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When Is a Critically Ill Cirrhotic Patient Too Sick to Transplant? Development of Consensus Criteria by a Multidisciplinary Panel of 35 International Experts

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Abbreviations

LT: Liver Transplantation

ACLF: Acute on Chronic Liver Failure

ICU: Intensive Care Unit

SOFA score: Sequential Organ Failure Assessment score

MELD: Model for End-stage Liver Disease

Abstract

Background

Critically ill cirrhotic patients are increasingly transplanted, but there is no consensus about futile liver transplantation (LT).

Therefore, the decision to delay or deny LT is often extensively debated. These debates arise from different opinions of futility among transplant team members. This study aims to achieve a multinational and multidisciplinary consensus on the definition of futility in LT and to develop well-articulated criteria for not proceeding with LT due to futility.

Methods

Thirty-five international experts from anesthesiology/intensive care, hepatology and transplant surgery were surveyed using the Delphi method. More than 70% of similar answers to a question were necessary to define agreement.

Results

The panel recommended patient and graft survival at 1 year after LT to define futility. Severe frailty, and persistent fever or less than 72 hours of appropriate antimicrobial therapy in case of ongoing sepsis were considered reasons to delay LT. A simple assessment of the number of organs failing was considered the most appropriate way to decide whether LT should be delayed or denied, with respiratory, circulatory and metabolic failures having the most influence in this decision. The thresholds of severity of organ failures contraindicating LT for which a consensus was achieved were a PaO₂/FiO₂ ratio <150 mmHg, a norepinephrine dose >1 µg/kg/min and a serum lactate level >9 mmol/l.

Conclusion

Our expert panel provides a consensus on the definition of futile LT and on specific criteria for postponing or denying LT. A framework that may facilitate the decision if a patient is too sick for transplant is presented.

Introduction

Liver transplantation (LT) of critically ill cirrhotic patients with extrahepatic organ failure is becoming more frequent.^{1,2} While short-term transplant-free mortality of such patients is extremely high without LT, their posttransplant outcome is merely good.^{1,3-6} Therefore, it is difficult to determine if patients are too sick to be transplanted and the definition of futile transplantation remains controversial.⁷ One-year survival rates reported for the most severely ill patients such as Acute on Chronic Liver Failure (ACLF) grade 3 differ significantly between studies, ranging from 44 to 83%.^{5,6,8,9}

The variability in outcomes may be due to the retrospective design of those studies as well as to a selection bias. Furthermore, patients which are too sick to be transplanted may have been excluded before considering this therapy. Conditions such as ongoing sepsis were not specifically evaluated, and there was no guidance whether LT could have been considered inappropriate or not. Therefore, it remains difficult to assess the posttransplant prognosis of these severely sick patients and to identify patients in which LT would be futile. In daily clinical practice, each decision of delaying or denying LT is extensively debated, with different individual views on futility of transplant. These vary by cultural believes, availability of resources and the specialty of the transplant provider (ie, hepatologist, intensivists/anesthesiologists or surgeon). The differing views on who is too sick to transplant affects the individual patient and also impacts on overall posttransplant outcome as well as on waitlist mortality of non- or less critically ill cirrhotic patients.

The aim of this study is to achieve a multinational and multidisciplinary consensus on the posttransplant outcome that should define futility of LT and on specific criteria that should postpone or deny the access of a patient to LT. A panel of experts were surveyed using the modified Delphi method, a recognized anonymous process used to establish consensus for clinical questions among healthcare professionals.¹⁰⁻¹³

Materials and Methods

The Delphi method used in this study used expert opinion applied to successive iterations of a given questionnaire. The goal was to encourage convergence of opinions and to identify dissent or nonconvergence. The process was conducted using previous recommendations on the Delphi method.^{14,15} This study was supported by the Liver Intensive Care Group of Europe (LICAGE). A scientific committee composed of C. P.B., F.S. and E. W. developed the questions and analyzed the answers. This study was exempt from approval from an ethic's board.

