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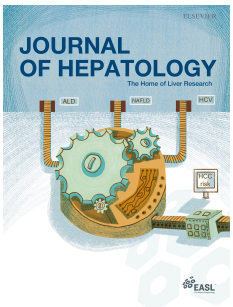

The novel SALT-M score predicts 1-year post-transplant mortality in patients with severe acute-on-chronic liver failure

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The novel SALT-M score predicts 1-year post-transplant mortality in patients with severe acute-on-chronic liver failure

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Submission declaration

This work has not been published previously (except in the form of an abstract during AASLD Meeting in November 2022, where was presented partial results of the work). It is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere, including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

Data Availability

The de-identified data are only internally available for the MODEL Consortium researchers after approval of the Ancillary Studies Steering Committee

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Conflicts of interest: Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Discovery, a spin out company from University College London, Hepyx Limited and Cyberliver. He had research collaborations with Yaqrit Discovery.

All other authors declare no conflict of interests.

Authorship and contributors

All the authors listed above participated in the study concept and design; acquisition of data; interpretation of data; critical revision of the manuscript for important intellectual content; obtained funding; and administrative, technical, or material support; study supervision). Ruben Hernaez, Yan Liu performed the statistical analysis. Ruben Hernaez, Constatine Karvellas and Rajiv Jalan drafted the initial manuscript.

The Consortium authors listed at the end of this manuscript, acquired the data, performed a critical revision of the manuscript, and agreed with the current manuscript.

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ABSTRACT

Background & Aims: Patients with acute-on-chronic liver failure grades 2/3 (severe ACLF) have 28-day mortality ranging from 30-90%. Though liver transplantation (LT) has demonstrated a survival benefit, the scarcity of donor organs and uncertainty regarding post-LT mortality among patients with severe ACLF may cause provider hesitation to proceed with LT. We developed and externally validated a model to predict 1-year post-LT mortality in severe ACLF, called the Sundaram ACLF-LT-M probability score, and estimated the median length of stay (LoS) after LT (ACLF-LT-LoS).

Methods: In 15 LT centers in the USA, we retrospectively identified a cohort of severe ACLF patients transplanted between 2014-2019, followed up to Jan'2022. Candidate predictors included demographics, clinical, laboratory values, and organ failures. We selected predictors in the final model using clinical criteria and externally validated them in two French cohorts. We provided measures of overall performance, discrimination, and calibration. We used multivariable median regression to estimate LoS after adjusting for clinically relevant factors.

Results: We included 735 patients, of whom 521 (70.8%) had severe ACLF (120 ACLF3,external cohort). The median age was 55 years, and 104 with severe ACLF (19.9%) died within 1-year post-LT. Our final model included age > 50 years, use of 1/2+ inotropes, presence of respiratory failure, diabetes mellitus, and body mass index (BMI, continuous). The c-statistic was 0.72 (derivation) and 0.80 (validation), indicating adequate discrimination and calibration based on the observed/expected probability plots. Age, respiratory failure, BMI, and presence of infection independently predicted median LoS.

Conclusions:The ACLF-LT-M score predicts mortality within 1-year after LT in patients with ACLF.The ACLF-LT-LoS score predicted median post-LT stay. Future studies using the ACLF-LT scores could assist in determining transplant benefits.

Impact and implications

Acute-on-chronic liver failure (ACLF) is a common syndrome, characterized by multi-organ failure in patients with cirrhosis associated with high-short term mortality. Liver transplantation (LT) may be the only life-saving procedure available to these patients but clinically unstability can augment the perceived risk of post-transplant mortality at one year.

We provided a parsinominous score with clinically, and readily available parameters to objectively assess 1-year post LT survival and predict median length of stay after LT.

Using modern estimation techniques, we developed and externally validated a clinical score model called the Sundaram ACLF-LT-Mortality score in 521 U.S. patients with ACLF with 2 or 3+ organ failure (s) and 120 French patients with grade ACLF-3. The area under the receiver operating characteristics curve was 0.72 in the development cohort and 0.80 in the validation cohort. We also provided an estimation of the median length of stay after LT in these patients.

Our models can be incorporated in the discussion of risks/benefits in patients with severe ACLF listed for LT. Nevertheless, the score is far from perfect and other factors, such as patient's preference and center-specific factors, need to be considered whe using these tools.

Graphical Abstract

The Sundaram ACLF-LT (SALT)-M score predicts 1 year survival after liver transplant in grade 2 and 3 ACLF

MODEL Consortium (development/internal validation)

15 Liver Transplant Centers, 521 patients with ACLF 2-3

External validation

Strasbourg and Villejuif, 120 patients with ACLF-3

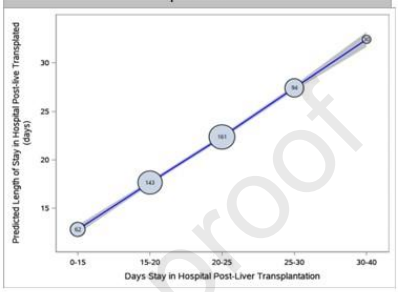
Tool: logistic regression using clinically meaningful variable selection in addition to modern selection techniques. Adequate power for 5 predictors. Used median regression to estimate median length of stay using the same principles.

- ✓ Age 50+
- ✓ Diabetes mellitus
- ✓ Body mass index (continuous)
- ✓ Circulatory failure (one or 2+ inotropes)
- ✓ Respiratory failure

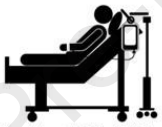
Sundaram ACLF –LT (SALT)-Mortality score predicts 1-year mortality probability post-LT

AUROC 0.72 (development)
AUROC 0.80 (external validation)

Able to assess median length-of-stay in days post LT



Adjusted for age, body mass index, diabetes use of inotropes, respiratory failure, prior h/o MDRB, RRT and WBC at LT



ACLF 2/3 & LT candidate?→ The Sundaram score can help in the discussions of LT in these patients

Abbreviations: MODEL: Multi-Organ Dysfunction and Evaluation for Liver Transplantation; ACLF: acute-on-chronic liver failure; LT: liver transplantation; MDRB: multidrug resistant bacteria; RRT: renal replacement therapy; WBC: white blood cell; AUROC: area under the receiver operating characteristics curve

INTRODUCTION

The natural history of a patient with cirrhosis changes when they develop an episode of liver-related complication such as variceal bleeding, ascites, hepatic encephalopathy, or bacterial infection. This condition is decompensated cirrhosis and is associated with a decrease in life expectancy to a median of 3-5 years [1]. In some cases, acute decompensation is associated with extrahepatic organ failure(s) (OFs), further increasing short-term mortality. This entity is defined as acute-on-chronic liver failure (ACLF)[2] and is prevalent across the globe [3]. Consistently, patients with two or more OFs have very high 28-day mortality (36% ACLF-2 [95% Confidence Interval, CI, 31-40%]; 68% ACLF-3, [95%CI, 63-74]) [3]. As there is no approved treatment for ACLF, these patients desperately need liver transplantation (LT) as a life-saving procedure.

However, LT in these critically sick patients is challenging due to the risk of post-transplant mortality, which is a consequence of circulatory failure requiring vasopressors, mechanical ventilation, or an infectious trigger as the culprit of ACLF development [4]. Furthermore, given limited organ availability, the care team may hesitate to pursue liver transplantation [5] despite excellent reported outcomes [6]. Thus, there is a lack of equity of access for severe ACLF patients across centers [5, 6]. Accurately predicting post-LT outcomes in patients with severe ACLF remains an unmet need. More granularity toward understanding transplant risk and benefits would be clinically relevant to select better patients likely to do well [7]. Therefore, we internally developed and externally validated a risk score that determines the probability of one-year mortality after LT in severe ACLF (patients with two or more organ failures [OFs]), andnamed it the Sundaram ACLF-LT (SALT) Mortality (M) probability score to honor the memory of the Consortium's founder[8]. As a secondary aim, we explored clinically important

variables that impacted the length of stay (LOS) and created a second prediction model called ACLF-LT LOS.

