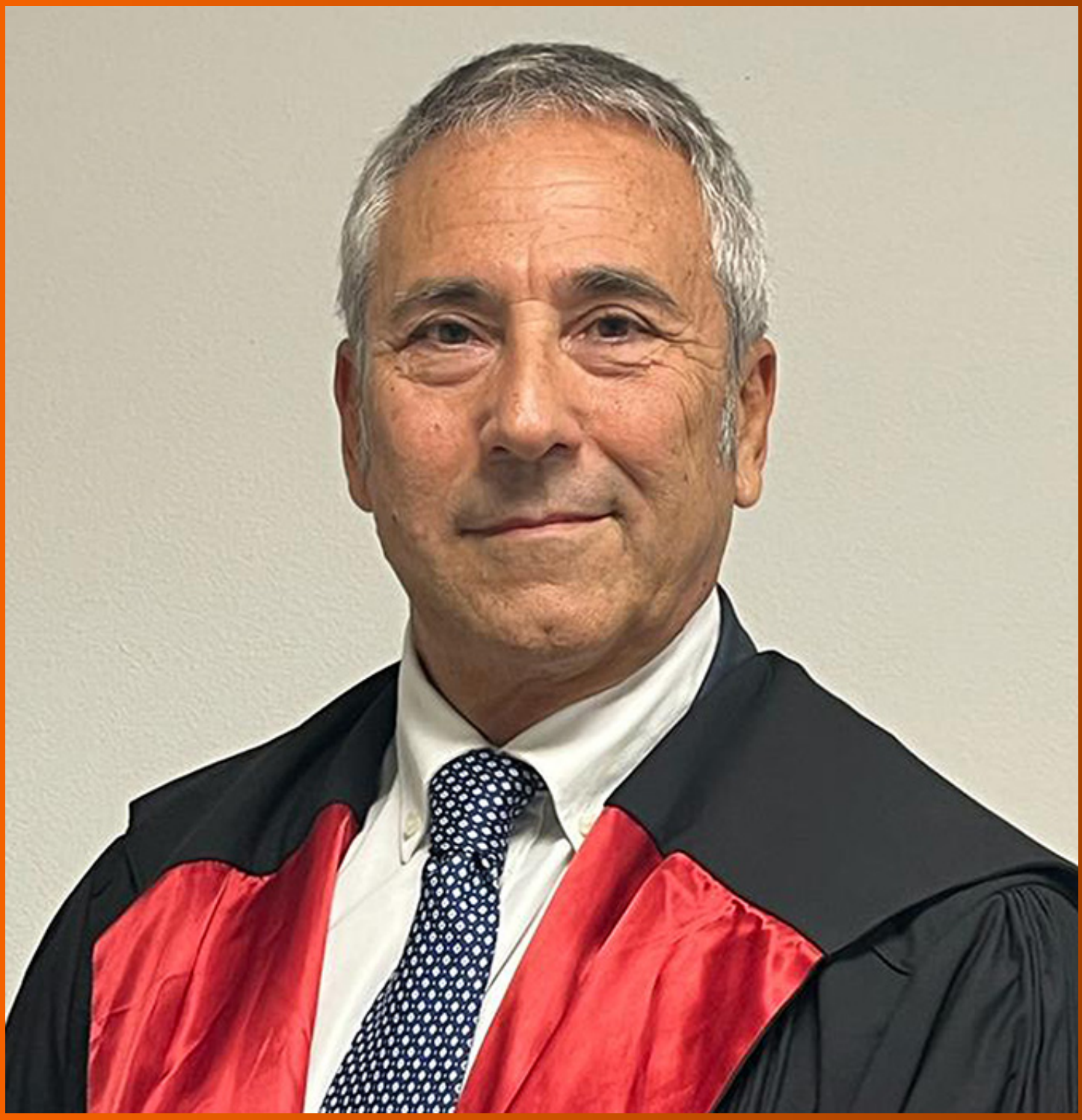

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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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EDITORIAL

Novel prognostic factors after radical resection of hepatocellular carcinoma: Updating an old issue

Lapo Bencini

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Abstract

In this editorial, I comment on the article by Li *et al* published in the recent issue of the *World Journal of Gastrointestinal Surgery* in 2023, investigating the role of some novel prognostic factors for early survival after radical resection of liver cancer. Liver cancer is an important burden among Asian and Western populations, despite recent advances in both medicine (from virus eradication to systemic target therapies) and surgery. However, survival after proven radical surgery remains poor, with recurrences being the rule. Many prognostic scores have been developed and validated to select those patients who will best benefit from radical liver surgery, although the final general and oncological outcomes continue to be highly jeopardized. Unfortunately, no single biomarker can resolve all these issues for hepatocellular carcinoma, and it remains to be proven whether some of them main-tain predictive power in the long-term follow-up. In the ongoing era of "preci-sion" medicine, the novel prognostic markers, including immune inflammatory and nutritional indexes could be of great help in better stratify surgical candi-dates.