Selection of the expert panel

Fifty international experts with peer-reviewed publications on this topic and/or guidelines were selected (by C. P-B. (intensivists), F. D (hepatologists) and O. S. (transplant surgeons) and received an invitation to participate in October 2018. Among them, 35 agreed (response rate 70%) and were included in the Delphi process during the 3 rounds of an electronically distributed Delphi method. The study was opened in December 2018 and concluded in May 2019. The final panel included 16 intensive care practitioners/anesthesiologists, 12 hepatologists and 7 transplant surgeons. Twenty-four (69 %) experts were from European centers (9 countries) and 11 (31 %) experts worked in non-Europeans centers (Figure S1, SDC, <http://links.lww.com/TP/B962>).

Delphi process

The content validity was examined using the keywords 'acute on chronic liver failure' AND/OR 'liver transplantation' AND/OR 'futility' from the literature review. These were used to identify outcomes consistent with futile or potentially inappropriate LT and with pretransplant factors influencing decisions to transplant a critically ill cirrhotic patient previously listed for LT. Different types of factors were assessed such as patient background, clinical situation before ICU admission, sepsis as precipitating event and assessment of organ

failure. During the 3 Delphi rounds, questionnaires (supplementary methods) were delivered electronically with automatic reminders until members of the expert panel returned a finished questionnaire. A short summary describing the conclusions from the previous round and the aim of the following one were provided.

Likert scales were initially used in most questions to quantify the degree of agreement between respondents. This was then frequently followed by a binary (yes/no) question to confirm the percentage of agreement among the panelists. A consensus was defined as more than 70% agreement in answers, based on Kendall's W coefficient of concordance indicating a satisfactory agreement when its value is 0.7 or greater.¹⁰ A space for written comments was left after each question; if a specific point was raised by the experts, it was included in the development of questionnaires for the following round.

From the possible methods of consensus-building, a modified Delphi methodology was chosen because it is well suited to group interactions involving different geographic sites and panelists do not need to meet in person. The anonymous nature of Delphi was considered as a key factor in avoiding a result that could be skewed by 1 or more persuasive panelists.

Statistical analysis

Results are displayed as mean \pm SD measuring concordance and discordance among the raters, or numbers (percentage). The association between the answers of the experts and their specialty and/or nationality was investigated using Kruskal Wallis, Mann Whitney and chi-square tests. Analyses were handled using IBM SPSS Statistics version 22.0 (IBM, Armonk, New York).

Results

Agreement on outcomes that define futility or inappropriateness of liver transplantation

The expert panel agreed on outcomes to determine futility. Ninety-seven percent of the experts agreed that outcomes should include both patient and graft survival. This showed panelist thought it was important to consider not just the individual patient but also the collective benefit of all patients awaiting transplantation. The experts selected 1 year survival following LT as the optimal time frame for futility assessment (83% of similar responses). Ten (28%) experts suggested that poor posttransplant quality of life was also an important patient-centered outcome and could be a useful variable to assess futility. However, all agreed that posttransplant quality of life was difficult to predict prior to transplantation.

Criteria for contraindications or delay of LT listed patients and admitted to an ICU for acute deterioration of liver failure

Next aim was to identify criteria that could postpone or even deny LT due to futility.

Patient history or clinical conditions before ICU admission

In a list of pretransplant conditions, panelists were asked if each individual condition might contraindicate LT. The panel could not reach a consensus on whether or not advanced recipient age should contraindicate LT; 55% of panelists thought age was not a limiting criterion, even if over 70 years (63% of similar responses only). Furthermore, only 57% of experts considered sarcopenia as contraindication for LT.

In contrast, 88% of the panel agreed that frailty of ICU patients prior to LT was an important variable to assess transplant eligibility of critically ill cirrhotic patients. Ninety-two percent of the experts agreed that severe frailty, i.e. completely dependence for personal care, (clinical frailty scale ≥ 7) is a contraindication for LT¹⁶ (Figure S2, SDC, <http://links.lww.com/TP/B962>).

Summary: The Delphi panelists recommended denying LT in case of severe frailty. No consensus was reached regarding the age of the recipient.