PATIENTS AND METHODS

According to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement for the risk score reporting [9], prediction model studies can be broadly categorized as model development, model validation (with or without updating), or a combination of both. We conducted a type 3 model development study with validation using external data [9], and we followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) report [10] for the initial data collection in the Multi-Organ Dysfunction and Evaluation for Liver Transplantation (MODEL) Consortium. The following describes the derivation cohort with model-building and validation strategies.

Derivation cohort: the MODEL Consortium

We retrospectively collected data from 15 transplant centers in the United States as part of the MODEL Consortium. The institutional review board approved the study protocol at Cedars-Sinai Medical Center and obtained subsequent approval from the other participating institutions' respective institutional review boards, including the Baylor College of Medicine (data analysis center). At inception, we conducted training sessions about data entry with each site investigator and relevant study staff to increase the accuracy of entered data. After data extraction from the central database, an additional query was sent to institutions in the event of erroneous or missing data, followed by a second round of data entry as needed.

We included patients 18 years or older who were transplanted from January 2014 through December 2019. We required a minimum of 2 days in the intensive care unit (ICU) at some point before LT surgery during their transplant hospitalization since most prior studies addressing futility were based on ACLF patients in the ICU [11]. We further excluded patients

listed as status-1a, re-transplanted, or who underwent multi-organ transplantation (except simultaneous liver and kidney transplantation -SLKT). We collected data regarding recipient characteristics at the time of hospital admission, the time of transfer to the ICU, and the time of transplantation.

Acute-on-chronic liver failure definition was based on the EASL-CLIF definition

Patients meeting the criteria for severe ACLF (grade 2 or 3) at the time of liver transplantation based on the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) criteria were included [3]. We defined renal failure as a creatinine ≥ 2.0 mg/dL and/or the use of any renal replacement therapy (RRT), such as intermittent hemodialysis (HD) or continuous renal replacement therapy (CRRT), at any point during their hospitalization. We did not consider a patient to have *renal failure* if the review of records indicated a need for dialysis due to chronic kidney disease or if their creatinine at LT was less than 1.5 times their baseline creatinine. We considered patients to have *respiratory failure* when they had a PaO_2/FiO_2 ratio <200 mm Hg and/or required mechanical ventilation specifically for respiratory support. We did not include *elective* mechanical ventilation in the definition of respiratory failure. We defined *circulatory failure* at LT if they required vasopressor support at the time of transplantation to maintain either a mean arterial pressure <70 mm Hg or for an indication of hypotension; we also recorded how many were used (none, one or 2+) [7, 12]. We defined the presence of multidrug-resistant bacteria (MDRB) and/or fungal infection by positive blood culture data and any point during pre-transplant hospitalization.

Study Outcomes: mortality within one year from liver transplantation and length of stay

The *primary outcome* was overall mortality within one year after the LT because this is a common benchmark used by government agencies to assess centers' LT performance [13]. As a *secondary outcome*, we examined the predictors associated with the median length of stay (LOS) following LT in patients transplanted from ACLF. We defined LOS as the time from LT to the *first* hospital discharge following LT.

Statistical analysis

Selection of predictor variables.

A priori, we chose clinically relevant variables associated with post-transplant outcomes in previous studies: age, body mass index (BMI), LOS, presence of diabetes mellitus (DM), chronic kidney disease, use of inotropes, or presence of respiratory failure. For key variables, data were missing from 0 to 4%. Assuming missing at random, we imputed missing data using the Multivariate Imputation by Chained Equations (MICE) procedure in R and created five imputed datasets with 50 iterations[14]. We included all candidate predictors and the outcome in the imputation model.

The Sundaram ACLF-LT (SALT) Mortality score development

Considering our small sample, we followed the TRIPOD recommendations and initially conducted validation with internal resampling (study type 1b) [9]. We did not use split-sample validation techniques because this small size could produce instability in performance estimates and lead to overestimation in the areas under the receiver operating characteristics

curve (AUROC)[15]. For the internal resampling, we built multivariable binary logistic regressions in each imputed dataset with the multiple imputation-bootstrapping methods [16] using 100 bootstrap samples from each imputed dataset. Subsequently, we analyzed the pooled model in each bootstrap training data and tested it in the original imputed data. We pooled regression coefficient estimates and standard errors according to Rubin's rules [17]. The model performance was estimated in the five imputed datasets and combined [16, 18]. All the candidate predictors were entered into the model and then removed from the pooled model using the Pooled Sampling Variance method (a pooling of the total covariance matrix)[19] and backward selection with p-value at < 0.157 [16, 20]. Because increasing age is clinically important as a surrogate of cumulative exposures and frailty, we included age in all the models. We studied linearity and non-linearity in the continuous candidate predictors and presented in the final model the best variable coding that showed the highest performance.

Internal validation, calibration, and performance measures.

We internally validated our prediction model with 100 bootstrapping across imputed datasets. We used backward selection in each bootstrap sample. We examined the pooled model performance using AUROC, Nagelkerke's R^2, scaled Brier score, and calibration plots. We calculated Nagelkerke's R^2 and AUROC to assess its discriminative performance. We demonstrated calibration by the calibration slope, plot, and Hosmer–Lemeshow (HL) test. We constructed the calibration plots across multiple imputed datasets, and the HL test with a p-value > 0.05 was considered evidence of good calibration [17]. A perfect calibration has a calibration slope of 1 and an intercept of 0 .

Comparison of discriminatory prediction with selected scoring models

We compared the SALT-M score our with other models with available information, including the model for end-stage liver disease with sodium correction (MELD-Na)[21], the change in MELD from ICU to transplantation over time (Delta-MELD)[22], donor (D) MELD-Na [23], the CLIF-C-ACLF score [24] and balance of risk (BAR) score [25].

External Validation cohorts: Strasbourg and Paul Brousse data

We included data from two large transplant centers in France: Strasbourg and Paul Brousse. For our validation effort, we required that participants should have been transplanted for severe ACLF (either grade 2 and/or 3), and with the completeness of the following variables: age, body mass index, the use of inotropes or mechanical ventilation, and diabetes mellitus status.

Sensitivity analysis with other variables.

After selecting our final model, we conducted several sensitivity analyses to assess the change in discriminative accuracy (AUROC) to predict 1-year post-LT mortality. In these analyses, we assessed factors the clinician could consider prognostic in mortality post-LT. For example, we included the cause of underlying chronic liver disease, triggers of ACLF, prior abdominal surgery, portal vein thrombosis, white blood cell count (WBC) at LT, MDRB and/or fungal infection during hospitalization, RRT, and MELD-Na at LT. We further examined the performance of the ACLF-LT-M score to predict 90-day mortality since it may be considered as a future benchmark in the USA [26], but also at six months and nine months. We also studied the discrimination of our model stratifying by ACLF grade 2 vs. 3 due to different mortality risks

at baseline, and examined center-specific mortality rates using a fixed effect model to account for these differences. While we used logistic modeling to build our score due to its methodological robustness, we also performed a time-to-event analysis using Cox proportional hazards model. In such a strategy, there was evidence of proportional hazards violation with BMI, thus, we presented Cox modeling as a secondary analysis.

Sample size for the Sundaram ACLF-LT (SALT)-M score development.

