Limitations of Current Liver Donor Allocation Systems and the Impact of Newer Indications for Liver Transplantation.

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Keypoints:

- There is an urgent need to modify the MELD-based models to reduce the waiting list mortality in patients with severe decompensation of cirrhosis and acute-on-chronic liver failure.
- Liver transplantation can significantly improve survival in patients with acute-on-chronic liver failure.
- Gaps remain regarding our understanding of optimizing survival among patients with severe decompensation of cirrhosis and acute-on-chronic liver failure, both before and after liver transplantation.
- To optimize patient survival after liver transplantation for acute-on-chronic liver failure we should determine how to prioritize those on the waiting list based on a scoring system able to predict in whom liver transplantation would be futile.
- NASH-related acute-on-chronic liver failure is an emerging issue which will require particular attention and prospective studies to understand the mechanisms leading to it, and to develop specific prevention and management.
- Early liver transplantation in patients with severe acute alcoholic hepatitis significantly increases survival rates compared to patients who are denied transplantation, if performed under stringent selection criteria.
- Gender, geographical disparity and the use of donors positive for different viruses still persist as the main areas of controversy in a liver transplant setting.

Abstract

Liver transplantation represents a life-saving treatment for patients with decompensated cirrhosis, a severe condition associated with the risk of dying while on the waiting list. When decompensation occurs rapidly in the presence of extrahepatic organ failures, the condition is called acute-on-chronic liver failure, which is associated with even higher risk of death, and liver transplantation can also markedly improve the survival of these patients. However, gaps remain regarding our understanding of priority and organ allocation as well as optimizing survival among patients with acute-on-chronic liver failure, both before and after transplant. Moreover, it is urgent to address inequalities in access to liver transplantation in severe alcoholic hepatitis and in NASH patients. Several controversies still exist on gender and country disparities as well as on the acceptance of suboptimal donor grafts. The aims of this review are to provide a critical perspective on the role of liver transplantation in these patient groups and address areas of uncertainty.

Introduction

Although more than 50 years have passed since the first liver transplant, with decade after decade improvement of organ and patient survival results, we are still discussing some aspects related to priority on the waiting list, to the severity score(s) of liver disease, and the management of severe decompensation of cirrhosis while waiting for a suitable graft. We then discuss if a transplant is always feasible in these cases (concept of futility). Whether donors with non-optimal characteristics can always (or should) be used independently of (or depending on) the clinical condition of the recipient. And lastly, in the panorama of indications for transplantation that is constantly evolving, how should we standardize access at European and international level? This is the common thread of the article.

1. Prognostic models

1. Prognostic models for allocation and new scoring systems

Liver transplantation (LT) represents a life-saving treatment for patients with decompensated cirrhosis (DC). DC is a severe condition and is associated with an average 15% risk of dying while on the waiting list (WL). When decompensation occurs rapidly in the presence of extrahepatic organ failure(s), this condition, labeled as acute-on-chronic liver failure (ACLF), is associated with even higher risks of death while on the WL compared to stable decompensation [1]. In these rapidly deteriorating scenarios, timely LT needs to be considered. However, there is an ongoing debate about which allocation model serves the best interest of patients with DC as LT candidates. Allocation models for predicting WL mortality or drop out need to be based on unbiased criteria including objectiveness, simplicity, repeated reproducibility, and short- (3 months) and mid-term (1 year) prediction of risk of death. Under this consideration, the Child-Pugh score is compromised due to the subjective interpretation of its clinical model variables of ascites and encephalopathy [2]. The first allocation model to overcome the limitation of non-objectivity was the introduction of the Model of End-stage Liver Disease (MELD) system [2]. Initially, MELD was developed to predict mortality after placement of a transjugular intrahepatic portosystemic shunt [3]. First introduced in 2002 in the USA and subsequently in most other countries, the majority of LT programs practice MELD-based allocation which prioritizes the sickest patients on the WL. Despite the advantages of the MELD score towards a more objective decision tool, the initially reported discriminatory model performance with a *c*-statistic of 0.78-0.87[4] has recently been revised to lower discriminatory ability in European patients with DC (*c*-statistics 0.65-0.68) [5, 6] (Table 1). The declining accuracy of the MELD score was also reported in DC patients listed for LT. In a recent study based on UNOS data [7], the c index of MELD was 0.7 in patients listed between 2014 and 2016. This observation probably reflects major epidemiological changes on the WL over the last decade, with more DC patients listed with very advanced liver diseases, and an increasing proportion of patients listed for HCC, fiercely competing with DC for organ allocation. Furthermore, two groups of listed

patients with DC might have additional disadvantages under a MELD-based allocation policy. Decompensated patients with MELD scores <15 have almost no chance of access to LT and patients with intermediate scores of 25-30 have a higher, 20-25%, risk of WL mortality. Therefore, there is an urgent need to modify the MELD-based models with improved prediction of WL mortality. Although the MELD score reflects dual organ function of liver and kidney, other important conditions and/or organ functions impacting the medical acuity of the decompensated patients are not captured by the score [8]. Some biomarkers reflecting inflammation (ferritin, CRP, white blood cell count (WBC)), cardiac (copeptin, proBNP) or renal dysfunction (NGAL, cystatin C), and portal hypertension (sCD 163, Von Willebrand Factor) have recently been identified as adding some independent predictive values to MELD (Table 1). One other important element expands to malnutrition and sarcopenia. Sarcopenia, which is a loss of muscle mass, is the main clinical result of malnutrition. A recent study of 630 patients awaiting LT demonstrated that insufficient protein intake was associated with an increased risk of mortality while on the WL [9]. Another recently published study found that sarcopenia was associated with WL mortality especially in low-MELD patients (MELD score ≤15) [10]. These findings highlight the need to include nutritional assessment data in allocation models.

