Author’s response to reviews

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

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Author’s response to reviews:

Point-to-point reply
“Extracorporeal liver support: trending epidemiology and mortality” (BMGE-D-19-00070)

Dear Sirs or Madams,

Please find attached our revised manuscript and the point-to-point reply in this document.

We thank the reviewers and the editorial team for their constructive comments to improve the quality of our manuscript.

The revised version underwent a thorough revision by a native speaking colleague to adhere with the linguistic standards of BMC Gastroenterology. Changes within the revised manuscript were highlighted.

We believe, that it is now acceptable for publication in BMC Gastroenterology and interesting for the broad readership of the journal as it is the very first article showing incidences of extracorporeal liver support therapies, describes subpopulation (peri-transplantation, primary vs. secondary liver dysfunction) and crude mortality rates in the “real-life-setting”.

If any questions arise, please do not hesitate to contact us.

Yours sincerely,

PD Dr. Thomas Wiesmann
On behalf of all authors –
Point-to-point reply

Reviewer #1 (G. Auzinger)
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.

We thank Dr. Auzinger for his constructive efforts in improving the quality of our manuscript. We fully agree with him, that the nature of our “real-life data study” does not answer the full scope of questions regarding indication and timing (and intelligent avoiding) of these therapies in critically ill patients. Nevertheless, we believe that our manuscripts shows the effect of non-regulated therapeutic options in our country resulting in widespread use of this extracorporeal therapy in “non-classic” patients. Thus, in our revised manuscript we carefully addressed the relevant limitations mentioned by Dr. Auzinger and the other reviewers to give a balanced viewpoint on the data and thus, data related limitations. Additionally, we added a paragraph with some opinions regarding future study topics.

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.

We apologize for the inadequate language. The manuscript was revised again by a native speaker to improve readability and linguistic quality.

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.

Wrong numbers in the manuscript were corrected appropriately.

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).

We appreciate Dr. Auzinger’s commenting on using the correct terminology. Indeed, our first version mixed up the correct definitions in an (failed) effort to keep the manuscript short. The complete manuscript was thoroughly revised to explain the shortcomings of the federal statistical data to correctly identify the specific etiology (acute liver failure; acute-on-chronic liver failure, decompensated chronic liver disease) The related inability to adhere to the correct definitions of “acute
liver failure” in our study are addressed in the discussion section. Thus, we decided to use the term “liver dysfunction” throughout the manuscript to avoid confusion with the specific definitions of acute liver failure, AoCLF etc.

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.

We thank Dr. Auzinger for his comment on potential subgroup analysis. When we started the data extraction for this study, our idea regarding the potential subgroupings were almost identical to his recommendations. However, we had to learn that the ICD codings of the individual patient data that feeds the federal statistical office database fails to provide any helpful (or at least analyzable data) information regarding this important aspect of onset (acute, hyperacute or subacute) or definite classification (e.g. ALF, AoCLF, ESLD). Thus, we had to choose the applied strategy to analyze a primary and secondary liver failure group. As this was not mentioned appropriately in our first draft, we added this topic to our limitations section in the revised manuscript. Hopefully, this interesting topic is addressed by other working groups with access to prospective clinical registries or large-scale dealing with ALF (e.g. ALFSG registry), ACLF (e.g. CANONIC study data) etc.. However, our primary study goal was defining the real-world utilization of defined ELS therapies in our country as well as exploring the settings where ELS is used (“peritransplant”, secondary liver dysfunction related to cardiothoracic surgery). We added the ideas of potential subgroups for ELS research in the discussion section of our manuscript.

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.

We agree, that ELS is not an established bridge-to-transplant therapy option as the FULMAR trial showed no clear benefits. Nevertheless, several centers in Germany and other countries still do rely on ELS in this patient population. We therefore carefully revised the sentence to address this fact without mentioning the unclear evidence for it.

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?

We appreciate the reviewer’s commenting on further detoxifying agents. TPE is one of several therapeutic options used as treatment option for ALF in Germany. When we planned our study, we were therefore interested in this option as well. However, the specific OPS code 8-820 for “therapeutic plasmapheresis” also includes “immunadsorption and other related therapies” in the current (2019) OPS definitions. Thus, we tried but in the end were unable to differentiate specific hepatic indications (TPE) from myriads of other indications for this treatment modality due to missing granularity of the
underlying insurance data source. However, we added a few lines to address these interesting options within our manuscript.

