FIRST REVIEWER

- It is a well written review on a topic where the research is ongoing.

Response: The authors wish to thank the reviewer for the comments, and the proposed corrections which have helped us improving the quality of our manuscript.

- The available data on modalities like Plasma exchange should be depicted in a tabular form. Similarly summary of available guidelines and any systematic review or meta analysis should be mentioned

Response: Table 2 was created, containing data from available guidelines, systematic reviews, meta-analyses or clinical studies included in our review. It presents summary of available guidelines, systematic reviews or meta analyses, or RCTs not only for Plasma exchange, but also for all the modalities included in our review.

- The discussion maybe enhanced by addition of the following : a. Chen, Y., Han, T., Duan, Z. et al. Clinical application of artificial liver and blood purification: expert consensus recommendations. Hepatol Int 17, 4–17 (2023). https://doi.org/10.1007/s12072-022-10430-8

Response: Table 3 was created, modified from this article, containing the main characteristics of liver replacement therapy systems presented in our review, with the addition of intended population to treat with these systems.

Thank you again for the time and effort spent for our manuscript!

SECOND REVIEWER

- This is a nice narrative review on extracorporeal devices in the setting of acute liver failure and acute on chronic liver failure. The paper is of interest and is well written. Table 1 is informative.

Response: The authors want to express their gratitude for your comments. Their accuracy is greatly appreciated.

- A main issue, in my opinion, is the actual applicability of such devices in clinical practice. In my opinion, only few patients with ALF and ACLF may receive a great benefit from these devices. This point should be discussed.

Response: Indeed, the reviewer's comment is to the point. Only a few patients will benefit and it is difficult to identify them. This subject is analyzed in depth in the 4th paragraph of discussion: ''A key point to this approach……. Nevertheless, proper validation of indications and application of suitable tools for identifying these patients represent fields for thorough future research.''

- Side effects / complications / contraindications are not properly discussed. For instance, patients with ACLF may suffer from hypotension, volume overload.

Response: Table 3 was adapted, containing in detail side effects / complications / contraindications of each method.

- Inflammation is one of the main drivers of ACLF, therefore removal of some inflammatory molecules as interleukines may be clinically relevant. However, it is not clear if the (temporary) removal of some of these molecules may change the underlying pathways, thus modifying prognosis. In other words, it is not clear if these devices could serve as game changers in patients with ALF/ACLF.

Response: This reviewer's comment is also to the point. We analyzed current data from liver failure pathophysiology and from the impact of the removal of inflammatory molecules by these systems on the course of the disease and on its prognosis in the 1th paragraph of discussion: '' Pathophysiologically, liver failure is regulated by immune-mediated… The clinical impact of the effect of LRT systems on the imbalance between pro- and anti-inflammatory mediators in liver failure remains unclear, and further studies are warranted in this field.''

- It would be interesting to see if Authors consider extracorporeal devices only as bridge to transplantation, thus reserving their applicability only in patients having this option.

Response: This interesting point is discussed in detail in the last paragraph of the discussion: '' At this point of time artificial LRT systems mostly serve as bridging therapies towards LT…. Ideally, the experience from RRT should be adapted, where technological progress and cost deterioration from widespread use have made RRT widely available, practically for every patient that needs it.'' We believe in widespread use of LRT systems, not restricted to patients with the option of liver transplantation, and we explain how we believe that this can be achieved.

- The Authors said that applicability of LRT is often underused due to lack of comparative trials. What can be the right setting, according to the Authors' view? Who should be enrolled (ACLF, ALF, both?). What should be the primary endpoints of these trials (overall survival, transplant-free survival, reduction of ACLF-grades, others)?

Response: The authors' point of view regarding the design of trials for ALF and ACLF and the more suitable endpoints of these trials is discussed in detail in paragraphs 6-7 of discussion: '' It is worth noting that the impact from the application of LSSs on OS and TFS remains unclear because of the lack of data…… and could present an interesting alternative for assessing the impact of LRT on patients' health status.

- I think that a brief explanation about differences in pathophysiology between ALF and ACLF should be added, also for non-expert Readers.