Attempts have been made to combine such predictors with MELD to improve prediction. Examples are the Sodium MELD [11], the composition of Sodium MELD and frailty index [12], the MELD and sarcopenia score [10, 13], which seems to outperform MELD notably in patients with MELD <15 [13]. Supporting this approach, the USA adopted the Sodium MELD score in 2016 as a further tool to reduce WL mortality. Also, in acute DC, the CANONIC-driven, Chronic Liver Failure Consortium (CLIF-C) AD model, combining white blood cell count, as a marker of systemic inflammation, with age and some sodium MELD components (INR, serum sodium and creatinine) has recently proven more accurate than MELD for prediction of 3-month mortality in DC [5]. Patients who fall into the dynamic category of ACLF with rapid decompensation and associated organ failures appear to have a better prediction of prognosis using new models based on

extrahepatic organ failures associated with liver disease. The pioneering CLIF C –driven CANONIC study [14] proposed diagnostic ACLF criteria that included the presence of organ failures. In this study, patients with ACLF had a 3-month mortality rate of 51%. A subsequent follow-up study using a six-organ failure assessment of liver, kidney, brain, coagulation, circulation, and respiration (CLIF-C organ failure sore) found a significantly better prognostic prediction in ACLF patients than the MELD score [5] (Table 1). A detailed discussion of allocation of organs to ACLF patients is proposed in the next section.

We anticipate that a future super allocation score should capture important recipient factors such as organ failures or dysfunctions (Table 1), global nutrition (sarcopenia) and physical performance (frailty) as well as chronic conditions (comorbidities) and should be directed to a more personalized allocation approach. Further refinement of allocation models needs to take both donor as well as recipient factors into account in order to serve both principles of equity (sickest first) and efficiency (maximization of utility) for the best possible allocation. Although such models have been developed [15-18], the vast majority of the current allocation models do not include donor factors. The transplant benefit [15] may also be considered to prevent futile use of organs. A very specific model integrating transplant benefit, that is weighing expected survival on the WL with mortality post LT, has recently been adopted in the UK. This model, called the Transplant Benefit Model, deserves careful evaluation but may pave the way to other innovative approaches for allocation.

2. Outcome of liver transplantation in patients with ACLF

LT can markedly improve survival in patients with ACLF, with 1-year post-transplant survival exceeding 80% [1, 19, 20]. However, gaps remain regarding our understanding of optimizing survival among patients with ACLF, both before and after LT.

2.1 Organ Allocation Policy among Candidates with ACLF

The current organ allocation policy gives highest priority to candidates with status-1A designation, while subsequent classification is based on MELD-Na score. However, this may not fully account

for mortality in patients with ACLF-3, partly because the MELD-Na score does not capture several of the extra-hepatic organ failures that may be present in the ACLF-3 setting (Table 2) [1, 21, 22]. One study from UNOS database demonstrated that patients with ACLF-3 and a MELD-Na score <25 have greater 90-day mortality than patients without ACLF and a MELD-Na score ≥35 (Figure 1a) [1]. This discrepancy may be related to a combination of mortality risk associated with the development of circulatory or respiratory failure, along with a perceived futility in full supportive care due to lower priority for transplantation. A follow-up study from the same database demonstrated that in a cohort of transplant candidates with a MELD-Na score ≥ 35, mortality was still higher among patients with ACLF-3, particularly those with 4-6 organ system failures, despite having similar priority for LT as patients with lower ACLF grades [22] (Figure 1b). Recently, data from an investigation of the Veterans Administration database corroborated these findings [21]. Utilizing standardized mortality ratio (SMR) to compare observed and expected mortality, the authors determined that the SMR was significantly higher for patients with ACLF versus decompensated cirrhosis, and furthermore, the SMR increased with rising grade of ACLF [21]. Finally, findings from another analysis indicated that patients with ACLF-3 have a greater risk of 14-day mortality relative to candidates listed status-1A, again independent of MELD-Na score [23]. Further investigation is therefore warranted regarding whether the presence of extra-hepatic organ failures should be incorporated into organ allocation policy, to reduce WL mortality.

2.2 Outcomes after Liver Transplantation

Outcomes for patients with ACLF at transplantation are variable due to the heterogeneity among studied populations. Initial data from the CANONIC study revealed a 75% 1-year post-LT survival among 25 patients transplanted with ACLF, of whom 38% had ACLF-3 and none had respiratory failure [24]. In another single center retrospective study of 140 transplanted patients with ACLF, of whom 30 had ACLF-3 at transplantation, the 90-day post-LT survival was 84.5% for those transplanted with ACLF-1, 77.2% for patients with ACLF-2, and 60% among recipients with

ACLF-3. Multivariable analysis determined the presence of ACLF at LT to be the strongest risk factor for post-transplant mortality [25]. More recent studies have demonstrated better outcomes. In a multi-center European study of over 250 patients transplanted with ACLF, and 73 patients transplanted with ACLF-3, 1-year survival was above 83% among all grades of ACLF [19]. It should be noted that individuals in this study who were transplanted with ACLF-3 were selected carefully, and those who had hemodynamic instability, acute respiratory distress syndrome, active gastrointestinal bleeding or uncontrolled sepsis were denied LT [19]. In a separate multi-center investigation of 152 patients in Europe, the following variables indicated high risk of 1-year mortality for patients transplanted with ACLF-3: age $\geq$ 53, leukocyte count $\leq$ 10G/L, lactate level 4 and the presence of mechanical ventilation with acute respiratory distress syndrome [26]. The authors derived the transplantation and multi-organ failure (TAM) score, allocating 1 point for the presence of each of these variables. A TAM score > 2 indicated a less than 10% post-LT survival at 1 year, while a score $\leq$ 2 was associated with a 1-year survival of 83.9% [26].

Several large studies from the UNOS registry have supported these findings, demonstrating a 1-year post-LT survival above 80%, even among recipients with 4-6 organ system failures at transplantation. In two studies from the UNOS registry, the requirement for mechanical ventilation at the time of LT was one of the strongest risk factors for 1-year post-transplant mortality among patients with ACLF-3 at the time of transplantation [1, 20], yielding a 10% decrease in survival rate (75.3% vs 85.4%), with only marginal improvement if utilizing a higher quality donor organ (76.5%) or transplanting within 30 days of listing (76.5%) [1]. A separate study of the UNOS database has revealed age to be a strong prognosticator for post-transplant survival among patients with ACLF-3, as transplantation of patients with ACLF-3 above the age of 60 yields a 1-year survival of 74.9% [27]. Regarding long-term survival outcomes after transplantation, one study has shown a 5-year survival after LT above 67% for transplanted patients with ACLF-3 [28]. Furthermore, after the first year post-LT, the percentage decrease in survival was similar among all ACLF grades [28].