Based on the recommendation for a binary outcome for developing a clinical prediction, our sample size of 521 and assuming eight candidate predictor parameters and a mortality rate within one year of 20%, we could target a mean absolute prediction error of 0.04 between the observed and the actual mortality rate [27]. We performed all analyses using SAS version 9.4 and R version 4.2.1 (R Core Team,2022, https://www.R-project.org) with the package MICE for the imputation and pooling procedures and *psfmi* for model estimation and validation [16]. We considered statistical significance when the two-sided P-value is less than 0.05.

Estimation of median length of stay (LOS) and development of the ACLF-LT-LoS score

We considered the same clinically important variables to predict these patients' median LOS after liver transplantation. Because the observed distribution of LoS post-LT was positively skewed, we used quantile regression- SAS QUANTREG-, in which one can predict any percentile of the distribution (labeled a “quantile”) instead of the mean as in traditional linear regression. In our quantile regressions, we determined the point estimates for the predictor slopes by minimizing the weighted function of the absolute value of the model residuals (in which the weights reflect the chosen percentile). We further evaluated the significance of the

model predictors in predicting the median LoS by assessing the residual denominator degrees of freedom. We then added the additional predictors one at a time. We also studied the linearity and non-linearity of continuous variables and modeled the variable to optimize the Akaike's information criterion (AIC). Most of the deaths post-LT occurred within the first 90 days, so we included death within three months as a variable in the model and other clinically essential variables associated with prolonged LoS. We chose the final model by having variables that providers consider important prognostic factors in LoS.

Bedside tool to assess mortality risk

We provided an online calculator to estimate the probability of 1-year mortality post-LT and estimated median LOS available at https://vocal.shinyapps.io/MODEL/

Patient involvement

There was no patient involvement in the input of this study

RESULTS

The Multi-Organ Dysfunction and Evaluation for Liver Transplantation (MODEL) consortium

Of 735 patients in the MODEL consortium, 521 had severe ACLF at the time of LT **Supplementary Table 1**. The 214 participants excluded from this analysis were older (aged 50+: 72.4 vs 64.7%), had more males (59.4 vs. 55.3%), had a higher prevalence of diabetes (33.2 vs. 22.5%), had lower mean MELD-Na (31.4 vs. 37.0), shorter mean LoS (25.7 vs. 29.6 days). In contrast, body mass index, survival, and one year were similar between the participants included in this analysis (n= 521) vs. not (n=214)- **Supplementary Table 2**. The analytical cohort was followed up for a median of 3.1 (1.6-5) years. The median survival time of these patients was 1,143 days (Q1-Q3, 579-1,827), and 104 (19.9%) died within one year of LT (range 6.3%-47.7%, median 16.7%, mean 16.3%). The median age of our population was 55 years (46-61), with 45% females, 61% Whites. The median body mass index was 29.8 kg/m^2 (25.0-35.3), and 22.5% had diabetes. Alcohol was the most common underlying chronic liver disease (~40%). Due to the severity of ACLF, the median MELD-Na at transplantation was 40 (36-40), 284 patients (54.5%) had ACLF-3 at the time of transplantation. More than half (52%) of the patients required inotropes at LT, 58.2% continuous renal replacement therapy, 25.3% had respiratory failure, and 18.2% had grade III-IV hepatic encephalopathy.

Natural history and baseline predictors of death within one year

The majority of post-transplant deaths occurred within the first three months post-transplant: 63 (60.6%) within three months, ten between 3 and 6 (9.6%), 18 (17.3%) between 6 and 9 months, and 13 between 9 to 12 months (12.5%). Of the known causes of death, the most common were infectious, including septic shock, with 21 deaths (20.2%), followed by multi-

organ failure (including other forms of shock) (11.5%), cardiac (e.g., cardiac arrest, myocardial infarction, 9.6%) and cancer (for example, one patient died from a recurrence of HCC, two of colorectal cancer, and two of cholangiocarcinoma) (8.7%) [**Figure 1**]. Compared to patients who survived, patients with severe ACLF who died after LT had a higher median body mass index (31.3 vs. 29.6 kg/m^2), a higher proportion of nonalcoholic steatohepatitis (NASH, 19.2 vs. 14.4%), HCV (22.1 vs. 13%), and a higher likelihood of respiratory, cardiac, renal and brain failure (**Table 1**).

Derivation of the SALT-Mortality score using clinically meaningful variables.

In the design of the prediction score, we *a priori* focused our attention on clinically important variables based on prior knowledge. The final model included age (≥50 years), BMI (continuous), use of inotropes (none, one, or 2+), presence of respiratory failure, and diabetes. The following formula provides the probability of death within one year following a liver transplant, adjusting for the shrinkage factor:

P(death within one year after LT)= 1 / [1 + exp(-(-3.412 + 0.366*(Age>50) + 0.032*BMI + 0.414*one pressor + 1.192*two or more pressors + 0.599*respiratory failure + 0.417*DM))]*100%

The SALT-M score predicts post-OLT mortality well, with good calibration and improvement over other scores

Our development model showed acceptable discriminative ability (AUROC of 0.72, 95%CI: 69-0.76) with some miscalibration (calibration slope coefficient 0.93 -95% CI: 0.73-1.13, 1 being a perfectly calibrated model). Also, considering the 20% event rate, a model with a Brier score of less than 0.16 is informative [28], being ours 0.09, **Table 2**, **Supplementary Figures 1 and**

2). Next, we compared the model with readily available scores. Overall, our development model had superior discriminative ability compared to other scores frequently used in patients listed for LT (**Supplementary Table 3** and **Figure 2**)

The SALT-M score was robust despite the addition of other clinical variables or analyses. We conducted sensitivity analyses to assess whether the AUROC changed significantly by adding other clinically relevant variables (**Supplementary Table 4**). The presence of MDRB infections, fungal, or both were not independently associated with within one-year mortality. Considering the severe inflammatory response in patients with ACLF, measured by white blood cell count, we found no independent association between WBC and post-transplant mortality within one year. The discriminatory ability to predict 3, 6 or, 9-months post-LT survival remained the same with AUROC between 0.71 and 0.74 (**Supplementary Table 5**). The Cox proportional hazard model using the same variables of the SALT-M score showed an AUROC of 0.69 (95%CI: 0.58-0.77), however, there was evidence of proportional hazards violation with BMI (**Supplementary Table 6**). The discriminatory performance of our model to assess 1-year post-LT mortality in ACLF 2 and 3 is reflected by an AUROC 68% and 76%, respectively (**Supplementary Table 7**). We used fixed effect model to account for the differences in the center-specific mortality thresholds and found that SALT-M score had similar discriminatory ability, independent of different center-specific mortality rates (Supplementary **Table 8**) [AUROC 0.73, 95%CI: 0.68-0.69, SALT-M model adjusted by center, fixed effect model)

The SALT-M score consistently performed well in the external validation sample.

There were 120 participants with complete data to validate our model. All of these participants had ACLF-3 and collapsed inotrope use as yes/no, rather than our original ordinal zero, one or two, or more inotropes. The French participants had a higher proportion of the use of inotropes (77% vs. 64%), higher respiratory failure (48% vs. 36%), and lower BMI (median 26 vs.30 kg/m^2) compared to the MODEL Consortium (**Supplementary Table 9**). Using the French cohorts, the AUROC of the SALT- M score was 0.80 (95%CI: 0.69-0.87) [**Table 3**], with a moderate underestimation (intercept 0.36, slope 1.38, **Supplementary Figure 3**).