Response: Differences in pathophysiology between ALF and ACLF were added: '' pathophysiology of liver failure, which presents certain features that differentiate ACLF from ALF. More specifically, ACLF is a clinical syndrome that is characterized by the acute decompensation of chronic, pre-existing liver disease, usually led by a precipitating event, such as an underlying infection and is often accompanied by multiorgan failure (MOF) and high mortality. The basis of the pathophysiological mechanisms in ACLF is the hyperinflammatory state, which is triggered by factors called pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) [2]. On the other hand, ALF represents a life-threatening condition that is usually the result of an offending agent, such as medications or viral infections in patients without pre-existing liver disease. It is characterized by an overwhelming systemic inflammatory response, hepatocyte necrosis and accumulation of bile acids and ammonia, which can lead to permanent liver damage, encephalopathy and cerebral edema [3,4].''

- The point about CRRT for isolated hyperammonemia without AKI should be discussed more in depth.

Response: A more detailed presentation of this indication of CRRT, without AKI in these patients was added: '' Renal replacement therapy (RRT) is often necessary in these patients either due to concomitant renal failure or due to a liver indication, in most cases hyperammonemia. Hyperammonemia is a common metabolic disorder, which is associated with cerebral edema and elevated intracranial pressure, especially in patients with ALF and rarely in those with ACLF. In fact, due to the serious complications associated with hyperammonemia, mainly regarding HE and cerebral edema [8], prompt initiation of RRT is indicated even in the absence of renal failure, when this serious metabolic derangement is present at these patients [8,9]. Although no specific cut-off for the initiation of RRT exists based solely on this indication, the majority of the studies suggest it's initiation when the value of ammonia is thrice greater than the upper limit of normal, or greater than 200 μmoles/L or when the patient shows severe encephalopathy [9].''

- I think that some data about emerging techniques (DIALIVE, and perhaps CARBALIVE) should be mentioned.

Response: A paragraph, with these emerging techniques was added:

''***Carbalive and Dialive***

Bacterial translocation remains one of the major causes for disease-related morbidity and mortality in patients with ACLF. An established method of prevention is the use of oral antibiotics, which are poorly absorbed by the gastrointestinal tract, however this approach comes with increased resistance and cost. CARBALIVE is a novel, non-antibiotic related intervention, which is under investigation. It consists of a microporous carbon absorbent, which is orally administered and removes bacterial endotoxins from the bowel, thus preventing the harmful consequences of inflammation, which usually accompanies bacterial translocation. Recent trials revealed positive preliminary results in patients with decompensated cirrhosis, while CARBALIVE seems to be safe and well tolerated. Another novel option for endotoxin removal and bridging to transplant in patients with ACLF is DIALIVE. It represents a dual filtration system. One filter removes toxin products from bloodstream and the other one removes and replaces albumin. Preliminary results are promising in terms of safety and tolerability. Data for both of these two modalities still need to be validated in larger randomized clinical trials [95].''

- In my opinion, the Authors rightly discussed about costs. Nevertheless, also indirect costs (e.g., patients must be treated in ICU, albumin supplementation is costly if protracted for long-time...) should be considered.

Response: The very interesting point of indirect costs was discussed in more depth in the 3th paragraph of discussion: '' Costs included in table 1 mainly regard direct costs from the use of each method, not including the expenses that emerge from the rest of the support that these patients require. However, indirect costs from ICU / HDU hospitalization that represent a significant burden worldwide [96], including albumin supplementation, antibiotic administration for hospital-acquired infections (a very frequent complication for these patients) and maintenance of the above-mentioned expensive health-care facilities, are not included. On the other hand, keeping these patients alive until LT is available while reducing their morbidity and mortality is another parameter that must be taken into consideration. Of note, there are studies that find these therapies cost-effectively superior to standard medical therapy alone [50]. Thus, the exact balance between cost and effectiveness of application of these methods remains to be elucidated.''

Thank you again for helping us to improve our work!

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Response: An English-speaking expert, Oikonomou KG, performed new English Editing for the revised manuscript (the original manuscript was edited by a professional English language editing company).

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

Response: Thank you for processing our manuscript. All the necessary changes have been performed to upgrade our manuscript's quality.

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Clinical Cases. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response: Thank you for processing and reviewing our manuscript. Your remarks and corrections are of great value!

Indeed, after thorough new search of the international bibliography, and with reference to your advices, the latest cutting-edge research results were added, for better improvement of our manuscript's value. 9 more references were added, making our reference list updated and complete.