3. Emerging and special subgroups

3.1 NASH and ACLF

NASH is an emerging disease and is becoming one of the leading indications for LT in the USA and a growing one for LT in Europe. NASH is strongly, but not-exclusively, associated with the dysmetabolic syndrome epidemic and is commonly associated with obesity, diabetes type 2, hypertension and dyslipidemia. These cofactors of NASH are also associated with cardiovascular diseases, particularity in NASH patients. The natural history of NASH is well described and its evolution can lead to DC and HCC. There is only a little information on the development of ACLF in NASH patients. In a recent study from the USA there was an increase in admissions for ACLF over the last years among patients with cirrhosis (5.9% between 2006 and 2014). There was a 63% increase of ACLF in NASH patients (3.5% in 2006-2008 to 5.7% in 2012-2014) vs. a 28% increase in patients with alcohol-related cirrhosis (5.6% in 2006-2008 to 7.2% in 2012-2014) and a 25% increase in patients with liver diseases from other etiologies (5.2% in 2006-2008 to 6.5% in 2012-2014). NASH-related ACLF patients had longer mean length of stay, and more frequent use of dialysis [29]. Obesity and type 2 diabetes were associated with liver disease progression [30].
In a recent study of LT in Europe, NASH represents 4% of the indications for LT between 2002 and 2016, with a regular increase and representing 8.4% of the indications for LT in 2016 [31]. In a study from the USA, the new registrants due to NASH were increasing by 170%, representing the second indication for LT. LT patients with NASH on the WL were significantly younger, had significantly higher BMI, higher frequency of diabetes, there were a higher proportion of woman in comparison to other indications [32, 33]. In a recent study from the USA, looking at all LT recipients from 2005 to 2016 in the UNOS Database, NASH represented 21.9%, 18.9% and 17.8% of recipients with ACLF1, ACLF2, and ACLF 3, respectively [1]. Interestingly, NASH represented 20.8% of the LT recipients without ACLF. This suggests that the percentage of NASH among LT recipients is quite stable according to the presence of ACLF or not. One particular point of patients with NASH is the risk of associated severe diabetes type 2, of severe or morbid obesity, and of

cardiovascular disease. This will require a rapid and intensive work-up in these patients. Obesity and type 2 diabetes have been associated with a higher risk of infection and a higher rate of drop out from the WL for LT. Prophylactic antibiotics therapy may be required in NASH patients with ACLF. The management of morbid obesity is quite complex, in some patients, an advantage has been suggested by performing a sleeve gastrectomy during surgery for LT, however this has been limited to expert centers in the management of obesity and has not been performed in patients with ACLF [34]. Therefore, it appears that NASH-related ACLF is an emerging issue which will require particular attention and prospective studies to understand the mechanisms leading to ACLF in NASH patients, and to develop specific prevention and management.

3.2 Severe acute alcoholic hepatitis

An increasing incidence of hospitalization for alcohol-associated acute hepatitis (AAH) has been seen both in the USA [35] and in Europe, with a parallel increase in mortality rates in recent years [36].

Severe cases (Maddrey Discriminant Function ≥32) not responding to corticosteroid therapy according to Lille score present a 6-month mortality rate of 75% [37]. However, despite the lack of effective therapies and high mortality rates, AH has for a long time been considered to be an absolute contraindication for LT by most transplant centers worldwide, mainly due to the lack of pre-transplant abstinence and the potential high risk of post-transplant alcohol relapse [37-40]. Therefore, LT for severe AH remains controversial also due to concerns about the limited organ supply. Recognizing an increasing body of favorable evidence, a convergence of practice guideline recommendations from leading hepatology and gastroenterology societies have suggested that the length of abstinence should not be a sole criterion for LT selection [41].

In 2011, a multicenter French-Belgian study demonstrated that early LT (eLT), if performed under stringent selection criteria, significantly increases survival rates in patients with severe AH not responding to steroid therapy when compared with patients with severe AH who were denied LT

[42]. However, eLT without requiring a minimum period of sobriety for severe AAH is controversial: many centers delay eligibility until a specific period of sobriety (such as 6 months) has been achieved [43]. The same group recently published an abstract reporting the long-term results in the cohort of patients initially reported in 2011, with the addition of more recent transplanted patients, in the same 7 centers and according to the same inclusion criteria. Sixty eight patients that had failed to respond to medical therapy underwent eLT, severe alcohol relapse reached 10.3% of cases in nearly 5 years. However, the overall patient survival was 82.6±5% at 1 year, 70±6% at 5 years and 56±7% at 10 years, confirming that AH could be a good indication for LT in selected patients [44].

Another multicenter study has been published [45], performed at 12 USA LT centers, confirming the high survival rates after eLT for severe AH (94% and 84% at 1 and 3 years) with rates of alcohol relapse ranging between 10% and 17% between 1 and 3 years of follow up. In this study, it seems that almost all (96%) of the 147 patients included with the diagnosis of AAH had underlying alcohol-related cirrhosis and the acuity of the onset of liver disease may be different from the experience in other centers. Patient with AAH who undergo eLT are usually admitted to hospital with a high MELD score. They consequently go to the top of the WL, opening the discussion on equity regarding the priority of patients already listed for different liver diseases. Only very restrictive criteria which should be comparable among different centers and different countries, could allow us to compare indications, contraindications and outcomes. AAH, in most cases, develops in already existing liver diseases and it is therefore quite unusual to see patients with pure AAH. Another issue that is raised when proposing eLT in patients with acute decompensation is the rate of relapse to alcohol consumption after LT. The study by Lee et al. [45] reported a 17% relapse within 3 years, which is acceptable. However, in a European study a 2 year alcohol relapse of 33.8% was reported [46]. In general if the rate of alcohol relapse is similar with or without the 6-months abstinence rule, we believe the rate of relapse is also acceptable after eLT, but it is crucial

that the studied populations are comparable, in terms of inclusion criteria and AAH definition in different studies.