Median Length of Stay (LOS) in patients transplanted

Using the same principle of selecting impactful clinical variables, we built on our ACLF-LT-LoS score as an exploratory analysis to assess independent covariates associated with the median LOS after LT. For example, we added in this model the presence of MDRB and/or fungal infection, the use of any form of RRT, higher WBC count at LT, or prior history of abdominal surgery hypothetically leading to longer surgery time. Overall the median (Q1-Q3) LOS in this cohort after liver transplantation was 20.0 (13.0-33.0) days, including those who died within one year. Given that 60.6% of deaths occurred within three months, we added mortality within 90 days as an independent variable to other variables of the ACLF-LT-LoS score. We removed the only two deaths that occurred on the same admission of the LT since all other deaths occurred after the first discharge from the LT. BMI showed a U-shape association with length of stay, thus, was transformed into a quadratic component. (**Table 4**). We found that older age, respiratory failure at LT, BMI, and MDRB/fungal infection were independently associated with median LoS. Other factors such as circulatory failure, WBC at

LT, the use of RRT, while not associated with median LoS, were still included within the ACLF-LT-LoS score because of clinical relevance and showed adequate calibration (**Figure 3**).

Clinical applicability

In **Figure 4** we show two different patient clinical scenarios using our two scores, which can be incorporated into the discussion of these patients. In these two patients with severe ACLF, the 1-year mortality probability is 53% with a median LOS of 31 days for a 60 year-old patient, compared to 19% mortality with a median post-LT LOS of 20 days. The tool can also be used in the following free online calculator https://vocal.shinyapps.io/MODEL/

CONCLUSIONS

Severe ACLF is common in hospitalized patients admitted with decompensated cirrhosis [3], and those who are transplanted have good outcomes. However, access to LT for patients with severe ACLF remains poor, and there is a need to identify patients who would most benefit from transplant more accurately. Hereby, our work provides three major findings that can guide decision-making for this clinical conundrum. *First*, the presence of older age, factors associated with metabolic syndrome (BMI and diabetes), and respiratory and circulatory failures were independent prognostic factors associated with one-year mortality after LT. In contrast, prior MDRB or fungal infections, the presence of abdominal surgery or portal vein thrombosis, among others, were not independent predictors of one-year mortality. *Second*, following strict methodological guidelines and adequate sample size, we developed and externally validated a new prognostic model, the SALT-M score, with acceptable calibration and diagnostic accuracy to predict the probability of death within one year after LT using objective and readily available clinical variables. *Finally*, we provided another score to understand factors associated with median LOS after LT, and showed that age, respiratory failure, BMI, and presence of infection were independent covariates associated with the median LoS.

How will the score be used? These patients were transplanted, so their transplant teams considered them good LT candidates. Despite this, the 1-year post-LT mortality was about 20% higher than patients transplanted without ACLF. In this study, we found a way to identify patients who are at a high risk of suboptimal outcome after one year (highest risk group), the use of which may allow more careful monitoring of this group post LT and perhaps allow

dealing with modifiable risk factors such as weaning from inotropes or mechanical ventilation, that could offer a way to impact survival. In the clinical vignette, we show the clinicians how to incorporate this model into clinical practice. ACLF is a dynamic disease, and patients at extremely high risk at assessment may improve during their hospital course. Likewise, those who are lower risk may deteriorate after listing, and when a door organ is available, they may have a very high model score. So, ideally, the SALT-M score should be applied sequentially. Nevertheless, due to the high mortality risk of patients with severe ACLF, it is a clinical dilemma whether to accept a marginal quality donor organ to allow for earlier LT or wait for either an optimal organ offer or improvement in the number of organ failures to increase post-LT survival. Using a Markov decision process model, we showed that LT yielded significantly greater overall survival probability *vs*. remaining on the waiting list for even 1 additional day (p <0.001), regardless of organ quality. Further, the probability of improvement from ACLF-3 to ACLF-2 should not change the recommendations to proceed with LT because the likelihood of organ recovery was less than 10%[29].

Compared with other scores, the SALT-M score was powered for its development and had the largest sample size to date, with granular patient data overcoming the limitation of transplant registry analyses [30]. The SALT-M score combines transplant candidates' baseline characteristics with patients' precise ICU parameters at the time of LT. The SALT-M score confirms the impact of age on the post-LT mortality outcomes for patients with ACLF-3 [31] and shows that diabetes and BMI are also cardinal comorbidities to consider. Concerning ICU characteristics, it confirms that respiratory status significantly impacts the post-LT outcome. Registry studies derived from the UNOS database have shown that intubation was associated

with poorer post-LT outcomes [32, 33]. Still, these studies lacked the granularity to assess respiratory status precisely (regarding the indication of intubation and PaO_2/FiO_2 levels). Previous data have shown that the combination of intubation and PaO_2/FiO_2 ratio<200mmHg was significantly associated with poorer post-LT outcomes [31]. However, we did not consistently collect the PaO_2/FiO_2 ratio or the *arterial* lactate before liver transplantation, so we could not reliably replicate in this Consortium the Transplantation for ACLF-3 Model (TAM), which is a score that has been described to predict mortality after one year from transplant in ACLF-3 [31]. Finally, the SALT-M score has circulatory failure as a key component. This confirms the importance of assessing the hemodynamic status of LT candidates in the ICU immediately before LT.

The SALT-M score is an important step forward to curve the traditional drop-out rate of 20% in listed patients [6], since the drop-out patients can certainly include some that are “too sick for liver transplant”. With our model, transplant teams can gain insights about transplant benefits in individual patients. One-year outcomes after the LT is a common benchmark used to assess centers’ LT performance (13). However, as we move towards 90-day and 365-day grafts in the USA, center-specific surgical organ acceptance practices (Summer of 2023), and medical death on waitlists metric (Summer of 2024)[26], the balance of the listing and transplant behaviors in individual centers are expected to adapt to these newly measured outcomes over the next 5-10 years. While we’re waiting for the implementation of these metrics, our ancillary analyses showed that center-specific mortality rates vary but our model discriminatory ability is still robust. This study underscores the importance of understanding which patients with ACLF should remain listed, be offered a transplant and use marginal donor organs.

ACLF care is a burden for all stakeholders. We showed that it increases healthcare costs and that we can estimate the median LOS in these specific populations. Further, an important proportion of these patients have an unmet need for palliative care specialty consultation at any point during their hospital stay [34, 35]. Gustot, Fernandez et al proposed that having a CLIF-C ACLF score of 64 or more (or four OFs) suggested futility and recommended withdrawal of care if patients were not transplanted candidates [11]. Plotting the SALT-M score value to the predicted probablity of post-LT transplantation mortality, it would not be unreasonable to consider whether patients with a score of more than 35 should undergo an LT in the setting of ACLF (**Figure 4**). The SALT-M estimates need to be considered with caution because, in 28% of the cases, the prediction may be incorrect based on the AUROC. Although our example shows a 21% post-LT mortality in the sample patient, it still could be considered a dismal outcome for that particular center. Future studies in ACLF may need to expand the survival time frame; rather than one year, we should look at five years (not available in our database): a national colloquium in the United Kingdom in 1998 concluded that patients should be offered liver transplantation only if there is an expected five-year survival of greater than 50%[36].

Further, we examined independent covariates associated with the median LoS to inform patients/caregivers and providers about the potential burden of prolonged hospitalization. This information can help when discussing prognosis and health equity in these patients with advanced liver disease [34, 37]. Hereby, we also provided an online calculator incorporating the probability of within 1-year mortality after LT and estimated median length of stay to guide the discussion further when assessing the risks/benefits of liver transplantation in patients with severe ACLF.