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, co factors such as ongoing congestion of the liver, drugs etc possibly playing a role.

The term “hypoxic hepatitis is now used throughout the manuscript to adhere with current terminology. As the reviewer correctly assumed, the granularity of the data does not allow for identification of distinct etiologies within the patient population in our study. Thus, we now use the terms “liver dysfunction” and “secondary liver failure” to avoid any misunderstandings. However, as the manuscript aims to describe the current practice of ELS therapies in our country, this missing information is of minor interest for our study purpose. However, it will be a topic that needs to be addressed in future research. Thus, we added a line to our discussion section to point this out.

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.

As written above, the data source does not provide any information regarding the specific types within the “primary liver failure” group. We improved our discussion section to rule out more clearly, why our manuscript data cannot provide more detailed insights.

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.

We fully agree, that this information would be very interesting for the readership. However, our federal statistical data analysis does not give us any information regarding this topic. These questions might be answerable by using aggregated patient data from big transplant units using ELS as a therapeutic option. We added a line to the discussion section regarding this interesting topic.

Reviewer #2 (Fuat Saner)
Wiesmann et al conducted a retrospective study about using rate of liver support systems in Germany between 2007 and 2015. The aim of the study was to recruit epidemiologic data about about frequency use of liver assistant device and crude mortality and morbidity for this patient cohort. They found that between 2007 and 2015 a total of 2886 patients were treated within this time frame. Overall mortality was 51.49%, whereas male population suffered from a higher mortality. While in the first 7 years main indication was liver dysfunction, since 2012 liver support system was more used in cardiac surgery due to ischemic liver injury. The conclusion of the authors was that since 2007 the using rate of liver support systems remains stable, while since 2012 the indication moved from hepatologic patients more to cardiac surgery patients. There are some major concerns, which should be addressed. First of all the authors should be define, what kind of liver assist devices they aimed to evaluate. There
are biological and non-biological systems. Within the non-biological systems the most used in the recent 20 years was MARS, Prometheus (FPSA) and plasmapheresis. This is not clear in the text and should be figured out. You should compare each by each and do not put all devices together and talk about liver support.

We thank Dr. Saner for his efforts in reviewing our manuscripts to improve its quality. According to his recommendation, we added a brief overview of different liver assist device in the introduction section. As we analyzed a federal statistics office data set which is built from ICD and OPS encodings, we are limited in our ability to differentiate between different liver support types. Our starting point before analyzing the data was to give an overview of ELS utilization in Germany. As written in reply to reviewer #1, the OPS code 8-858 for “liver dialysis” does not differentiate between “MARS” and “Prometheus” as both have to be encoded with the same coding number. Therapeutic plasmapheresis has an unspecific coding in the OPS system which made it impossible to extract cases in which plasmapheresis was performed due to hepatic dysfunction. Thus, we are only able to give an overview of the “albumin dialysis” techniques. Bioartificial systems were not available in Germany outside study settings due to lack of approval by the responsible authorities. We revised our manuscript accordingly to point out this limitation more clearly.

Introduction: First sentence: "Acute liver failure (ALF) might occur in patients with preexisting (acute-on-chronic, 3 ACLF [1]) or non-preexisting (ALF) liver disease." Well ALF is clear defined as acute onset of liver dysfunction (transaminases at least 3 times above baseline), coagulopathy (INR > 1.5), jaundice and hepatic encephalopathy (see O'Grady, Gastroenterology 1989 and Lancet 1993). The EASL (European Society of study of the Liver) stratified patients in acute liver injury, which means acute hepatitis without encephalopathy and acute liver failure, which includes hepatic encephalopathy. ACLF is a distinct liver failure which is first figured out in 2013 (Moreau et al m Gastroenterology 2013).

We apologize for using the wrong terminology in the introduction section. Our data does not allow to categorize the patient population within different disease states. Thus, we revised the manuscript to eliminate any misleading terms. We decided to use the term “liver dysfunction” as discussed above.

Your statement that liver assist devices are poorly evaluated is not correct. Only for MARS you will find more than 500 pubmed citation. Please remove this statement. Line 10: "detoxification functions (e.g. hyper-ammonemia and other protein-bound molecules) 10 to improve morbidity and mortality." Ammonia is not protein bound, It is a very small molecule, can easily diffuse between different cells. Ammonia can also easily removed with hemodialysis. Your statement that Liver assist devices is an established treatment option is also not correct. It is a possible treatment, but till today, beside the high-volume plasmapheresis (Larsen, J Hepatol 2016) no device had shown any benefit on survival. Discussion p. 12, line 21. It is the FUMAR and not FULMAR study.