To inform ongoing debate and policy, a mathematical model has recently been proposed to simulate early vs delayed LT for patients with AAH and different amounts of alcohol use after transplantation: abstinence, slip (alcohol use followed by sobriety), or sustained use. The study estimated life expectancies of patients receiving early vs delayed LT (6-month wait before placement on the WL) and life years lost attributable to alcohol use after receiving the LT. Patients offered eLT were estimated to have an average life expectancy of 6.55 years, compared with an average life expectancy of 1.46 years for patients offered delayed LT. Patients who were offered eLT and had no alcohol use afterward were predicted to survive 10.85 years compared with 3.62 years for patients with sustained alcohol use after LT. Compared with delayed transplantation, eLT increased survival times in all simulated scenarios. However, the net increase in life expectancy should be confirmed in prospective studies [47].

Another pilot study on eLT was performed in Italy including patients with AAH who had a first episode of decompensation of chronic liver disease; were non responders to medical therapies; after obtaining consensus of the paramedical and medical staff with social integration and supportive family members; with assessment of psychiatric and addiction profile; and no comorbidities. Preliminary data confirmed excellent patient survival since all patients were alive with no alcohol relapse at a median follow-up of 17 months (range 9-41 months); significantly higher compared to patients not responding to medical therapy and denied transplantation [48]. A prognostic score, the SALT score (Table 3), using four objective pre-transplant variables, was proposed in order to predict the alcohol use after eLT; the latter identifies candidates with AAH for early LT who are at low risk for sustained alcohol use post-transplant. This tool may assist in the selection of patients with AAH for early LT or in guiding risk-based interventions post-LT [49].

There is an ongoing discussion about using the ACLF classification in patients with AAH to define the risk of death. It is well known that about 60% of precipitating events in patients who develop

ACLF is due to alcohol abuse [14]. The discussion on the nomenclature of AAH and ACLF is due to the different prognostic models and underlying pathophysiology. In AAH, hepatic inflammation is thought to be predominant, and multi organ failure is a key component ACLF-3 that is often infection-related. The key issue is about attributing priority for transplantation to give to the two populations, since different scores on the risk of mortality without LT and rate of survival after LT are discussed [19, 24, 25, 37].

4. Areas of uncertainty and adequate timing regarding LT for DC and severe ACLF

Adoption of MELD almost two decades ago dramatically changed our conception of allocation. Yet, there is an increasing body of evidence that efficiency of MELD-based systems is now hampered by intrinsic limitations, notably because MELD does not adequately capture organ failures/dysfunctions and inflammation in DC patients, and because of the increasing number of patients listed for HCC. Large-scale prospective cohort studies are therefore urgently needed, first to test recently developed predictive models integrating new predictors of mortality and second to look for next generation predictive biomarkers and statistical models, prompting the LT community to move from the MELD to the post MELD era, based on robust evidence.

Moreover, given the high mortality associated with ACLF-3, candidates who have develop this condition would likely benefit from early LT. However, the potential advantages of rapid transplantation may also include improved post-transplant survival when transplantation occurs in less than 30 days compared to more than 30 days (82.2% vs 78.7%) [1]. However, findings from other studies have indicated that transplantation after clinical improvement yields better post-LT survival than early LT. A single-center proof-of-concept study revealed that patients transplanted after improvement of ACLF, defined as recovery of at least one organ system failure, yielded a superior 90-day post-transplant survival as compared to recipients transplanted with ACLF and similar to that of patients without ACLF prior to transplantation [50]. In a larger registry study, 1 year post-transplant survival substantially increased in patients with ACLF-3 who improved ACLF

grades to 0-2 (88.2%) versus those who remained at ACLF-3 at LT (82.0%) [27]. In particular, improvement in circulatory failure, brain failure, and requirement for mechanical ventilation were associated with greater post-LT survival. This study also compared the effect of timing of transplantation versus improvement in organ failures on post-LT survival. The findings demonstrated that compared to transplantation in patients with ACLF-3 within 7 days of listing, improvement from ACLF-3 to ACLF 0-2 resulted in greater post-transplant survival (87.6 vs 82.7%, $p<0.001$) even if performed after 7 days from listing [27]. The question of the "transplantation window" and the precise criteria for deciding on a transplant have not yet been determined. There is no consolidated data on the best time for transplantation. Should patients be transplanted during their stay in the ICU or after recovery from ICU? What criteria should be used to determine indication, timing or contraindication for LT? Although intensive care management has made significant progress, the outcomes of ACLF cirrhotic patients remain poor without transplantation and the proportion of transplanted patients among ACLF is still too low. In the future, we should work to improve the transplantation rates of these patients without deteriorating the results.

Although progress has been made regarding the safety of LT in patients with severe ACLF, there are two primary areas that need to be addressed to optimize survival. First is to determine how to prioritize patients with severe ACLF, particularly ACLF-3, on the WL in order to both minimize WL and post-LT mortality. Second, is creating a scoring system to determine in which patients transplantation would be futile. Although studies thus far have demonstrated excellent post-LT survival even among patients with 4-6 organ failures, the data may reflect a selection bias which does not account for factors such as sarcopenia, frailty, or uncontrolled infection. Prospective investigations are therefore imperative to establish reliable determinants of futility, such that WL priority can be allotted to patients with severe ACLF who would benefit from LT.

4.1 Potentially inappropriate versus life-saving liver transplantation in critically ill patients

Under the sickest-first allocation policy, many transplant centers face an increased proportion of critically ill patients on the WL [51].

