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Letter to the editor

Comment on: Acute rejection after liver transplantation is less common, but predicts better prognosis in HBV-related hepatocellular carcinoma patients

Dear Editor;

We read the recent article "Acute rejection after liver transplantation is less common, but predicts better prognosis in HBV-related hepatocellular carcinoma patients" published by Mao and colleagues with great interest [1]. The authors stated that preoperative tumor-related immunosuppression may persist after liver transplantation (LT) in HCC patients, and reduce the incidence of acute rejection (AR). We would like to share our opinion and criticisms about this valuable work.

We would like to point our concerns regarding the author's immunosuppressive treatment strategy that includes 28-day course of corticosteroids and tacrolimus which is than is switched to sirolimus. Fairfield and colleagues [2] showed that protocols including steroids have a risk of AR that is reduced by 1.33 folds when compared to steroid-free protocols or in protocols in which the steroids are discontinued during postoperative early period. We prefer to give steroids for three to six months (preferably 3 months) with a dose of 5 mg/day and give appropriate doses of vitamin D and calcium supplements based on bone mineral density measurements.

There are various opinions regarding the use of calcineurin and mammalian target of rapamycin (mTOR) inhibitors in the post-LT period. mTOR inhibitors are given in order to reduce the dose of calcineurin inhibitors to avoid side effects of calcineurin inhibitors and to increase patient and graft survival in non-HCC patients. mTOR inhibitors are used for their antineoplastic effects which provides a reduction in the risk of tumor recurrence in HCC patients. We have some concerns regarding the switch of the calcineurin to mTOR inhibitors as the authors proposed. We usually prefer a combination of calcineurin inhibitor and mTOR inhibitor for patients transplanted for HCC and also in patients transplanted for benign conditions who experienced calcineurin inhibitor related nephrotoxicity in the postoperative period. We usually start with standard combination therapy for immunosuppression therapy including calcineurin inhibitors, antimetabolites and steroids. We then discontinue antimetabolites in the postoperative first month and start mTOR inhibitors in patients transplanted for HCC. If the patient experiences nephrotoxicity due to calcineurin inhibitors, we discontinue antimetabolites and reduce the calcineurin inhibitors' dose and start the mTOR inhibitors regardless of the postoperative timing of the patient. In studies comparing the everolimus +tacrolimus combination therapy to tacrolimus alone showed that although there was no significant difference in terms of glomerular filtration rate, overall survival and graft loss rates, the acute rejection episodes were significantly lower in the everolimus + tacrolimus combination therapy [3–6]. In studies which tacrolimus is switched to everolimus monotherapies, the AR episodes increased significantly and they had to stop that arm of the study [4,5]. We usually prefer to add everolimus to tacrolimus-based protocols as the in the postoperative first month to prevent adverse effects on wound healing and we adjust the doses in order to reach trough levels of 5–8 ng/ml for tacrolimus and 3–5 ng/ml for everolimus. As a result, we reduce the risk of AR by using a combination therapy and we can avoid adverse effects of tacrolimus by reducing its dose by adding a lesser nephrotoxic agent; everolimus. The authors state that they start pulse steroid therapy to patients diagnosed with AR and if the patients is steroid resistant, they repeat the biopsy and start either anti-lymphocyte globulin or anti-thymocyte globulin therapy. In our opinion the authors are referring to acute cellular rejection. The authors should state their rates of antibody mediated rejection (AMR) or plasma cell rich AR; furthermore, the authors should give the frequencies of AMR, the number of AR episodes or the chronic rejection rates among the 56 patients with AR. Because the classical management protocols do not have an effect on these later types of AR [7,8].

The authors state that in patients with HCC, the incidence of AR increases after the posttransplant first month; while the incidence of AR is highest within the postoperative first month for non-HCC patients. In our opinion, the increased incidence of AR in patients with HCC after the first postoperative month can be explained by the delayed interval between removal of the tumor and gradual decrease in the intensity of the immunosuppressive environment created by the tumor. In fact, if the correlation between AR and biologic characteristics of the tumor such as serum levels of alfa-feto protein levels, Des-gamma carboxyprothrombin are analyzed, the effect of the tumor burden on development of AR can better be understood.

In our opinion there may be some mistakes in the statistical analysis of the variables expressed in Table 1 provided by the authors. we have recalculated the results and summarized them in Table 3. The risk of AR in HBV + benign end-stage liver disease (BESLD) group in the first month is 2.29 higher when compared to HBV + HCC group. In other words, there is no subjective tendency as the authors have stated [1]. We detected a difference in the favor of the HCC group only in the posttransplant first month. If Table 2 and the statistical method of mentioned study are analyzed, it is seen that the authors should have used repeated variance analysis. However, we could not see any results regarding this analysis neither in the table nor in the results section of the manuscript. The authors have stated that they have used manual grouping for the study groups which is a significant source of bias. This risk would have been eliminated if the authors used propensity score matching.

Analysis of the Tables 3 and 4 shows that the authors have classified the 128 patients with HCC according to Up-to-7 and Hangzhou criteria and they have compared the groups in terms of AR and immune-inflammation status. Furthermore, Tables 5 and 6 shows that they performed a univariate and multivariate analysis of the impact of compatibility of the tumors with Up-to-7 and Hangzhou criteria on patient survival. There seems to be

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Table 1
Comparison of HBV + HCC and HBV + BESLD groups in terms of postoperative acute rejection.

	HBV + HCC group ($n = 372$)	HBV + BESLD group ($n = 226$)	X^2	OR	95%CI	P	Phi
Total AR			0.457	1.26	0.72–2.20	0.499	0.289
Acute rejection (+)	32 (8.6)	24 (10.6)					
Acute rejection (−)	340 (91.4)	202 (89.4)					
Within 1 mo			3.855	2.29	2.06–4.90	0.050	0.088
Acute rejection (+)	12 (3.2)	16 (7.1)					
Acute rejection (−)	360 (96.8)	210 (92.9)					
Beyond 1 mo			0.691	0.64	0.27–1.49	0.406	0.042
Acute rejection (+)	20 (5.4)	8 (3.5)					
Acute rejection (−)	352 (94.6)	218 (96.5)					

Statistical analysis was performed by SPSS using Yates continuity correction. OR calculated with Medcalc. References group: HBV + HCC.

serious error that has been made regardless of the content of the article. As it is known very well that Zheng and colleagues [9] have defined the Hangzhou criteria in 2008. However, this study is retracted by the editorial board of the journal in 2019 [10]. This decision to retract this study was based on the foundations of an editorial titled "Organs from Executed people are not a source of scientific discovery" which was written by the editor in chief of the same journal [11]. Zheng and colleagues have not responded to this retraction which is a sort of proof that inappropriate donors had been used in their study. For this reason, the authors cannot use the Hangzhou criteria for classification of the HCC tumors in the present study. We believe this fact should be noted for historical purposes.

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Ethical approval

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Consent

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CRediT authorship contribution statement

Akbulut S and Sahin TT: Reviewed the literature and wrote the manuscript. Akbulut S and Sahin TT: Supervised the writing process and revised the manuscript.

Research registration

Not applicable.

Guarantor

Akbulut S and Sahin TT, are the guarantors for the present commentary and they take full responsibility for the comments and the auxiliary data presented in the commentary article.

Declaration of competing interest

No conflict of interest about this letter to the editor.

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