The role of infection in liver transplant candidacy

The type of precipitating event leading to ICU admission was important to 72% of panelists. In particular, ongoing sepsis was thought to be a contraindication or reason to delay LT in 88% of the panelists. Criteria for ongoing sepsis include a persistent fever higher than 39°C, leukopenia lower than 500/mm³ and a history of respiratory tract infection or of spontaneous bacterial peritonitis appropriately treated for less than 72 hours (Table 1). Interestingly, leukocytosis and urinary tract infection (independent of the duration of antimicrobial therapy) were not considered as contraindications for LT. In total, 71% of panelists agreed that patients previously infected with Pan Drug Resistant (PDR) *Enterobacteriaceae* (ie, nonsusceptible to all agents in all antimicrobial categories) should not be transplanted. Conversely, previous infections with eXtensively Drug-Resistant (XDR) or multidrug resistant (MDR) *Enterobacteriaceae* were not considered as a contraindication.¹⁷

Summary: Ongoing sepsis was considered a contraindication to immediate transplantation. Panelists thought spontaneous bacterial peritonitis and respiratory tract infections should be treated with appropriate antimicrobials for at least 72 hours before proceeding with LT. Previous infection with PDR (but not XDR or MDR) *Enterobacteriaceae* was considered as contraindication.

The role of pretransplant organ failure scores in LT candidacy

The panelists were asked to rank their impression of the value of severity of illness score for deciding whether to proceed with transplantation by assigning a value from 1 (worst) to 4 (best) (Figure 1A). The highest ranked score was the simplest one that was based on the number of organ failures (mean value 3.4 (SD, 0.1)). The ACLF grade which was specifically developed for cirrhotic patients) was also highly scored (mean 3.1 (SD 0.2), higher than

“general” Sequential Organ Failure Assessment (SOFA) score.^{18,19} The MELD score was deemed the least useful (mean 1.9, SD 0.1), Figure 1A). The ranking of the scores did not vary by specialty nor nationality of the experts.

Summary: The panelists agreed that LT candidacy should consider immediate pretransplant number of organ failures. The ACLF score was the highest ranked for patient assessment before transplantation

The role of the type of organ failure for the decision to delay or deny LT

To evaluate the effects that each organ has on the decision to proceed or delay LT, we asked for input on 7 distinct organ systems. Panelists ranked each according to their importance (from 1, the least important to 7, the most important) for their impact on the decision process to proceed with LT (Figure 1B). Three organ systems were ranked with much higher mean scores than the others. These were respiratory failure assessed by PaO₂/FiO₂ ratio (mean (SD)= 5.4 (1.5)), circulatory failure assessed by vasopressor (epinephrine and norepinephrine) requirements (mean (SD)= 5.3 (1.6)) and metabolic failure defined as increase of lactate concentrations (mean (SD)= 4.7 (1.4)) (Figure 1B). Failure in these 3 organs were, by consensus, considered essential in the decision making process (86, 83 and 72% of agreement among experts for respiratory, circulatory and metabolic failures respectively). Conversely, the experts attributed a score below 3 (across the range 1-7) to liver and coagulation failures suggesting that they had little impact on transplant decisions. Finally, no agreement was reached about the role of renal and neurological failure criteria (respectively 53 and 63% of similar responses). Of note, the ranking of these organ dysfunctions varied significantly according to the specialties of the experts (Figure 1C). Renal failure was more important for hepatologists than for other specialties, and cerebral failure was judged relatively less important (Figure 1C).

Summary: A consensus was reached ranking respiratory, circulatory, and metabolic failures as essential considerations in determining LT candidacy.

The influence of the severity of respiratory, circulatory and metabolic failures on LT candidacy

Eighty-nine percent, 91% and 72% of the panelists agreed that either severe circulatory, respiratory or metabolic organ failure alone would contraindicate LT. Threshold values for norepinephrine dose, PaO₂/FiO₂ ratio and serum lactate levels that influenced decision-making were benchmarked. Consensus was achieved regarding PaO₂/FiO₂ ratio < 150 mmHg (Figure 2A) and norepinephrine levels > 1 µg/kg/min (Figure 2B) as values sufficient to postpone LT. Although serum lactate values were more variable, 81% of panelists considered a serum lactate level above 9 mmol/l as a contraindication for transplantation (Figure 2C). Threshold values for norepinephrine that panelist thought contraindicating LT differed according to specialties; surgeons accepted higher thresholds than other specialists (Figure 2D). Likewise, the thresholds of PaO₂/FiO₂ and serum lactate chosen by the panelists also varied according to their countries of practice: French experts accepted very high lactate levels more frequently than the other European experts (p=0.04, Figure S3A). Panelists from the US tended to be more permissive regarding the PaO₂/FiO₂ ratio (p=0.09, Figure S3B, SDC, <http://links.lww.com/TP/B962>). Finally, a trend towards an improvement or stability of the clinical course (for example no increase in lactate levels and norepinephrine doses and no decrease of PaO₂/FiO₂ ratio) was considered as a prerequisite for proceed with LT by 71% of the experts.