Despite the "only rescue option", futile outcome of LT needs to be avoided due to donor organ shortage and limited health care resources. The majority of studies define futile outcome as 90-day [51, 52] or 1-year [53, 54] post-transplant mortality. On the other hand, futile treatment is understood as almost zero-chance of surviving despite LT. Many aspects in LT including MELD-based allocation or HCC criteria are highly regulated but widely accepted delisting criteria, when a patient is literally too sick for transplantation, are lacking. Therefore, the decision on when post-transplant mortality risk is too high in severely decompensated patients is still a challenge in the clinical assessment of LT candidacy, even in the scenario of receiving the best donor organ [8]. A recent study in high acuity recipients with ACLF or ALF found that ARDS defined by PaO_2/FiO_2 ratio <200 and pre-transplant lactatemia were independently associated with poor 90-day prognosis after LT [55]. Furthermore, high vasopressor requirement and ongoing sepsis are repetitively reported criteria to defer or deny LT in order to avoid futile LT outcome [8, 19]. A multidisciplinary expert panel study explored criteria for when not to proceed with LT due to high severity of critical illness [53]. Experts from anesthesiology, critical care, hepatology and transplant surgery suggested thresholds contradicting LT in the presence of severe ARDS (PaO_2/FiO_2 ratio <150), high vasopressor requirement (norepinephrine dose >1µg/kg/min), and lactatemia (>9 mmol/l). Another study identified MELD score, pre-transplant septic shock, cardiac risk and comorbidities as independent predictors of futile outcome (90-day mortality) after LT in 40+ MELD patients [51]. Therefore, a prediction model of 90-day mortality integrating risk factors of ACLF patients would be a helpful tool to address potential futility in this high-risk population of LT candidates. However, the medical challenge of undesired futile LT outcome also extends into ethical issues since the potential rescue of a single critically ill patient, regardless of costs, must be weighed against the benefits of aggregated patients on the WL. In extreme recipients with low utility, LT

may work in a few cases and thus cannot be considered as futile treatment. Therefore, these scenarios are beyond the narrow definition of physiological futility and are better described by potentially inappropriate LT [8]. Even with a perfect risk prediction of 90-day mortality after LT, it remains a matter of debate how much predicted risk of death defines futile or potentially inappropriate LT in ACLF patients. We anticipate that a future personalized allocation system should not only prioritize patients based on recipient and donor criteria but also needs to integrate criteria, when LT is highly likely to be potentially inappropriate in ACLF patients.

5. Areas of controversy in liver transplant setting

5.1 Gender disparity

Disparities in access to LT by sex, documented more than 20 years ago [56], continue to persist. Introduction of MELD-Na worsened the sex disparity [57]. Women having a lower likelihood of LT than men at the same MELD-Na score [57], are more likely to be delisted due to death or becoming too sick [58], and have higher hospitalization rates after listing [59]. This difference is accounted for by shorter stature, fewer MELD exceptions and the underestimation of renal dysfunction by creatinine among women [57, 60]. Modeling suggests that adding 1 or 2 MELD points for women would provide more equitable access to LT [57].

5.2 Geographic disparity

Geographic disparities are well-recognized, with many countries considering rules for broader sharing of organs [61-64]. Patients living in rural areas, lower income and education and those with public (versus private) insurance are particularly affected, reflecting less resources to access a LT center [65, 66]. The USA recently implemented an acuity circle approach (using 150-mile radius of the donor hospital) in an attempt to reduce geographic disparities. However, reconfiguring organ distribution is a challenging issue. For example, a modeling study evaluating use of distance and population density “circles” to define organ distribution in the USA found little improvement over

the older donor service area (DSA) system [67]. The complexity of addressing geographical barriers to LT is further highlighted by a recent USA survey that found strong public support for maximizing outcomes after LT, but also for keeping organs local, and considering cost in allocation decisions [68].

6.3 HIV, HBV, HCV positive donors

Maximizing use of donors is an additional means for addressing disparities in access to LT and use of donors positive for hepatitis C, hepatitis B and HIV have increased in many countries.

A) Use of HIV-positive donors was made possible in the USA by the Hope Act and countries without restrictions have used HIV-positive donors in HIV-positive recipients (D+/R+) [69]. Superinfection appears to be rare in this context and graft and patient outcomes (with modest duration follow-up) is comparable to those receiving HIV-negative organs. A case report of LT of HIV D+/R- in a mother-child pair suggests this is possible with the use of antiretroviral therapy in donor and recipient, but long-term follow-up is needed [70]. This may be relevant in countries with high rates of HIV among donors

B) For donors positive for HBsAg, only recipients with HBV should be offered these organs due to known persistence of cccDNA in the liver and certainty of HBV transmission [71, 72]. Donors must be carefully assessed for liver disease pre-implantation. No significant HBV-related disease has been observed in HBsAg D+/R+ recipients treated with life-long antiviral therapy, except in patients co-infected with hepatitis D virus, [73], so the latter should be considered a contraindication to the use of HBsAg-positive donors. Whether there are long-term consequences (beyond 5 years), such as risk of liver cancer, is unknown.

C) HCV-viremic donors have traditionally been used for HCV-positive LT recipients (D+/R+) with outcomes shown to be comparable to those receiving from HCV-uninfected donors. However, there has been rapid uptake of using HCV-viremic donors in HCV-negative recipients (D+/R-), fueled by the availability of safe and effective direct-acting antivirals

(DAAs) for HCV [74-77]. Early results are encouraging, with HCV D+/R- transplants with high rates of sustained virologic response achieved post-LT. Early treatment is preferred, typically starting DAAs within days to 1-2 weeks of LT, rather than delaying for weeks or months, to minimize the risk of hepatic and extrahepatic complications [78]. A higher risk of acute and chronic rejection has been reported when DAA therapy is delayed [76, 77], highlighting the importance of monitoring for immune-mediated events in the context of DAA therapy [79, 80].

Conclusions

In conclusion, although more than 50 years have now passed since the first liver transplant was performed, there are still several aspects of liver disease that are not addressed in a equitable way between the different countries, different hepatological and surgical centers dedicated to transplantation. There are several controversial aspects of the transplantation timing in patients with severe liver disease decompensation, particularly when organs other than the liver are involved. Early transplantation in acute alcoholic hepatitis is performed in several centers, but the ethical aspects persist. Also between science and ethics is the use of donors that are positive for different viruses. Finally, the right answer for transplantation in very sick patients remains a delicate balance between utility, benefit and justice.