Our study has some limitations that deserve attention. First, we did not capture the change in the clinical setting (change from or to the ICU to stepdown/ward), but we feel that our results are still robust since we have considered organ failure(s) at the time of LT. Despite the exclusion of elective intubations, respiratory failure still did not capture those with lung parenchymal disease - a situation most transplant centers will not offer OLT to until there is resolution on imaging and improved oxygen requirements. These should be fixed with prospectively collected data. On the other hand, the dedicated curation of our database creation with rigorous methodology using modern estimation techniques and appropriate sample size allowed us to provide this SALT-M for its clinical application confidently. Second, the study's retrospective nature inherently creates biases, which we tried to minimize by collecting detailed and consecutive data from each clinical site. Also, limiting the data collection to a relatively recent period ensured the availability of granular data with less than 4% missing data. Third, given the retrospective nature of our study, it fails to consider the role of frailty and sarcopenia, which are important determinants of post-transplant mortality. Growing evidence indicates that sarcopenia in transplant candidates is an independent predictor of post-transplant survival and length of stay [38, 39]. We used BMI, but this is an imperfect measure of sarcopenia. Therefore we believe that future studies in the field of ACLF and LT should address the use of non-invasive tools to assess the prognostic value of sarcopenia [40, 41]. Finally, our ACLF-LT-LOS is still considered an exploratory analysis but can give patients and providers a sense of the burden of hospitalization when transplanting severe ACLF. Future directions of the SALT-M score will include its application to prospective cohort studies (e.g. CHANCE study- [6]), whether it can be expanded to ACLF 1, and whether

additional pre-transplant characteristics ACLF influences our predictive ability (e.g., arterial lactate at LT, PaO2/FiO2). In fact, arterial lactate at LT, as a surrogate of circulatory failure, could improve the SALT-M performance given prior positive associations in the setting of transplanted ACLF-3 patients [5, 31].

Additionally, given some deaths due to occult malignancy and cardiac failure in this setting of rapid evaluation in unstable and/or critically sick patients, teams should, where possible, perform appropriate investigations, particularly in high-risk groups. Unfortunately, 25% of the causes of death were not available in this study. Future studies addressing mortality outcomes in ACLF post-transplant should standardize the cause of death to understand five major categories: cardiovascular, cerebrovascular, cancer, infectious, graft-related, and others.

In **conclusion**, we have developed a novel and important decision-making clinical tool that provides essential and relevant information to decide whether the benefits of liver transplantation in patients with severe ACLF balance the risk of mortality and length of stay.

Abbreviations.

ACLF: acute-on-chronic liver failure; AUROC: areas under the receiver operating characteristics curve; BMI: body mass index; CI: confidence interval; CRRT: continuous renal replacement therapy; DM: diabetes mellitus; EASL-CLIF: European Association for the Study of the Liver-Chronic Liver Failure; HD: hemodyalisis; LOS: length of stay; LT: liver transplantation; MDRB: multi-drug resistant bacteria; MICE: Multivariate Imputation by Chained Equations; MODEL: Multi-Organ Dysfunction and Evaluation for Liver Transplantation; OF(s): organ failure(s); RRT: renal replacement therapy; STROBE: STrengthening the Reporting of OBservational studies in Epidemiology ;TRIPOD: Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis;

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The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government.

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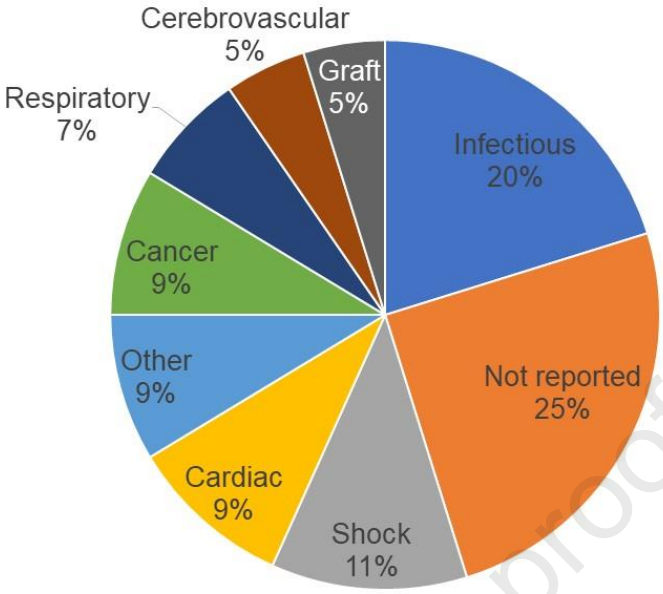
Figure Legends

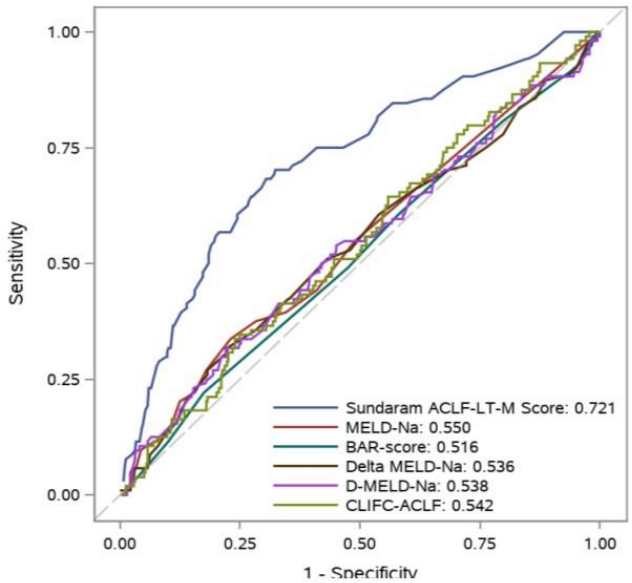
Figure 1. Proportion of causes of deaths in the MODEL Consortium (n=521)

Figure 2. Discriminatory prediction of different models used in liver transplant candidates to predict one-year post-liver transplantation (Aurea under the receiver operating characteristics curve).

Figure 3. Calibration plots showing observed vs. predicted probability 1-year mortality and median length of stay between liver transplantation and first hospital discharge.

Figure 4. Example to illustrate how to use clinically the Sundaram ACLF-LT (SALT)-Mortality score and the ACLF-LT-LOS score



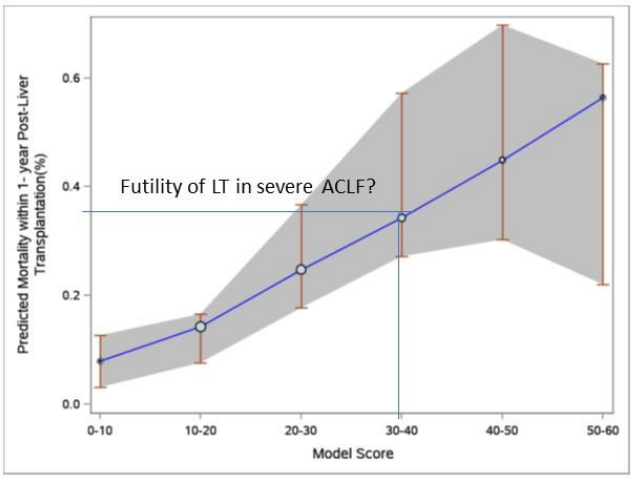


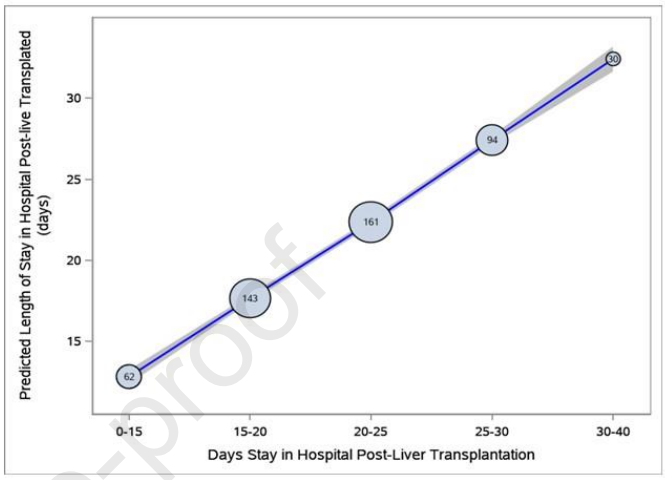
- ✓ Model for end-stage liver disease with sodium correction (MELD-Na) [21]
- ✓ Change in MELD from ICU to transplantation over time (Delta-MELD) [22]
- ✓ Donor (D)-MELD-Na [23]
- ✓ Chronic Liver Failure- C-Acute-on-chronic liver in ACLF (CLIF-C-ACLF) [24]
- ✓ Balance of risk (BAR) score [25]