Key Words: Hepatocellular carcinoma; Liver cancer resection; Liver surgery; Prognostic factors; Immune index; Nutritional index

Core Tip: Survival after radical surgery for liver cancer remain poor, with important perioperative complications and many organ recurrences. Prognostic scores have been developed and validated to select those patients who will best benefit from radical liver surgery, although the final general and oncological outcomes continue to be highly jeopardized. Some novel prognostic markers, including immune inflammatory and nutritional indexes could be of great help in better stratify surgical candidates.

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INTRODUCTION

Liver cancer represents a leading cause of cancer death worldwide, with an overall percentage of almost 5%, second only to colonic and lung cancers[1]. Nevertheless, there are some important geographic differences in the epidemiologic features of liver cancer, mainly related to the wide variation in exposure to different risk factors for chronic hepatitis, such as viral infections, alcohol consumption, obesity, diabetes, and toxins[2,3]. However, if there is a trend toward a reduction in some of these factors (*i.e.*, mass vaccination, control of diabetes with metformin, reduction in alcohol intake, aspirin and statin intake)[4], there are others expected to increase, such as obesity in Western and developing countries, leading to a general trend toward a global burden to increase by 55% by 2040[1,5].

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer because it includes up to 85% of cases, with a disappointing prognosis and long-term survivorship, despite a multimodal, aggressive, medical/surgical approach[6].

The state of prognostic factors in surgically resected patients is one of the hot topics when dealing with primary liver cancer (HCC) because most of them have a prolonged natural history due to recent improvements in both medical and surgical therapies. However, for such patients, surgery can be harmful, while in liver, recurrences are frequent, and survival is poor.

Many prognostic scores have been developed and validated to select those patients who will best benefit from radical liver surgery[7], although the final general and oncological outcomes continue to be highly jeopardized. Unfortunately, no single biomarker can resolve all these issues for HCC, and it remains to be proven whether some of them maintain predictive power in the long-term follow-up. In the ongoing era of "precision" medicine, the novel prognostic markers, including immune inflammatory and nutritional indexes could be of great help in better stratify surgical candidates.

For HCC, the most commonly reported scoring and staging systems include the Child-Pugh score, the ALBI (Albumine/Bilirubine) score, the Model for End-Stage Liver Disease (MELD) score, the Barcellona Clinic Liver Cancer (BCLC, updated 2022), and the Japanese HCC Score. Despite peculiar application in specific contexts (*i.e.*, transplant candidates or Japanese), a panel of experts recommends the use of BCLC to drive the management of HCC, with the Child-Pugh score to assess liver function, although the ALBI score should be implemented in future studies[6].

Among the proposed algorithms, surgery (including liver resection and transplantation) remains one of the main options for fit patients, suffering from a mild burden of cancer and good liver function[7]. The 5-year survival after radical resection is approximately 70%, with 80% recurrence[8,9] and a perioperative mortality rate below 5%, even in cirrhotic patients[10]. Moreover, surgery remains superior to other local therapies, such as transarterial chemoembolization (TACE) or radiation or systemic therapy, even in the case of multiple resectable nodules with some vascular involvement[11]. Indications for surgery are reported in the European Association for the Study of the Liver recommendations[12].

Despite the therapeutic option chosen, it would be essential to select those patients who may better benefit from the medical proposal, identifying some clinical or molecular characteristics that are able to influence the treatment response and the natural history of disease. Tumor burden and spread (including the number and dimension of the lesion and the presence of extrahepatic disease), together with the assessment of liver function, are grossly employed but are not able to obtain a deeper stratification of patients in similar BCLC classes[4,7].

The use of the old biomarkers alpha fetoprotein (AFP), ALBI and Child-Pugh score are supported by robust literature evidence, but some recent molecular signatures have been studied to define interpatient heterogeneity. A very promising association of atezolizumab plus bevacizumab is the object of the IMBrave phase 3 trial, identifying gene signatures for T-cell and myeloid inflammation that were correlated with prognosis[4,13,14]. According to these findings, combination therapy with immune checkpoint inhibitors (ICIs) could become the standard of care for advanced HCC.

Several other inflammatory markers, including the neutrophil-to-lymphocyte ratio and the C-reactive/AFP-based CRAFITY score, may play a role in the ongoing course of immune-oncology[15-18]. Interestingly, immunotherapy also seems to be promising in both neoadjuvant and adjuvant settings, where sorafenib failed to show survival advantages[19-21].

In nonalcoholic fatty liver disease, the tumor immune microenvironment is impaired, mainly due to CD4+ T cells, which alter the efficacy of ICI therapies, as proven by the reduced response (27% *vs* 35%) in this subset of patients when considering the results of the IMBrave 150 trial)[10,14]. These considerations could introduce the concept of "personalized" medicine.