An algorithm derived from the Delphi process for deciding to proceed with or postpone LT in critically ill patients criteria is shown in Figure 3.

Summary: A threshold of PaO₂/FiO₂ ≤ 150 mmHg, norepinephrine dose ≥ 1 µg/kg/min and lactate level ≥ 9 mmol was considered a contraindication to LT. A trend towards an

improvement or stability of the patient's clinical course was considered as essential to proceed to LT.

Discussion

An interprofessional liver transplantation Delphi panel agreed on endpoints to identify futility of LT in critically ill candidates. These included patient and graft survival at 1 year after LT. Consensus was also reached about specific patient conditions, ongoing sepsis and intensity of organ failures that could justify to delay or cancel LT. Using these criteria, an algorithm that may help clinicians to determine if LT could be futile and should be delayed or denied for critically ill transplant candidates was proposed.

Various endpoints have been used to assess LT futility in the literature, most of them relying on post-LT patient survival at different time points.^{7,20} The expert panel suggested that in the current era of allograft shortage, the collective utility, this means the pool of potential candidates who might not receive a life-saving graft due to the realization of a futile LT should also be taken into consideration. The combined endpoint of 1-year patient- and graft survival allows to select patients which will most benefit from transplantation, without recognition of futile transplantation, defined as death or graft failure. More than one-fourth of the experts considered post-LT quality of life as an appropriate patient-centered surrogate marker to help in the decision about transplantation futility. This assessment is however subjective and often not feasible because requiring to ask patients in the early phase of their disease what they would consider a meaningful quality of life.

Previous studies suggested specific pretransplant conditions to help decide if a cirrhotic patient admitted to the ICU is too sick for transplantation.^{20,21} Our experts agreed that frailty was the only preoperative condition that would delay or deny LT. Complete dependence from personal care (severe frailty (clinical frailty scale ≥ 7)) was considered as a contraindication to LT. This is supported by literature data which suggest that severely frail

patients have significantly more postoperative complications.^{16,22} Age (even over 70) was not a limiting criteria, suggesting functional status is more important for outcome. Surprisingly, the experts also did not consider sarcopenia as a contraindication to LT although the extensive Kyoto studies by Kaido et al report a significantly lower short-term outcome in sarcopenic liver recipients.²³ The findings of their study including 72 recipients needs further confirmation.²³

Sepsis is one of the most frequent precipitating events of ACLF but also a frequent reason for delisting or denying LT in critically ill patients.^{8,24} However, survival without transplant of these patients is poor.²⁵

For this reason, objective criteria are required to stratify between patients with good or bad outcome. The experts agreed on some specific criteria, such as duration of appropriate antimicrobial therapy that should be met before proceeding to LT in patients with ongoing sepsis. The source of infection was also very important in decision-making; while respiratory tract infection and spontaneous bacterial peritonitis should be appropriately treated for at least 72 hours, urinary tract infection was not recognized as contraindication. This distinction is supported by a previous study that showed that urinary tract infections have a lower impact on ACLF outcome.^{8,26} A history of previous infection with a pan-drug resistant *Enterobacteriaceae* (ie, nonsusceptible to all agents in all antimicrobial categories) was considered a contraindication for LT. This is notable because antimicrobial resistant infections in this population are likely to increase and question the access to LT in the future.²⁷ Persistent fever > 39°C and leukopenia lower than 0.5 g/l were also deemed sufficient to delay LT in patients with ongoing sepsis. The panel likely chose these 2 criteria as they reflect a still evolving infectious process and an immunocompromised status that may both hamper post-LT prognosis.²⁸

Several organ-failure scores, designed to predict outcome of critically ill cirrhotic patients, have been assessed for the prediction of posttransplant survival. A recent study by Sundaram et al indicated that MELD score in patients with multiple organ failure does not accurately predict post LT survival.¹ The panelists are of the same opinion and conclude that MELD score should not be used to postpone or deny LT. ACLF grade was the highest valued score, but a simple assessment of the number of organs failing was deemed to be the best tool to potentially delay or cancel LT in these patients.⁸