ACLF-LT score vs. predicted within 1-year mortality risk post-LT and Length of Stay in Severe ACLF

1-year post-LT mortality

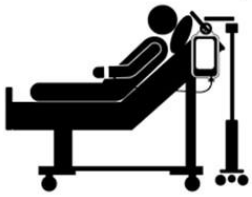
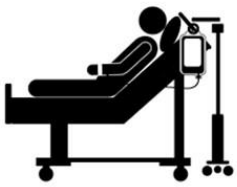
Median LoS after LT





Curve represents model predictions; circles represent predicted numbers who died. Circle size is proportionate to number of deaths at a given score. gray arear is the confidence interval. ACLF: acute-on-chronic liver failure; LT: liver transplantation; LoS: length of stay

Acute-on-chronic Liver Failure (ACLF)- Liver Transplantation scores

	Sundaram ACLF-LT (SALT)-Mortality score: Predicts 1-year mortality probability post-LT		Median length-of-stay in days	
	✓ 60 years ✓ BMI 30 kg/m^2 ✓ 2 pressors ✓ Respiratory failure ✓ Diabetes	53% mortality	✓ MDRB infection ✓ RRT ✓ WBC 20k at LT	31 days
	✓ 40 years ✓ BMI 35 kg/m^2 ✓ one pressor ✓ Respiratory failure ✓ No diabetes	19% mortality	✓ No MDRB infection ✓ No RRT ✓ WBC 12k at LT	20 days

Abbreviations: BMI: body mass index, MDRB: multidrug-resistant bacteria, WBC: white blood cell count in thousands; RRT: any form of renal replacement therapy during hospitalization
Note: an online calculator will be available

Table 1. Baseline characteristics by status at one year from liver transplant in severe ACLF

Variables	N=521		Alive (n=417)		Dead within one year post LT (n=104)		p-value
	Median (p25-p75)	miss %	Median (p25-p75)	miss %	Median (p25-p75)	miss %	p
Age, years	55.0 (46.0-61.0)	0.0 %	54.0 (45.0-61.0)	0.0 %	57.0 (49.5-60.5)	0.0%	0.201
≤ 50yr	184 (35.3)		155 (37.2)		29 (27.9)		
Female, n(%)	222 (42.6)		170 (40.8)		52 (50.0)		0.136
Race, n(%)							0.057
White	318 (61.0		246 (59.0)		72 (69.2)		
Black	60 (11.5)		46 (11.0)		14 (13.5)		
Hispanic	98 (18.8)		87 (20.9)		11 (10.6)		
Other	43 (8.3)		37 (8.9)		6 (5.8)		
Etiology, n(%)							**0.037**
HCV	77 (14.8)		54 (13.0)		23 (22.1)		
Alcohol	207 (39.7)		171 (41.0)		36 (34.6)		
NASH	80 (15.4)		60 (14.4)		20 (19.2)		
Other	157 (30.1)		132 (31.7)		25 (24.0)		
Hepatocellular carcinoma, n(%)	58 (11.1)		45 (10.8)		13 (12.5)		0.626
Triggers							0.737
Hepatic	31 (6.0)		26 (6.2)		5 (4.8)		
Extrahepatic	239 (45.9)		186 (44.6)		53 (51.0)		
Others (e.g., incarcerated hernia, anemia, hyperkalemia)	28 (5.4)		23 (5.5)		5 (4.8)		
Unknown	223 (42.8)		182 (43.7)		41 (39.4)		
Presence of diabetes, n(%)	117 (22.5)		83 (19.9)		34 (32.7)		**0.005**
Presence of CKD, n(%)	158 (30.3)		110 (26.4)		48 (46.2)		**<.0001**
Body mass index, kg/m^2	29.8 (25.0-35.3)	3.8 % (*)	29.6 (24.7-34.6)	5.8 %	31.3 (26.3-36.5)	1.4%	**0.013**
BMI group, n(%)							0.198
< 25 kg/m^2	123 (23.6)		120 (28.8)		23 (22.1)		
25- < 30 kg/m^2	130 (25.9)		106 (25.4)		24 (23.1)		
30- < 35 kg/m^2	118 (22.7)		95 (22.8)		23 (22.1)		
≥35 kg/m^2	130 (25.0)		96 (23.0)		34 (32.7)		

White blood cell, count/mm3	8.4 (5.4-12.3)	1.9 %	8.4 (5.4-12.3)	3.8 %	7.90 (5.4-12.3)	1.0%	0.300
Albumin, mg/dL	3.1 (2.7-3.5)	0.6 %	3.10 (2.7-3.6)	1.0 %	3.00 (2.6-3.4)	0.2%	0.175
MELD-Na	39.5 (35.6-42.8)	0.8 %	39.7 (36.1-43.0)	1.0 %	38.9 (33.8-41.9)	0.2%	0.133
Glucose, mg/dL	115 (96-155)	0.8 %	115 (97-152)	1.0 %	115 (90-167)	0.2%	0.223
Bilirubin, mg/dL	17.4 (9.3-27.8)	0.8 %	17.4 (9.2-28.6)	1.0 %	17.4 (9.8-26.9)	0.2%	0.634
Creatinine, mg/dL	1.5 (0.96-2.3)	0.4 %	1.5 (1.0-2.2)	1.0 %	1.53 (0.9-2.3)	0.2%	0.817
INR	2.5 (1.9-3.0)	0.4 %	2.5 (1.9-3.1)	1.0 %	2.3 (1.7-2.9)	0.2%	0.636
ACLF category, at admission ICU, n (%)							0.435
Non-ACLF	73 (14.0)		54 (13.0)		19 (18.3)		
ACLF-1	80 (15.4)		63 (15.1)		17 (16.4)		
ACLF-2	171 (32.8)		142 (34.1)		29 (27.9)		
ACLF-3	197 (37.8)		158 (37.9)		39 (37.5)		
ACLF category, at LT, n (%)							**0.0233**
Non-ACLF	--		--		--		
ACLF-1	--		--		--		
ACLF-2	237 (45.5)		200 (48.0)		37 (35.6)		
ACLF-3	284 (54.5)		217(52.0)		67 (64.4)		
Vasopressor medication use, n(%)							**<.0001**
None	250 (48.0)		220 (52.8)		30 (28.9)		
One pressor	146 (28.0)		120 (28.8)		26 (25.0)		
Two or more pressors+	125 (24.0)		77 (18.5)		48 (46.2)		
Renal replacement therapy at transplant, n (%)							**0.011**
Unknown/missing	1 (0.19)		1 (0.2)				
None	85 (16.3)		70 (16.8)		15 (14.4)		
HD	129 (24.8)		115 (26.4)		14 (13.5)		
CRRT	306 (58.7)		231 (55.2)		75 (72.1)		
Brain failure at transplant, n(%)	95 (18.2)		66 (15.8)		29 (27.9)		**0.004**
Ventilator use at transplant, n (%)	252 (48.4)		184 (44.1)		68 (65.4)		**<.0001**
Respiratory failure, at transplant , n(%)	132 (25.3)		88 (21.1)		44 (42.3)		**<.0001**
MELD-Na, median (Q1-Q3)- capped at 40	40.00 (36.0-40.0)		40.0 (36.0-40.0)		39.0 (34.0-40.0)		0.087
Fungal infection							0.675
Presence of fungal infection, n (%)	88 (16.89)		69 (16.55)		19 (18.27)		
Presence of multidrug resistant bacteria (MDRB), n(%)	208 (39.92)		164 (39.33)		44 (42.31)		0.579

