Peer Review File

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Review Comments:

Reviewer A:

In this study, Authors revealed the usefulness of CONUT score for predicting the prognosis of HCC patients within Milan criteria treated with RFA.

This study is important because nutritional and immune status has a significant impact on the prognosis of HCC patients.

Reply: Thank you for the kind comments and positive feedback for our work. We cherish the opportunity to revise the manuscript.

I have some question.

Comment 1:

I may have missed it, but how did you assess tumor differentiation? Please describe whether it is pathological or imaging.

Reply: We thank the reviewer for the comment. All patients included in this study underwent needle biopsy for pathological diagnosis. In this study, tumor differentiation was assessed according to the WHO classification of digestive system tumors by a pathologist and classified to one of three types of differentiation: well, moderate, or poorly differentiated (1). Tumor differentiation was determined by two pathologists with at least 5 years of experience. Thank you very much.

Changes in the text:

Tumor differentiation was assessed according to the WHO classification of digestive system tumors by two pathologists with at least 5 years of experience (1).

Reference

1. WHO Classification of Tumours Editorial Board. WHO classification of digestive system tumor 5th edition. Geneva, Switzerland, World Health Organization:229-39.

Comment 2:

Lymphocytes are affected by pancytopenia due to liver cirrhosis, while Alb and cholesterol are affected by the liver's ability to synthesize.

Please consider a few more implications of CONUT score due to liver disease as opposed to other diseases.

Reply: We thank the reviewer for the thoughtful comment.

The CONUT score has been shown to be an effective tool with which to determine and monitor the immunological and nutritional status of hospitalized patients. High CONUT scores are associated with poor prognosis in malignancies such as HCC, gastric carcinoma, colorectal carcinoma, and urothelial carcinoma (1-4).

The CONUT score is composed of serum albumin, total lymphocyte count, and total cholesterol. Serum albumin level is not only an important marker of hepatic functional reserve, but also a reliable indicator of immunological and nutritional status. Low serum albumin levels reflect poor hepatic functional reserve, poor immunological status, and poor nutritional status (6,7).

HCC is an inflammation-related cancer. More than 90% of HCC patients in China have chronic inflammation caused by hepatitis B virus (HBV) infection and cirrhosis (5). Total lymphocyte count plays a crucial role in host cell-mediated immunity. Meanwhile, cirrhosis-induced pancytopenia may reduce lymphocyte count. Previous systematic reviews have verified that a low preoperative lymphocyte count is independently associated with poor prognosis in HCC patients (8,9).

Cholesterol is a major component of the cell membrane and participates in cellular metabolism. Serum cholesterol level indicates the energy reserves available to the body (7). The liver plays an important role in cholesterol metabolism. One study demonstrated that low serum cholesterol levels limit the immunological competence of immune cells by altering the structure of immune cell membranes, which may explain the correlation between low cholesterol levels and poor prognosis in patients with HCC (10).

Each component of the CONUT score is directly associated with liver disease (e.g., hepatitis, cirrhosis, HCC). A high CONUT score usually indicates a decrease in relative albumin, cholesterol, and lymphocyte count, indicating reduced immune capacity and poor nutritional status. Each component of the CONUT score is now considered to play a key role in the occurrence, development, and progression of HCC. The application of CONUT score to account for the three biomarkers described above may provide clinicians with a more accurate and comprehensive index for immunological and nutritional status, which may explain the superiority of CONUT over other individual biomarkers as a prognostic factor in patients with liver disease.

References

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3. Tokunaga R, Sakamoto Y, Nakagawa S, et al. CONUT: a novel independent predictive score for colorectal cancer patients undergoing potentially curative resection. Int J Colorectal Dis 2017;32:99-106.

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nomogram to predict overall survival of patients with HBV-associated hepatocellular carcinoma after curative hepatectomy. Clin Transl Oncol 2019.
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8. Yao W, He JC, Yang Y, et al. The Prognostic Value of Tumor-infiltrating Lymphocytes in Hepatocellular Carcinoma: a Systematic Review and Meta-analysis. Sci Rep 2017;7:7525.
9. Ding W, Xu X, Qian Y, et al. Prognostic value of tumor-infiltrating lymphocytes in hepatocellular carcinoma: A meta-analysis. Medicine (Baltimore) 2018;97:e13301.
10. Kritchevsky SB, Kritchevsky D. Serum cholesterol and cancer risk: an epidemiologic perspective. Annu Rev Nutr 1992;12:391-416.

Changes in the text:

We added these sentences to the **Discussion** section:

"Meanwhile, cirrhosis-induced pancytopenia may reduce the lymphocyte count."

"Meanwhile, the liver plays an important role in cholesterol metabolism."

"Each component of the CONUT score is directly associated with liver disease (e.g., hepatitis, cirrhosis, HCC). A high CONUT score usually indicates low serum albumin, low cholesterol, and low lymphocyte count, indicating reduced immune capacity and poor nutritional status. Each component of the CONUT score is therefore considered to play a key role in the occurrence, development, and progression of HCC. Use of the CONUT score to account for the three biomarkers described above may provide clinicians with a more accurate and comprehensive index for immunological and nutritional status, which may explain the superiority of CONUT over other individual biomarkers as a prognostic factor for patients with liver disease."

Comment 3:

Is the following a mistake? P6 line 4: moderate (2.5-4.9) →2.5-2.99 ? P11 line 3: Figure 3B→ 2B ?

Reply: We appreciate the reviewer's careful review. We apologize for these two typographical errors. We have corrected these typographical errors in the revised manuscript. Thank you very much.

Changes in the text:

P6 line 4: "moderate (2.5-2.99)"; P11 line 3: "Figure 2B".

Reviewer B:

Comment 1:

Well considered.

This paper is useful for future treatment planning.

Reply: We appreciate the kind comments and positive feedback provided by the reviewer for our work. We cherish the opportunity to revise the manuscript.