Not all types of organ failure were considered to be of equal importance. The highest weight in the decision to proceed or not with transplantation was given to respiratory failure followed, in order of importance, by circulatory and metabolic failure. Respiratory and circulatory failures have been shown to significantly affect post-LT survival in several studies.^{1,4,29} In contrast to the vast majority of studies that only rely on mechanical ventilation and vasopressor requirements to define respiratory and circulatory failure, specific thresholds that reflect the severity of organ failure ($\text{PaO}_2/\text{FiO}_2$ ratio < 150 mmHg and norepinephrine level $> 1\mu\text{g}/\text{kg}/\text{min}$) and that can be used by the clinicians to help in the decision to transplant or not, are provided in the here presented survey. The $\text{PaO}_2/\text{FiO}_2$ ratio threshold chosen by the experts was more permissive than the $\text{PaO}_2/\text{FiO}_2$ ratio < 200 mmHg that predicted a poor post-LT outcome in 2 previous studies.^{29,30}

Metabolic failure assessed by serum lactate levels reflects alterations of numerous metabolic functions (eg, mitochondrial dysfunction) involved in the pathogenesis of ACLF.³¹ Notably again, the threshold (> 9 mmol/l) chosen by the experts to contraindicate LT is higher than the lactate levels above 4 or 5 mmol/L reported in the literature to be associated with worse posttransplant outcomes.^{29,30} This perhaps reflects the experts' unease with denying sick patients a chance at LT despite indicators of poor outcomes.

Interestingly, the threshold dose of norepinephrine chosen by the experts for LT varied according to their specialty, surgeons being more liberal than their other team colleagues. The thresholds of PaO₂/FiO₂ ratio and serum lactate also differed according to the experts' country of practice, reflecting cultural heterogeneity among regions regarding LT in critically ill cirrhotic patients.

The relatively low impact of coagulation and liver failure on post-LT outcome in ACLF may explain the marginal importance assigned by the experts to these criteria.³² The relevance of renal and cerebral failures could not be determined. Different specialties generated different opinions: the hepatologists considered renal failure more and cerebral less important, probably reflecting their dominant role in treating such comorbidities.

Finally, in accordance with the recent study of Huebener et al. showing that the clinical course of ACLF before LT is an important factor predicting postoperative outcome, the experts agreed that a worsening of the clinical situation at time of allograft offer should delay or contraindicate LT.³³

As with any modified Delphi process, this study has some limitations. It was impossible to capture all the potential conditions or circumstances that may be part of the decision making process to proceed or not with LT.

For instance, it was opted to focus on listed patients and active alcohol use or comorbidities such as coronary disease or obesity were not taken in consideration. This consensus mainly addressed deceased-donor LT, as this is the most common clinical practice of the members of our expert panel. Nevertheless, some high-volume transplant centers from Asia report favorable 5-year survival rates in living-donor liver transplantation for ACLF patients.⁶ Finally, the here presented methodological process requires to be validated. While some of the experts' conclusions are corroborated by existing data from the literature, additional studies using different approaches are warranted. The differences in expert opinions by

specialty and by country of practice were limited by the number of panelists. They should also be confirmed by an international assessment of liver transplantation practice in ACLF patients.

This study provides a consensus on the posttransplant outcome that should define futility of LT and on specific patient conditions, ongoing sepsis and intensity of organ failures that may justify to cancel or postpone the transplantation LT. A framework including these criteria is provided in order to make a difficult decision easier in case a patient is too sick to be transplanted. This work may pave the way for a better use of the scarce liver allograft in critically ill cirrhotic patients.