Abbreviations

AAH: alcohol-associated acute hepatitis; ACLF: acute-on-chronic liver failure; ARDS: Acute respiratory distress syndrome; CLIF-C: Chronic Liver Failure Consortium; DC: decompensated cirrhosis, eLT: early liver transplantation; HCC: hepatocellular carcinoma; MELD : Model of End-stage Liver Disease; NASH: Non-alcoholic steatohepatitis; LT: Liver transplantation; SMR: standardized mortality ratio; TAM: transplantation and multi-organ failure; WL: waiting list;

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Table 1: Biomarkers and predictive models with added predictive value of mortality in cirrhotics compared to MELD

Predictor	Author (Ref)	N patients	End-point	Cut-off	HR	C-index	95% CI	p
Nutrition								
Protein intake	Ney et al. [9]	630	Waitlist mortality	Protein intake < 0.8 g/kg	1.8		1.2-2.7	0.006
Sarcopenia	Montano-Loza et al. [13] Durand et al. [81]	669 376	Waitlist mortality Waitlist mortality	L3 Skeletal Muscle Index MELD vs MELD-sarcopenia Psoas diameter/Height > 16.8 mm/m	2.26 0.86	0.73 vs 0.77	1.73-2.94 0.78-0.94	<0.001 0.03 0.001
Encephalopathy								
Minimal encephalopathy	Ampuero et al. [82]	117	Death		4.36		1.67-11.37	0.003
Serum ammonia	Patwardhan et al. [83]	494	3-month mortality or LT	Ammonia > 60 µmol/l	1.22		1.03-1.38	<0.01
Inflammation								

Neutrophil to Lymphocyte Ratio	Leithead et al. [84] Kalra et al. [85]	570 107	3-month mortality Death	2 <Neutrophil/Lymphocyte < 4.9 Neutrophil/Lymphocyte ≥ 5 Neutrophil /Lymphocyte ≥ 4	3.17 6.02 4.4		0.70-14.37 1.28-28.41	 0.043 0.023
CRP	Cervoni et al. [86]	583	6-month mortality	CRP > 29 mg/l à J0 et J15 MELD vs MELD + CRP	1.65	0.769 vs 0.796	1.04-2.64	0.035 0.019
25 Hydroxyvitamin D	Trepo et al. [87] Finkelmeier et al. [88] Stokes et al. [89]	324 251 65	12-month mortality Death 24-month mortality	25(OH)D3 < 10 ng/ml 25(OH)D3 < 6 ng/ml 25(OH)D3 < 6 ng/ml	4.33 1.703 6.32		1.47-12.78 1.038–2.794 1.28-31.18	0.008 0.035 0.012
Ferritin % Transferrin Saturation	Walker et al. [90] Maras et al. [91]	191 120	6-month mortality 1-month mortality	Ferritin > 200 µg/l MELD vs MELD-Ferritin CST > 20%	4.62 3.34	0.7 vs 0.86	1.17-18.2 1.58-7.03	0.03 0.001 0.002
	Portal Hypertension							
sCD163	Waidmann et al. [92]	244	Survival	sCD163 < 4100 ng/l	0.237		0.134-0.419	< 0.001
vWF:Ag	Ferlitsch et al. [93] Kalambokis et al. [94]	286 102	Death Death	vWF :Ag > 315% vWF :Ag > 321%	2.92 1.006		1.72-4.97 1.002-1.01	<0.001 0.002

Hemodynamics								
Copeptin	Kerbert et al. [95] Sola et al. [96]	184 265	6-month death or LT 6-month death or LT	Copeptin > 12,3 pmol/l Copeptin > 14 pmol/l	3.36 1.66		1.26-8.98 1.14-2.43	0.016 0.008
ProBNP	Pimenta et al. [97]	83	6-month mortality	BNP > 130.3 pg/ml	2.86		1.11-7.38	0.03
Renal Function								
Urine NGAL	Ariza et al. [98] Barreto et al [99]	716 132	1-month mortality 3-month mortality	MELD vs MELD + uNGAL	1.77 1.1	0.81 vs 0.86	1.42-2.21 1.06-1.13	0.017 0.04
Cystatin C	Seo et al. [100] Markwardt et al. [101]	78 429	Death 3-month mortality or LT	Cystatin C > 1.5 mg/l	6.09 3.1		1.41-26.4 2.1-4.7	< 0.001
New Statistical Models								
Models	Jalan et al. [6]	1016				**C index for**		

						3-month mortality		
CLIF C AD model (CANONIC cohort without organ failure)			**CLIF C AD**			**0.743**	**0.704-0.783**	
			vs Child-Pugh score			0.651	0.601-0.701	<0.001
			vs MELD score			0.649	0.602-0.697	<0.001
			vs MELD Na			0.681	0.633-0.728	<0.001
CLIF C ACLF model	Jalan et al.[5]	275						
CANONIC cohort			**CLIF C ACLF**			**0.732**	**0.691-0.773**	
			vs Child-Pugh score			0.655	0.605-0.705	<0.001
			vs MELD score			0.659	0.615-0.710	<0.001
			vs MELD Na			0.663	0.617-0.709	<0.001
		225						
Validation cohort			**CLIF C ACLF**			**0.736**	**0.696-0.776**	
			vs Child-Pugh			0.647	0.599-0.695	<0.001

			score					
			vs MELD score			0.635	0.585-0.684	<0.001
			vs MELD Na			0.637	0.588-0.686	<0.001
MELD Na + frailty	Lai et al. [12]	536	**MELD Na + frailty**			**0.82**		
			vs MELD Na			0.80		<0.001
			Frailty index			0.76		
MELD sarcopenia	Montano-Loza et al. [13]	669	**MELD-sarcopenia***			**0.85**	0.81-0.88	
			In MELD < 15 only**			**0.85**	0.77-0.92	
			vs MELD overall*			0.82	078-0.87	0.1
			vs MELD < 15 only**			0.69	0.56-0.82	0.02
MELD sarcopenia encephalopathy score	Van Vugt et al. [10]	585	**MELD + sarcopenia$_{M*}$ + encephalopathy + Age**			**0.851**		

		MELD sarcopenia$_{M***}$			0.834		NA
		vs MELD			0.839		
		MELD Na			0.824		

*MELD sarcopenia in the whole population

** MELD sarcopenia in patients with MELD < 15

***Sarcopenia as defined by Martin et al. [102]

Table 2 - Summary of studies regarding transplantation for ACLF-3

Study (Year)	Type of Study	Total Patients with ACLF-3	Waitlist Outcomes	Post-LT Outcomes	Significance	Limitations
Artru (2017) [19]	Three single centers from January 1, 2008 to December 31, 2014	73 transplanted	N/A	1-year survival 83.6%	Found LT can improve survival of ACLF-3 (with similar rates to lower ACLF grades)	Lack of power for multivariate analysis Case-control study with control cases from one single center
Levesque (2017) [25]	One single center from January 2008 to December 2013	30 transplanted	N/A	1-year survival 43.3%	Confirmed ACLF as independent predictor of 90-day mortality Proposed scoring system to identify potentially futile LT	Small sample Limited variables used to build statistical propensity score
Thuluvath	UNOS	2,515 at	30-day	1-year	Identified	Short time to LT

