To the reviewers,

Thank you for your constructive and thorough review of our manuscript entitled “The epidemiology and outcomes of acute liver failure in Australia” submitted to World Journal of Hepatology.

Please find below responses to your questions and comments. All text changes have been highlighted in blue in the re-submitted manuscript.

Name of journal: World Journal of Hepatology
Manuscript NO: 48519
Title: Epidemiology and outcomes of acute liver failure in Australia
Reviewer’s code: 03471268

1. Although paracetamol toxicity is the most common aetiology of ALF, the rate of waitlisted for ELT is relatively low (11/84) and the percentage of TFS is higher (73.8%) compared to those in ALF induced by other drug or toxins. Does that mean ALF patients induced by other drugs or toxins are much more serious and need more attention?

AU: It is certainly true that paracetamol induced ALF behaves differently from non-paracetamol drug and toxin induced acute liver injury. This is highlighted in the King’s College Criteria where indeterminate hepatitis and non-paracetamol drug induced liver injury get an extra point of severity. The poor prognosis without transplantation of these two aetiologies has been added into the discussion (page 14). Similarly the use of King’s college criteria which differentiates transplant suitability based on aetiology has been added to the main text (page 6).

2. According to the authors, ELT are usually performed for severe cases without contraindication, is there any difference in OS after ELT for patients with different aetiology?

AU: Thank you for your comment. Outcomes following ELT based on aetiology would be interesting to assess. Outcomes after liver transplantation did not differ based on aetiology of ALF, however our sample size is too small to accurately answer this question. Only three patients with paracetamol induced ALF were transplanted. For non-paracetamol aetiologies, the overall survival to discharge from hospital was over 80% with no significant difference based on aetiology due to the small sample size.

Before making the decision about whether ELT is needed, is there any other critical factors needed to be considered for the doctors except for the clinical presentation? For example, the aetiology?

AU: King's College Criteria for acute liver failure were used to in this study to help predict the need for liver transplantation. This information has been added into the main text (page 6). King's College Criteria differs based on the aetiology of ALF with a separate criteria for paracetamol from non-paracetamol causes, with an extra point of severity for non-paracetamol drug induced liver injury. Therefore aetiology is taken into account. Other critical factors include any medical or psychosocial contraindications to transplantation which are detailed in the manuscript.

3. Paracetamol are usually taken by the patients combined with other products. In this case, how to determine that the ALF is caused by paracetamol rather than other drugs?

AU: Thank you for your comment. Paracetamol toxicity typically behaves differently from most other non-paracetamol drug and toxins causing acute liver failure. Certainly, in the case of polypharmacy overdose, other drugs may be implicated as a cause of acute liver failure. The retrospective nature of this study limits assessment, and therefore the decision about aetiology was determined by the treating team at the time based on the clinical presentation and history. This has been added to the methods section of the manuscript (page 8)

Reviewer's code: 03077466

This study focused on single-center data and needed to analyze more data or multi-center data. Why did not the author analyze the data from 1988 to 2017?

AU: Thank you for your comment. We acknowledge this our small sample size is a limitation to this study, however unfortunately no data from other Australian centres were available. The data from 1988 to 2001 has already been published (Gow et al. *J Gastro Hepatol*, 2004) and we thought it more appropriate to analyse new data and compare this to previously published data rather than representing data from the previously published series.

2. The author compared the current data to the historical data and should interpret more about the two groups of data.

AU: Only basic data were available for comparison from the historical series and hence further analysis was not performed. This data has been summarized in Table 2 and Table 3.

Reviewer's code: 03011567

1. Could the authors give information around wait list times in the cohort of patients listed for transplant? In particular in the 7 patients who died after ELT was there any difference in wait list times compared to the 35 survivors?

AU: Thank you for this comment. Unfortunately only days (not hours) on the waitlist are recorded on our unit database. The mean waitlist time was 4.7 days with a standard deviation of 5.3 for all patient undergoing transplantation. We don't feel the data is accurate given we only have information in days. There was no difference in wait times between those who died post-transplant and those who survived, however given it is only recorded in days, this is inaccurate and has therefore has not been added to the text. We acknowledge this is a limitation of the study.

2. In the not waitlisted for ELT cohort 27% of patients died who did not have contraindications for ELT - the false negative group. This compares to 11% of patients with spontaneous survival in patients who got listed for ELT. What criteria for listing were in fact used. Did they change over time? Could the authors provide some information about that.

AU: King's College Criteria has been used in both cohorts to assist with the decision to waitlist patients for liver transplantation. This has been added into the text on page 6. However, the exception to this is in paracetamol induced ALF where our unit protocol is to wait for 48-72 hours before listing this cohort of patients, given the high rates of spontaneous survival following paracetamol toxicity (page 15).

3. It would also be interesting to know how many patients did have evidence of increased ICP overall and has the incidence decreased over time as it has in the UK and the US?

AU: Thank you for this important comment. Only one patient in this cohort died of cerebral oedema (page 16). Details of death secondary to cerebral oedema were not available from the

historical cohort. Unfortunately results of intracranial pressure monitoring are not available. This is in part as the unit has moved away from using intracranial pressure monitoring, and using aggressive prevention and treatment strategies instead. This has been detailed on page 16 of the manuscript.