Is transarterial embolization plus two-stage hepatectomy the optimal strategy for the treatment of spontaneous rupture of hepatocellular carcinoma?

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We were intrigued to read the retrospective study by Wang *et al.* "*Propensity score matching study of 325 patients with spontaneous rupture of hepatocellular carcinoma*" (1) published in the latest issue of *Hepatobiliary Surgery Nutrition*. The authors elaborated the extremely significant conclusion that transarterial embolization (TAE) plus two-stage hepatectomy might be the optimal treatment for spontaneous rupture of hepatocellular carcinoma (RHCC) patients, whose overall survival (OS) and disease-free survival (DFS) aren't significantly different compared with non-ruptured hepatocellular carcinoma (NHCC) patients undergoing hepatectomy, and had a better prognosis than other treatment, including TAE alone and one-stage hepatectomy. We highly appreciate the author's research results. However, when we read the document, there were some shortcomings.

Firstly, we observed that the author presented inappropriate interpretations of *Tab. 1*. Before propensity score matching (PSM), the author stated that the parameters such as maximum tumour diameter, microvascular invasion (MVI) and Child-Pugh grade were higher in RHCC than in NHCC. Other variables, including haemoglobin, albumin and cirrhosis, were lower in RHCC than NHCC. At the same time, in the discussion, the authors thought that MVI incidence and

tumor-node-metastasis (TNM) stage were higher in RHCC than that in NHCC patients before PSM. In our opinion, it can only be explained that there is no statistical difference between the above parameters in *Tab. 1*. In other words, the results between these continuous parameters cannot be compared numerically.

Secondly, we have a couple of questions about the article. It is well known that there is a wide variety of treatment modalities for RHCC. We noticed that the author only used the word "main treatment" to perform the multivariate Cox analysis in *Tab. 3*, and did not elaborate on the comparison of treatment modalities. Since the different treatment results in a different outcome, we would like to know whether the "main treatment" stands for TAE alone or for single-stage hepatectomy compared with TAE + two-stage hepatectomy. Then, the authors formulated this significant conclusion that the risk of death for patients with RHCC who underwent one-stage hepatectomy was 1.545 times that of patients who underwent TAE + two-stage hepatectomy (*Tab. 3*). It is therefore advisable for researchers to provide a more detailed explanation of 'main treatment' in *Tab. 3*. Meanwhile, we noticed numerical errors in the results on in-hospital mortality of RHCC patients: the authors reported the mortality rate of RHCC patients as 0.8% in the abstract of the article,

while it was reported as 0.9% in the OS analysis. We were of the opinion that the researchers should double-check the results of the manuscript. In the survival analysis, we also found several inconsistencies between the figures and the tables. In the cohort studies after PSM, the 3- and 5-year OS rates for the NHCC patients who were treated conservatively were zero in *Tab. 4*, while their survival result contradicts that in *Fig. 2*. Similarly, the 5-year OS rates for the NHCC patients who received TAE alone were zero in *Tab. 4*, whereas their survival outcome did not match that in *Fig. 3*.

Thirdly, the survival prognosis and optimal treatment for RHCC patients are still controversial. In this retrospective research, the RHCC patients with TAE followed by two-stage hepatectomy were only 30 cases, which accounted for 9.2% of all the RHCC patients. However, 52% of RHCC patients underwent single-stage liver resection. Although the authors used the PSM analysis, we felt that there was a high degree of bias in this conclusion due to the small size of the sample. Therefore, we considered the data to be insufficient to conclude that TAE followed by two-stage hepatectomy might be the optimal choice for RHCC patients. Apart from this, we found that the author overlooked a problem with the time interval from diagnosis to hepatectomy, which might have an impact on the survival of those who underwent TAE + two-stage hepatectomy. Zhang *et al.* (2) showed that the RFS in the hepatectomy alone group (one-stage hepatectomy) was significantly better than that in the two-stage group (TAE + two-stage hepatectomy) (P=0.031). For this phenomenon, the researchers took into account that the median time between diagnosis and hepatectomy was significantly longer in the two-stage hepatectomy group than in the one-stage hepatectomy group. In addition, the authors also emphasised that the early resection of RHCC and the removal of haematoma and intra-abdominal haemorrhage may reduce the risk of post-operative recurrence and improve the long-term prognosis. More importantly, intrahepatic spread or distant metastasis of tumour cells due to delayed hepatectomy was probably the main reason for the poorer RFS in two-stage hepatectomy. Moreover, the authors described in the discussion that "treatment of radiofrequency ablation should be considered if bleeding persists after TAE treatment". We would therefore like to know what the evidence-based medicine view is on this therapeutic strategy.

In conclusion, we would like to thank all the authors for their excellent contributions to the exploration of the optimal treatment plan for RHCC patients. In our opinion, the treatment of RHCC needs to be comprehensively evaluated according to the patient's condition and tumour characteristics, and in clinical practice, doctors should choose different treatment options according to the different situations of RHCC patients. In addition, we hope that the author will add the experiments to compare the prognosis of RHCC patients and obtain more accurate and reliable scientific conclusions.

Acknowledgments

Footnote

References

1. Wang W, Meng T, Chen Y, et al. Propensity score matching study of 325 patients with spontaneous rupture

of hepatocellular carcinoma. Hepatobiliary Surg Nutr 2022;11:808-21.

2. Zhang W, Zhang ZW, Zhang BX, et al. Outcomes and Prognostic Factors of Spontaneously Ruptured Hepatocellular Carcinoma. J Gastrointest Surg 2019;23:1788-800.