ACCEPTED

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Figure Legends

Figure 1. Organ failure-based scores and types of organ failures ranked according to the relevance for the decision whether or not a critically ill cirrhotic patient should be transplanted

A. Ranking of different organ failure scores. A score from 1 to 4 was attributed to every score by experts according to the relevance for the decision whether or not a critically ill cirrhotic patient should be transplanted (4 as highest priority and 1 as the lowest). Results are given as mean (\pm SD) score obtained by each endpoint

B. Ranking of types of organ failures. A score from 1 to 7 was assigned to every type of organ failure by experts according to the relevance for the decision whether or not a critically ill cirrhotic patient should be transplanted (4 as highest and 1 as lowest priority). Results are presented as a mean (\pm SD) score obtained by each endpoint

C. Ranking of types of organ failures according to the specialty of the experts

Figure 2. Threshold reflecting the severity of respiratory, circulatory and metabolic organ failures that should contraindicate LT

A. PaO₂/FiO₂ thresholds reflecting respiratory failure

B. Norepinephrine level thresholds reflecting circulatory failure

C. Serum lactate thresholds reflecting metabolic failure

D. Norepinephrine level thresholds chosen by the experts according to their specialty

Figure 3. Algorithm for the decision of liver transplantation in critically ill cirrhotic patients with multiple organ failures.

SBP: Spontaneous Bacterial Peritonitis, PNE: Pneumonia

Table 1. Consensus situations in which an infection could lead to postponing LT

Criteria (at the time of graft proposal)	Similar response rate
Persistent fever >39°C	89%
Leukopenia < 500/mm ³	74%
Pneumonia treated with less than 72 hours of appropriate antimicrobial treatment	88%
Spontaneous bacterial peritonitis treated with less than 72 hours of appropriate antimicrobial treatment	71%
Previous infection due to a pandrug resistant <i>Enterobacteriaceae</i>	72%