Changes were made as suggested. We revised the complete introduction section.

Moreover you cannot compare blind your patient population (by the way you did not mentioned, what kind of patients they are) with the FUMAR study, where all patients were listed high-urgency and transplanted within 16 h.

We decided to mention some mortality rates of previous ELS trials (and the underlying liver dysfunction) in our discussion to show, that the high mortality rates are typical in these severely ill patients. Our aim was not to make any comparisons to demonstrate any benefits of a specific therapy.
We revised this section to avoid this misunderstanding and hope, that it is now acceptable.

Moreover, the use of any kind of liver support in cardiac failure does not make any sense. The cited studies in your manuscript provides a limited number of patients (13 against 14 and 14 against 14). In the study of 2004 there was no benefit, just bilirubin improvement and the other in MARS group there was a decreased 30 day mortality. I suppose that in 90 days almost 90% of the patients will pass However, the main issue in these patients is the recovery of the heart, which seems to be successful particular

We fully agree with the author, that the ELS use in the cardiac surgery population is more than questionable. We mentioned the retrospective observations by Sparks et al and Banayosy et al. to point out, that ELS therapies are performed in this specific setting (without giving any personal rating of this approach) without any evidence. One of our study goals was simply to describe the fact, that ELS therapies are performed in this subpopulation and that these numbers are increasing. Therefore, our first and current manuscript draft closes with the remark, that ELS applications should be restricted to study settings to avoid futile extracorporeal therapies in clinical practice.

The whole manuscript has some potential for improvement. My suggestion are stratifying the patients device depending and according the diagnosis. It is impossible to put all patient and liver assist devices together and try to get a conclusion.

We thank Dr. Saner for his helpful comments on improving the quality our manuscript. However, we kindly have to refuse his proposal as we are unable to extract the dedicated diagnosis for individual patients from our federal statistics office’ data set. Our primary study goal was to deliver the very first “real-life” data on ELS utilization and not to draw conclusions regarding outcome benefits of ELS therapies for dedicated disease states. With our data, we are able to describe incidences as well as distributions of age and gender. Temporal trends were explored. Moreover, we show that ELS therapies are widely used outside “typical” indications of primary liver dysfunction. The increasing ELS utilization in the secondary liver dysfunction subpopulation is a questionable trend that was never described before in literature. Thus, we believe that our manuscript has a relevant value as it gives insights into the real-life use of these extracorporeal therapies in liver failure patients, call it a “past and current state of affairs regarding ELS-usage in Germany” if you wish.

Reviewer #3 (Norman Leslie Sussman)

The manuscript by Wiesmann et al. describes the use of extracorporeal liver support in Germany from 2007 to 2015. The paper is interesting in that it demonstrates the ongoing use of an expensive technology that has no proven benefit, demonstrated by several controlled trials, and referenced in this manuscript. To their credit, the authors suggest that ELS be used only in clinical trials.

We thank Prof. Sussman on commenting of our manuscript. As he mentioned, we tried to balance the discussion in our revised manuscript as there is an area of friction regarding the specific patient populations that might benefit from such a purification therapy.

As an aside, I feel that purification devices such as MARS should not be termed liver support since they have no liver function. The weaknesses of the paper are the limitations of the data as acknowledged by the authors. The paper will benefit from minor editorial revisions.
Terminological changes were made in the revised manuscript as recommended by all reviewers to adhere with current scientific and clinical terminology. We screened the current literature for the exact terminology of different extracorporeal therapies. Despite the fact, that MARS & Co. do not “support or assist the liver” or even “replace” it as correctly mentioned by the reviewer, all these different terms are currently used throughout literature (by the way: even after a Pubmed screening searching for publications by the three respective reviewers, there were > 7 different categorial names). The German OPS code literally translates into “liver dialysis” which is only rarely used in academic literature. The MeSH term for these therapies is “artificial liver” which is also potentially misleading. In the end, we decided to adhere to the term “extracorporeal liver support (ELS)” within the revised version and would like to ask the editors to give a final recommendation on this topic.

Our discussion section was expanded to fully address relevant limitations. Finally, proof reading was performed by a native speaker to reach an adequate linguistic standard.