

2- 34680 Answering Reviewers

1) Review: 00036318

RM: This is an interesting and well-written study and I recommend acceptance as it stands.

A: Many thanks!

2) Review: 02526287

RM: We read with interest the paper entitled "The Effect of Neuropsychiatric Medication on Pediatric Non-alcoholic Fatty Liver Disease" by Slowik et al ([NO°:34391](#)).

A: misrouted mail

3) Review: 00053433

RM1: This is an interesting cross-sectional study aimed at evaluating the incidence of herb-induced liver injury (HILI) following treatment with herbal Traditional Chinese Medicine (TCM). The manuscript is generally well written and has scientific value, given the recognized lack of data on the subject.

A: Many thanks!

RM2and3: Nevertheless, authors are kindly asked to consider the following comments and suggestions:

1. Although minor ALT elevations ($< 5 \times \text{ULN}$) can indeed prove to be clinically insignificant, those cases should not be excluded from the final analyses, since they can represent true HILI cases, albeit milder ones. In fact, ALT elevations $> 3 \times \text{ULN}$ with symptoms have traditionally been considered as clinically meaningful HILI cases. In addition, the time frame used for follow-up assessment (1-3 days before discharge) could have missed worsening toxicity during longer follow-up.
2. It is not clear whether causality assessment using RUCAM has been performed also in cases with milder ALT elevations (between 2 and 5 xULN). This would have been particularly important for symptomatic cases.

A: The focus of our study was on ALT levels $> 5 \times \text{ULN}$, considering thereby real HILI cases. Cases with ALT elevations between 2 and 5 x ULN are per definition not real but milder HILI due to treatment with TCM herbs, not requiring additional causality proof using RUCAM. As all patients with real HILI had a good outcome with ALT normalization during the relatively short follow-up periods, this favorable outcome can be expected also for patients with milder HILI.

RM4: The exclusion of pre-existing liver disease solely based on normal pre-treatment ALT levels, the exclusion of patients with abnormal ALT levels at baseline who could have developed clinically significant HILI (a separate analysis for those cases with ALT elevations > 3 times the baseline value would suffice), the exclusion of milder HILI cases (with ALT < 5

xULN, some of them probably symptomatic), and the application of causality assessment on patients exposed to herbal mixtures (and not to single herbs) are significant limitations of the study and should be briefly discussed.

A: A single normal pre-treatment ALT value likely excludes pre-existing liver disease, though little uncertainty remains, which would decrease rather than increase the overall frequency of HILI by TCM. By study protocol, patients with increased ALT values were explicitly not included, although it would have been of interest how TCM treatment influences increased pre-treatment ALT values.

RM5:

4. Authors are suggested to provide Tables 5 and 6 as supplementary material.

A: We cordially prefer keeping the table 5 in the main text, as these data are the juice of our paper, and transparent presentation in the main text is urgently needed and will prevent unnecessary discussions in the future. We agree to present table 6 as supplementary material.

Dear Prof. Fang-Fang Ji,
attached you will find reference No 45 replaced with a different reference.
Concerning ref. No. 26, Prof. Teschke confirmed that this book chapter is in press.
Please, look at the additional document attached. Further, I made a small correction
in "Research frontiers" at the end of the article.

Sincerely
Dieter Melchart