(2018) [20]	database from February 27, 2002 to September 30, 2016	listing 3,556* transplanted	mortality >92%	survival >81.0%	number of organ failures, age, and mechanical ventilation as independent predictors of post-LT survival	(up to 5 days after listing in >3 organ failures) Unable to identify cause of decompensation
Sundaram (2019) [1]	UNOS database from 2005 to 2016	5,355 at listing 6,381 transplanted	28-day mortality 43.8%	1-year survival 78.9%	Demonstrated waitlist mortality is highest among ACLF-3 patients regardless of MELD-Na Identified presence of mechanical ventilation as strongest predictor of post-LT mortality	Potential for misclassification of decompensating event in database Unclear indications for use of mechanical ventilation
Sundaram	UNOS	5,099 at	21-day	N/A	Demonstrated	Potential for

(2019) [23]	database from 2002 to 2014	listing	mortality 32.7%		14-day waitlist mortality is greater in ACLF-3 patients compared to status-1a listed patients	misclassification of decompensating event in database Excludes patients listed status-1a with exception points
Artzner (2020) [26]	Five centers, years 2007-2017	152 transplanted	N/A	1-year survival 83.9% vs 8.3% depending on TAM score	Developed TAM score to help determine futility of LT for ACLF-3	TAM score derived from 22 patients with ACLF-3 and mortality within 1 year. Minimal information on donor organs

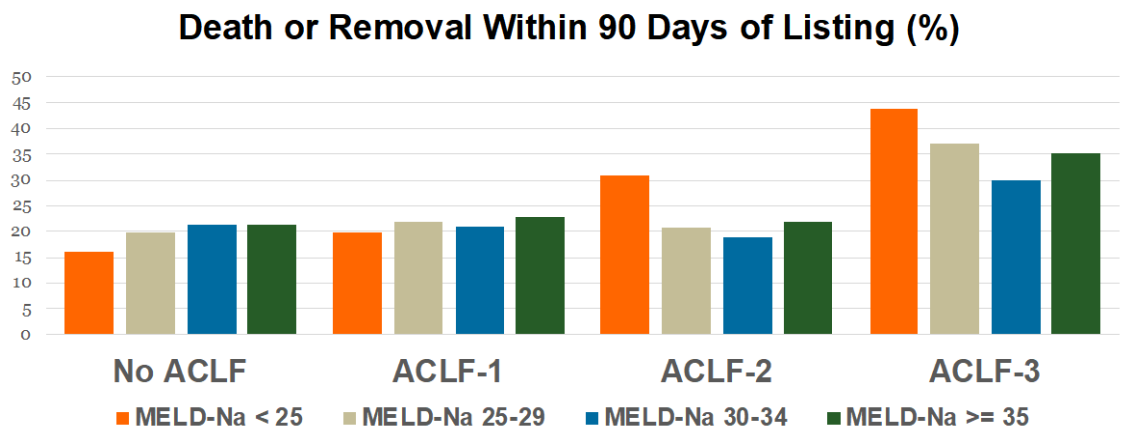
** Study separately analyzed number of organ failures by 3, 4, and 5-6 organ failures. Data shown in table reflect combination of 3 or more organ failures.*

TABLE 3. SALT Score to Predict Sustained Alcohol Use Post-LT [49]

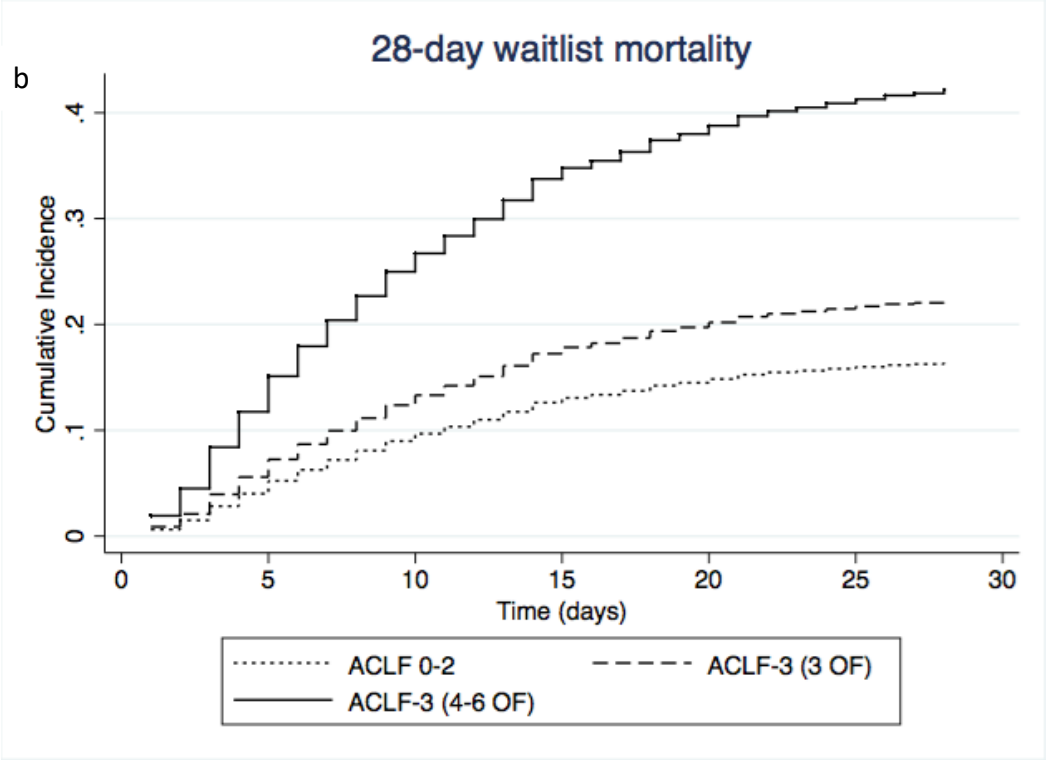
Variable	**Points**
>10 drinks/day at presentation	+4
≥2 prior failed rehabilitation attempts	+4
Any history of prior alcohol-related legal issues	+2
History of non-THC illicit substance abuse	+1