Figure 1

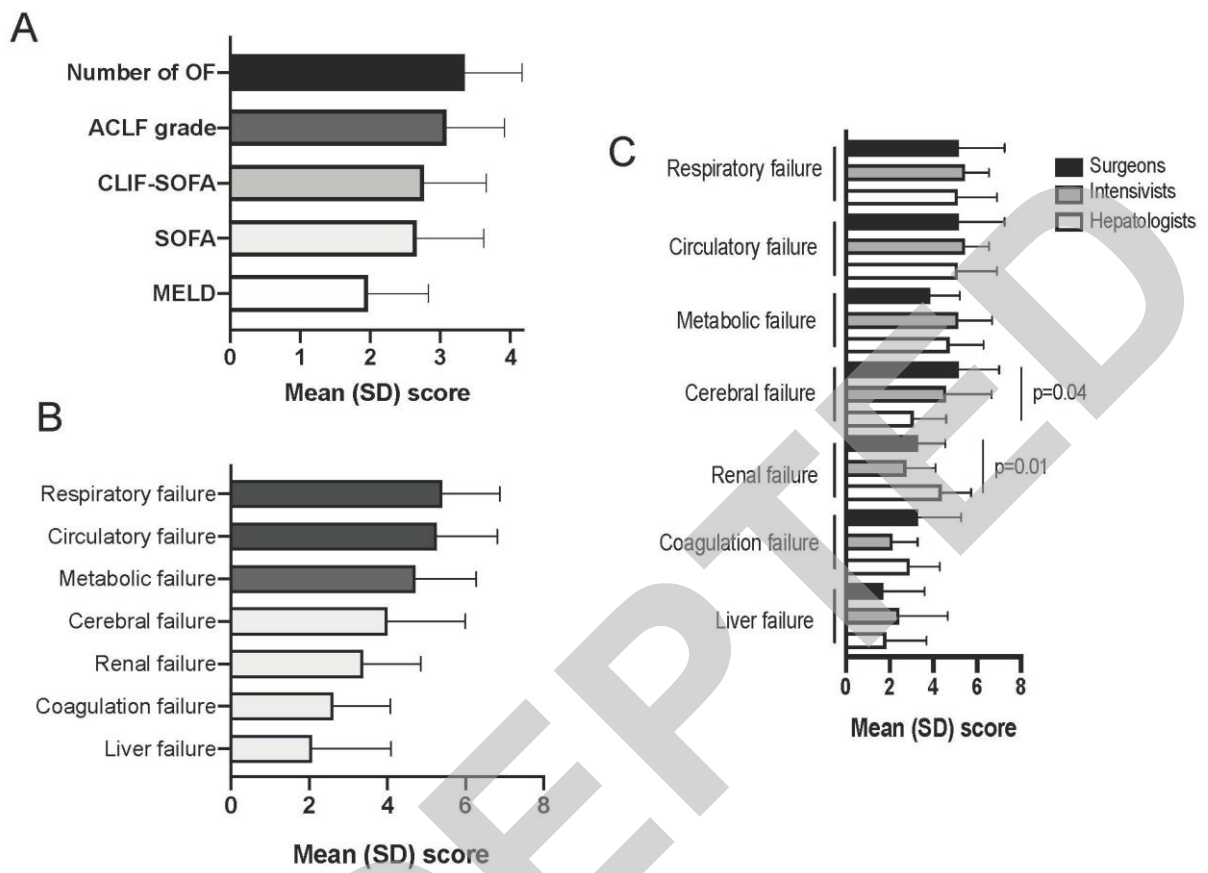


Figure 2

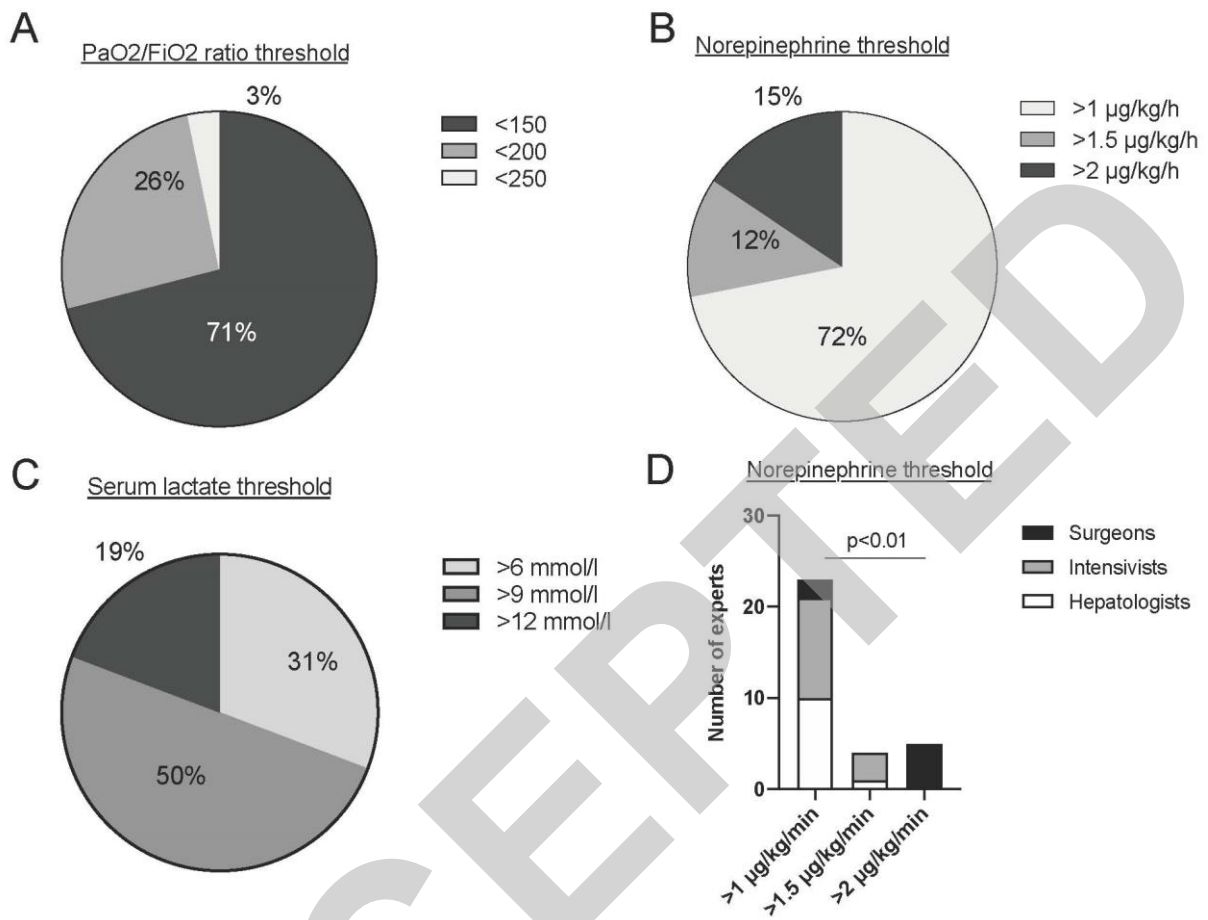


Figure 3

