Reviewer’s report

Title: Extracorporeal liver support: trending epidemiology and mortality - A nationwide database analysis 2007-2015

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Reviewer: G. Auzinger

Reviewer's report:

Dr Wiesmann and colleagues report in this manuscript on Extracorporeal Liver Support (ELS) device use in Germany during a 9 year observation period.

This is an area of practice where there is paucity of RCT data for clinicians to take guidance from. It is an observational descriptive study which utilises nationwide data from the Federal Statistical Office which is a strength, as well as a weakness of the study. ELS use in Germany is not regulated per se but remunerated through a specific procedures code, therefore the authors were able to provide in detail information as to the exact number of device interventions undertaken during the observation period; at the same time there are major drawbacks relating to the descriptive nature of the investigation and paucity of detail in relation to diagnostic coding, as the indications and timing of device use particularly in relation to Liver Failure bridge to or use after Liver transplantation are far from clear.

The paper is reasonably well written but would benefit from critical appraisal by a native English speaking reviewer. There are expression / phraseology errors such as "ELS utilization and case-concomitant..." on page 3 or "provisioning of ELS" page 13, "was only a minor aspect in clinical practice" Discussion 2nd paragraph.

Major revision points:
2015 incidence rates of ELS quoted in the abstract don't match percentage figures given in the Results section of the manuscript or the Table.

The authors describe ALF in the Introduction however mix decompensated chronic liver disease and or AoCLF patients into this group. In fact most of the patients appear to have suffered from acute decompensation of CLD as in cirrhosis, rather than ALF. Preexisting chronic liver disease is in fact an exclusion criteria for ALF - Trey and Davidson Progress in liver disease 1970; Bernal and Wendon NEJM 2014.

The ALF definition given in the 2nd sentence of the Introduction is wrong (see above publications).

It maybe worthwhile grouping patients into hyperacute, acute and subacute LF (O'Grady Lancet 1993) depending on jaundice to HE interval to better risk stratify, which is of particular importance in relation to any attempts made to utilise ELS as "bridge to recovery".
The authors should attempt to not only group patients into primary liver support or secondary i.e. post CTS use of ELS, but also provide separate data for ALF as per internationally recognised definitions vs acute decompensation of CLD cases. This is particularly important when reporting on bridge to Liver Transplantation for HU cases or Emergency Liver Transplantation (ELT) as commonly referred to in the Anglo American literature.

ELS is not an established therapy as a "bridge to transplant" in ALF - Introduction page 5 - as the only RCT to that effect did not show a benefit of using MARS in that indication - FULMAR trial Saliba Ann Int Med.

The authors only talk about detoxifying devices, there are many cell based devices usually combined with detoxifying columns or modalities; although not really used outside RCT's this should be commented on in the Introduction and Discussion parts of the paper.

When talking about the use of detoxifying methods of ELS, high volume TPE should be mentioned as it is the only modality that has shown an outcome benefit in ALF patients in a RCT setting Larsen et al J Hepatology 2016. Is TPE used in Germany, or is there an OPS code for it?

The term "ischemic liver failure" or hepatitis has been superseded by "Hypoxic hepatitis" the authors should change terminology throughout the manuscript accordingly.

Are all the cases of secondary liver failure due to "hypoxic hepatitis" or are there patients with a predominant refractory hyperbilirubinemia phenotype? Presumably there is not enough granularity in the data available for interrogation to access this information; this should however be commented on in the Discussion. Hypoxic hepatitis is commonly reversible after restoration of flow and relief of right ventricular failure/dysfunction; there are however subsets of patients who develop refractory jaundice; this is a poorly understood pathology often multifactorial in etiology. Septic bile transporter defects, cofactors such as ongoing congestion of the liver, drugs etc possibly playing a role.

Outcome section Results: Apart from comparing "Primary vs secondary etiologies" it would be helpful to compare outcomes in the ALF vs decompensated CLD groups within the "Primary Liver failure" cohort. The authors document on the difficulties of getting information as to when ELS was used in the context of Liver Tx i.e. bridge to transplant vs postoperative support for graft dysfunction. This would have been very valuable as larger scale information regarding outcome of graft dysfunction treated with ELS is lacking.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?
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Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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Not relevant to this manuscript

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