Figure 1. Waitlist mortality in ACLF patients. (a) Waitlist mortality across different grades of ACLF and MELD-Na score categories. (b) Waitlist mortality across different grades of ACLF, in a cohort of patients with MELD-Na score ≥ 35 (p<0.001)

a



b



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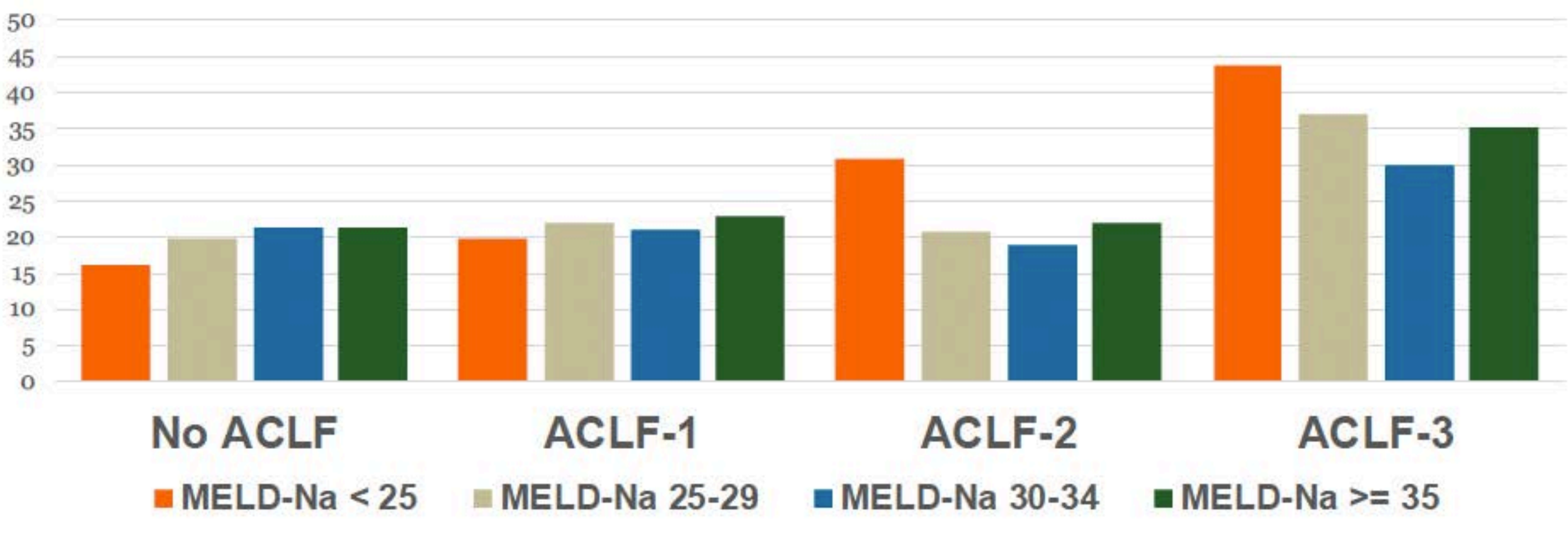
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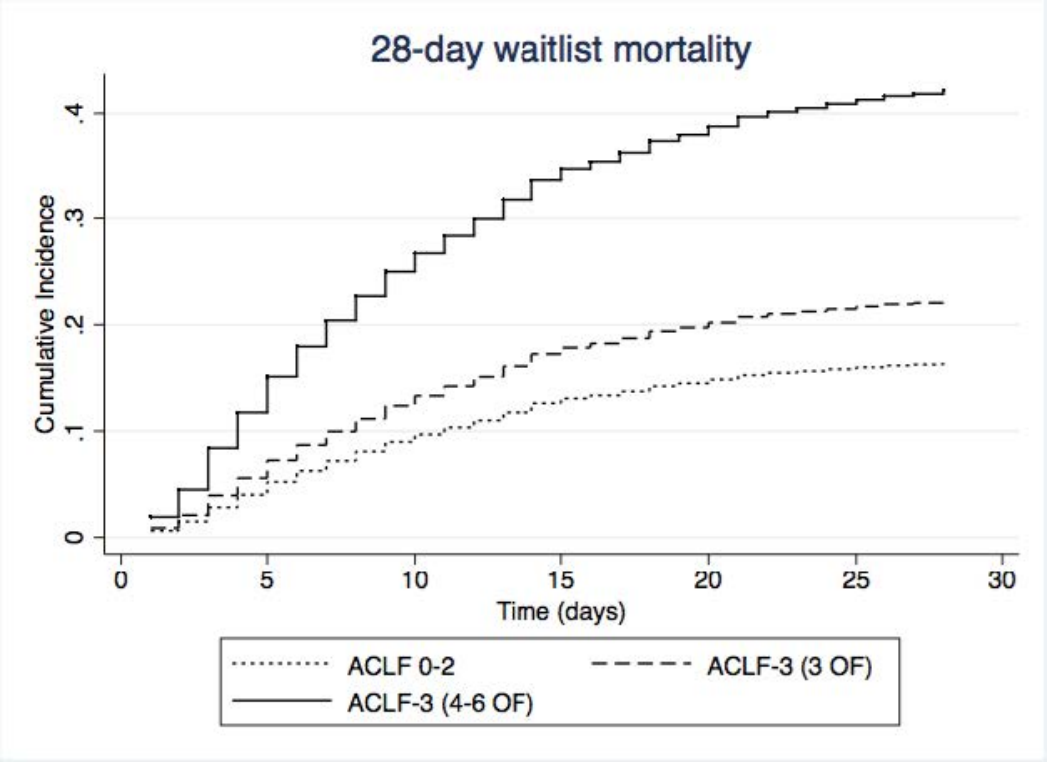
28-day waitlist mortality
Cumulative Incidence
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