Presence of fungal or MDRB, n(%)	266 (51.06)		211 (50.60)		55 (52.88)		0.677
Yes							
Donation after cardiac death	73 (14.0)		57 (13.67)		16 (15.38)		0.119
Donor age, years	36.0 (26.0-50.0)	4.0 %	36.0 (27.0-50.0)	1.9 %	37.0 (26.0-49.0)	0.5%	0.685
Length of stay in ICU before transplant (days)	7.0 (4.0-13.0)	0.0 %	7.0 (4.0-13.0)	0.0 %	7.0 (4.0-13.0)	0.0%	0.093
Length of stay after liver transplant (days)	20.0 (13.0-33.0)	1.3 %	20.0 (13.0-32.0)	1.0 %	18.0 (12.0-34.0)	0.7 %	0.924
Days from waitlisting to liver transplantation, days	7.0 (3.0-36.0)		7.0 (3.0-36.0)		7.0 (3.00-36.0)		
Survival post-LT (days)	1143 (579-1827)	0.0 %	1351 (947-1933)	0.0 %	60.5 (18.5-203.5)	0.0%	**<.0001**

(*) represents missingness

For descriptive statistics, mean with standard deviations or median with range were calculated for continuous data, while proportions (%) were used for categorical data. Comparisons between different events/groups, we used independent Student's t -test or the Wilcoxon's rank-sum test if the distribution was not symmetric for continuous variables. The Mann-Whitney U $\chi 2$ test was used for categorical variables.

Table 2: Regression coefficients of logistic regression of the apparent and internally validated.

	Model Development			Internal validation
Predictors	**ß-coefficient (SE)**	**Odds (95% CI)**	**p-value**	**ß-coefficient***
Intercept	-3.57 (0.57)		<0.001	-3.41
Variable selection				
Age group				
Age ≤50	Reference			
Age>50	0.39 (0.26)	1.48 (0.89-2.46)	0.13	0.37
Body mass index (continuous)	0.03 (0.02)	1.03 (1.00-1.06)	0.03	0.03
Inotrope use				
None	Reference			
One	0.44 (0.30)	1.56 (0.87-2.79)	0.14	0.41
Two or more	1.28 (0.28)	3.59 (2.06-6.26)	0.00	1.19
Respiratory failure (EASL-CLIF criteria)	0.64 (0.25)	1.91 (1.16-3.13)	0.01	0.60

Diabetes mellitus	0.45 (0.26)	1.56 (0.93-2.61)	0.09	0.42

Performance, discrimination and calibration		
Performance	**Apparent performance (95% CI)**	**Optimism-Corrected** (95%CI)**
Nagelkerke's R^2	0.16 (0.10-0.22)	0.13 (0.11-0.16)
Brier score	0.11 (0.06-0.16)	0.09 (0.07-0.11)
AUROC (95% CI)	0.72 (0.69-0.76)	0.71 (0.69-0.72)
Calibration slope	0.99 (0.79-1.19)	0.93 (0.73-1.13)

Abbreviations: EASL-CLIF: European Association for the Study of the Liver- Chronic Liver Failure; AUROC: Area under the receiver operating curve; CI: confidence interval; SE: standard error

* Regression coefficients after adjustment for overfitting by shrinkage (shrinkage factor 0.85).

** Optimism-corrected performance = apparent performance–optimism.

Table 3. Discrimination and calibration analysis comparing the Sundaram ACLF-LT (SALT)-M score and the external validation cohorts from Strasbourg and Hôpital Paul-Brousse, France, in patients transplanted in the setting of ACLF-3 (n=120)

	Derivation and internally validated data MODEL Consortium		**External data (Strasbourg and Paul-Brousse)**	
Parameters	Coefficient	p-value	Coefficient	p-value
Intercept	-4.38	<.0001	-8.39	<.0001
Age 50+	0.63	0.061	2.68	0.002
Body mass index, continuous	0.04	0.020	0.12	0.003
Inotropes use (yes/no)	1.25	0.001	1.13	0.085
Presence of respiratory failure	0.59	0.055	1.28	0.013
Presence of diabetes mellitus	0.90	0.008	0.68	0.243
Performance	**Internally validated model performance**		**Externally validated model performance**	
Nagelkerke's R^2	0.17 (0.13-0.20)		0.23 (0.22-0.23)	

Brier score	0.11 (0.07-0.14)	0.15 (0.01-0.02)
AUROC (95% CI)	0.73 (0.70-0.75)	0.80 (0.69-0.87)
Calibration intercept	-0.15 (-0.34-0.03)	0.36 (0.33-0.40)
Calibration slope	0.84 (0.62-1.06)	1.38 (1.37-1.39)

Using multivariate logistic regression

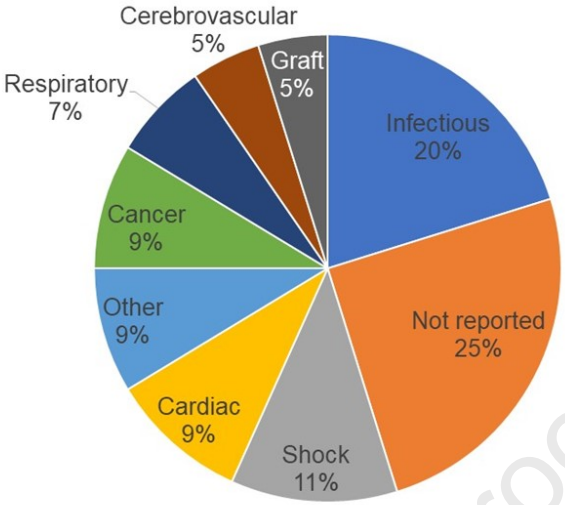
Table 4. Predictors of length of stay (days), calculated using median regression (*)

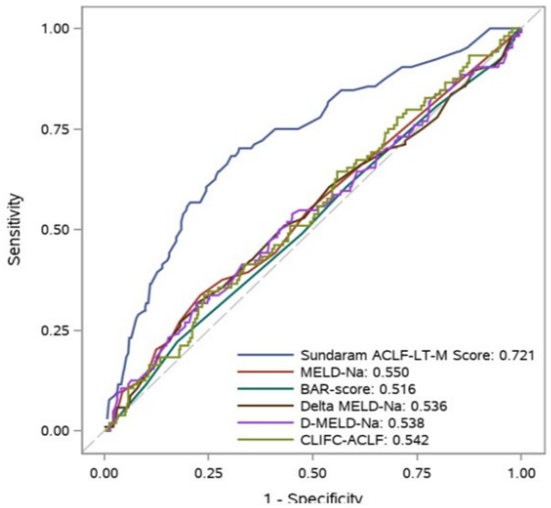
	Full Model		**Selected model (ACLF-LT-LoS)**		**Baseline model (variables included in the ACLF-LT-M)**	
	Coeff (SE)	**p**	**Coeff (SE)**	**p**	Coeff (SE)	p
Intercept	42.51 (11.81)	0.000	45.65 (11.02)	<.0001	44.43 (12.63)	0.001
Age >50	4.08 (1.52)	0.007	3.83 (1.35)	0.005	2.98 (1.54)	0.053
One inotrope (vs. none)	1.92 (2.22)	0.387	2.43 (1.83)	0.185	2.11 (1.87)	0.261
2+ inotropes (vs. none)	0.58 (1.88)	0.757	1.49 (1.69)	0.380	-0.94 (1.88)	0.620
Presence of Diabetes mellitus	1.72 (1.55)	0.268	1.05 (1.69)	0.534	-0.73 (1.94)	0.706
Presence of respiratory failure at LT	6.26 (2.35)	0.008	5.95 (2.45)	0.016	6.84 (2.51)	0.007
BMI, continouus	-1.82 (0.73)	0.013	-1.99 (0.70)	0.005	-1.56 (0.79)	0.050
BMI*BMI	0.02 (0.01)	0.029	0.03 (0.01)	0.013	0.02 (0.01)	0.088
Dead within 90 days	-4.61 (2.15)	0.033	-4.20 (1.77)	0.018	-4.06 (1.89)	0.032
MDRB or fungal infection	4.76 (1.53)	0.002	4.56 (1.58)	0.004		
WBC at LT	0.25 (0.11)	0.022	0.18 (0.11)	0.117		
Renal replacement therapy	-0.04 (1.46)	0.978	0.55 (1.49)	0.713		