From an ideal point of view, we could find some novel biomarkers that are able to achieve early diagnosis and surveillance for recurrence and to drive treatment choice and prognosis, mainly permitting the selection of patients with the best balance between harm and outcome. At the state of the art, no single biomarker can show all these requisites and is merely utopistic that it will happen further. It is more likely to identify several biomarkers or a mixture of them to be targeted in different contexts with different purposes.

Piñero published a very comprehensive review of the well-known and novel biomarkers for HCC, although they concluded that AFP still remains the most performant in predicting surgical outcomes[22].

Without a well-codified biologically based predictive biomarker, the surgical candidates, according to the BCLC algorithm, include a multitude of patients, with a wide range of long-term outcomes, while most of them are expected to develop early recurrences (within one year). A second challenge is that even those patients successfully operated on maintain a poor long-term prognosis, not only related to recurrence (*i.e.*, liver failure or distant spread).

To address some of these challenges, Li *et al*[23] reported some correlations between the systemic immune inflammatory index (SII) and geriatric nutritional risk index (GNRI) and HCC operation prognosis (radical resection). The assessment of the immune/inflammatory response before surgery was recently developed[24,25], together with the nutritional status in older people, and the study raises some interesting issues[26].

The study was retrospective and included data from 100 Chinese HCC patients. The SII was calculated using a previously published formula based on neutrophil, platelet, and lymphocyte counts, while the GNRI originated from albumin and the ratio between actual weight/ideal weight. The Authors investigated the predictive efficacy of the SII and GNRI in radically resected HCC patients using receiver operating characteristic curves, and the relationships between these indexes and survival using Kaplan–Meier or Cox regression.

After 1 year of follow-up, 24 patients died, and 76 survived. According to the proper statistical calculations, the main results were that the SII and GNRI combination was higher in predicting outcome than the SII or GNRI alone, and the SII was higher than the GNRI. Moreover, the proportion of advanced tumors, according to the TNM stage, was higher in patients with SII > 309.14. Interestingly, older patients (> 70 years) had lower GNRI scores.

The main finding of this study was that the 1-year survival rate was lower in those patients who had a preoperative SII > 309.14 and GNRI ≤ 98, both of which were identified as independent for survival by Cox regression analysis. In detail, impaired SSI reduced the chance of being alive ten times and GNRI 4 times after one year of follow-up.

The results of this study support that in a subgroup of older malnourished patients and patients with activated abnormal inflammatory and immune responses, the benefits of radical surgery for HCC should be carefully balanced with risks. In addition, when considering the proportion of "patients at risk" in this cohort, almost half of them (47%) were within the cutoff for the impaired inflammatory/immune response group, and 20% could be considered "malnourished", highlighting the clinical importance of those issues.

However, it remains to be proven whether these novel prognostic tools maintain predictive power in the long-term follow-up, even with patients retreated with alternative locoregional or systemic therapies that can prolong survival. Further similar studies are also needed for prospective validation of the GNRI index in older or frail patients and its relationship with survival. In other words, the present study excluded those patients who died in the perioperative period, while a correlation with nutritional status could be advocated. Finally, the definition of survival reduction could be integrated with the incidence of liver recurrences, which best predict the treatment outcomes in the early period.

The importance of the tumor microenvironment in driving its progression and invasion has been largely studied[27]. From a perspective point of view, the authors of the present study[23] hypothesize that the SII is an efficient inflammatory immune index reflecting immune function and inflammatory responses. In brief, an increase in the SII indicates an increase in platelets and neutrophils and a decrease in lymphocytes, suggesting an enhanced inflammatory response with weak immune functioning. On the other hand, disease-related malnutrition, caused by both reduced nutritional intake and high tumor metabolism, correlates to the incidence of perioperative complications and, definitely, to survival[28,29]. These explanations are very interesting and support the theoretical background of Lin and coworkers' findings[23].

Nevertheless, due to a scarce source of well-conducted, liver resection-addressed papers, a word of caution should be maintained to decide which of the immune/nutritional indexes are to be included in the final decision of resect/not resect patients suffering from HCC.

CLINICAL IMPLICATIONS

Liver surgery for HCC is still gravated by perioperative complications, especially in older patients, and in those with uneventful recovery early (within one year), recurrence and survival are not completely satisfactory. Two issues should be balanced in this context. First, in Asian and Western countries, the population is aging, with older patients being at greater risk for surgical complications and postoperative cirrhotic/healthy liver failure. Second, the oncological/surgical outcome must be matched with alternative, local, less invasive approaches, such as percutaneous ablation or TACE.

CONCLUSION

The decision to candidate older patients affected by HCC to receive resective surgery should be multidisciplinary. Several preoperative factors should be considered, including comorbidities, anesthesiologic risks, liver function and burden of cancer. In the ongoing era of "precision" medicine, the novel prognostic markers, including nutritional assessment and systemic inflammatory responses, seem promising for stratifying patients with a better prognosis.

FOOTNOTES

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