Abdominal surgery	1.82 (1.52)	0.230				
Model Fit						
ADJUSTED R^2	11.0%		11.1%		9.2%	
Akaike's information criterion (lower better)	2029.3		2028.4		2050.7	

Abbreviations: LT: liver transplantation, BMI: body mass index; MDRB: multidrug resistant bacteria; WBC: white blood cell count.

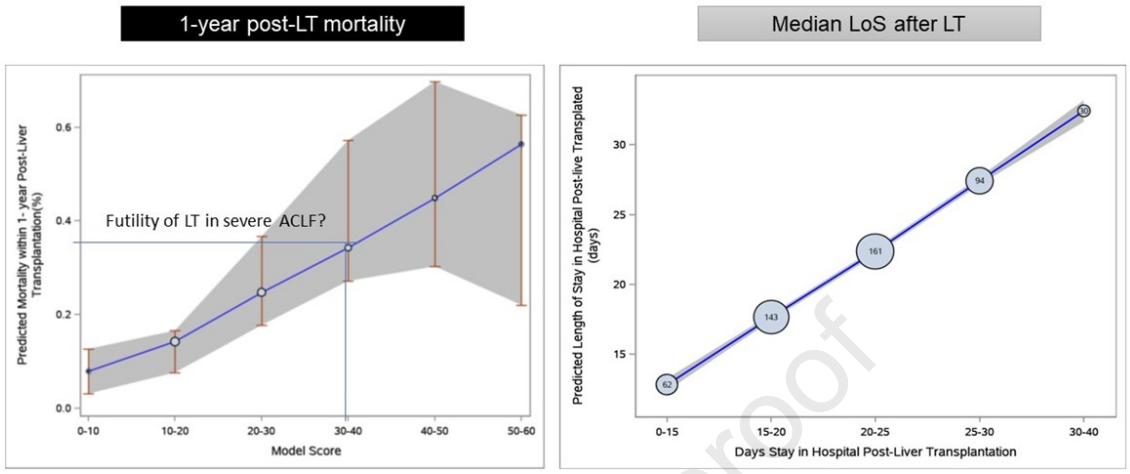
(*) excluded two patients that died after the liver transplantation and before their first discharge and using quantile regression





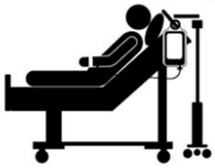
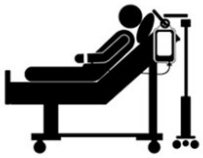
- ✓ Model for end-stage liver disease with sodium correction (MELD-Na) [21]
- ✓ Change in MELD from ICU to transplantation over time (Delta-MELD) [22]
- ✓ Donor (D)-MELD-Na [23]
- ✓ Chronic Liver Failure- C-Acute-on-chronic liver in ACLF (CLIF-C-ACLF) [24]
- ✓ Balance of risk (BAR) score [25]

ACLF-LT score vs. predicted within 1-year mortality risk post-LT and Length of Stay in Severe ACLF



Curve represents model predictions; circles represent predicted numbers who died. Circle size is proportionate to number of deaths at a given score. gray arear is the confidence interval. ACLF: acute-on-chronic liver failure; LT: liver transplantation; LoS: length of stay

Acute-on-chronic Liver Failure (ACLF)- Liver Transplantation scores

	Sundaram ACLF-LT (SALT)-Mortality score: Predicts 1-year mortality probability post-LT		Median length-of-stay in days	
	✓ 60 years ✓ BMI 30 kg/m^2 ✓ 2 pressors ✓ Respiratory failure ✓ Diabetes	53% mortality	✓ MDRB infection ✓ RRT ✓ WBC 20k at LT	31 days
	✓ 40 years ✓ BMI 35 kg/m^2 ✓ one pressor ✓ Respiratory failure ✓ No diabetes	19% mortality	✓ No MDRB infection ✓ No RRT ✓ WBC 12k at LT	20 days

Abbreviations: BMI: body mass index, MDRB: multidrug-resistant bacteria, WBC: white blood cell count in thousands; RRT: any form of renal replacement therapy during hospitalization
Note: an online calculator will be available

The Sundaram ACLF-LT (SALT)-M score predicts 1 year survival after liver transplant in grade 2 and 3 ACLF

MODEL Consortium (development/internal validation)

15 Liver Transplant Centers, 521 patients with ACLF 2-3

External validation

Strasbourg and Villejuif, 120 patients with ACLF-3

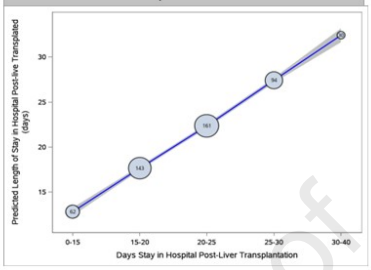
Tool: logistic regression using clinically meaningful variable selection in addition to modern selection techniques. Adequate power for 5 predictors. Used median regression to estimate median length of stay using the same principles.

- ✓ Age 50+
- ✓ Diabetes mellitus
- ✓ Body mass index (continuous)
- ✓ Circulatory failure (one or 2+ inotropes)
- ✓ Respiratory failure

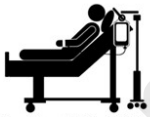
Sundaram ACLF –LT (SALT)-Mortality score predicts 1-year mortality probability post-LT

AUROC 0.72 (development)
AUROC 0.80 (external validation)

Able to assess median length-of-stay in days post LT



Adjusted for age, body mass index, diabetes use of inotropes, respiratory failure, prior h/o MDRB, RRT and WBC at LT



ACLF 2/3 & LT candidate?→ The Sundaram score can help in the discussions of LT in these patients

Abbreviations: MODEL: Multi-Organ Dysfunction and Evaluation for Liver Transplantation; ACLF: acute-on-chronic liver failure; LT: liver transplantation; MDRB: multidrug resistant bacteria; RRT: renal replacement therapy; WBC: white blood cell; AUROC: area under the receiver operating characteristics curve

Highlights

- -Liver transplantation (LT) for patients with acute-on-chronic liver failure (ACLF) with two or more organ failures is challenging. Furthermore, factors associated with the length of stay (LoS) after LT in these patients are important for the clinicians and patients.
- -We derivated and externally validated a model to predict 1-year mortality after LT in patients with ACLF-grade 2 or 3. We also explored factors associated with median LoS.
- -In a cohort of 521 US and 120 French patients, we found that age, presence of diabetes, body mass index, the presence of respiratory failure, and circulatory failure predicted with reasonable accuracy death within one year (72% accuracy in the development, and 80% in the validation cohorts).
- -In addition, the prior presence of infection, use of renal replacement therapy, and leukocyte count at liver transplant also influenced median LoS
- -Our scores can help in discussions with patients and care teams when patients are considered “too sick” for LT.