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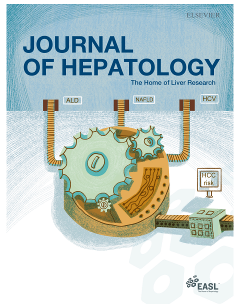

Performance of the model for end-stage liver disease score for mortality prediction and the potential role of etiology

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PII: S0168-8278(21)01948-6

DOI: https://doi.org/10.1016/j.jhep.2021.07.018

Reference: JHEPAT 8373

To appear in: *Journal of Hepatology*

Received Date: 17 February 2021

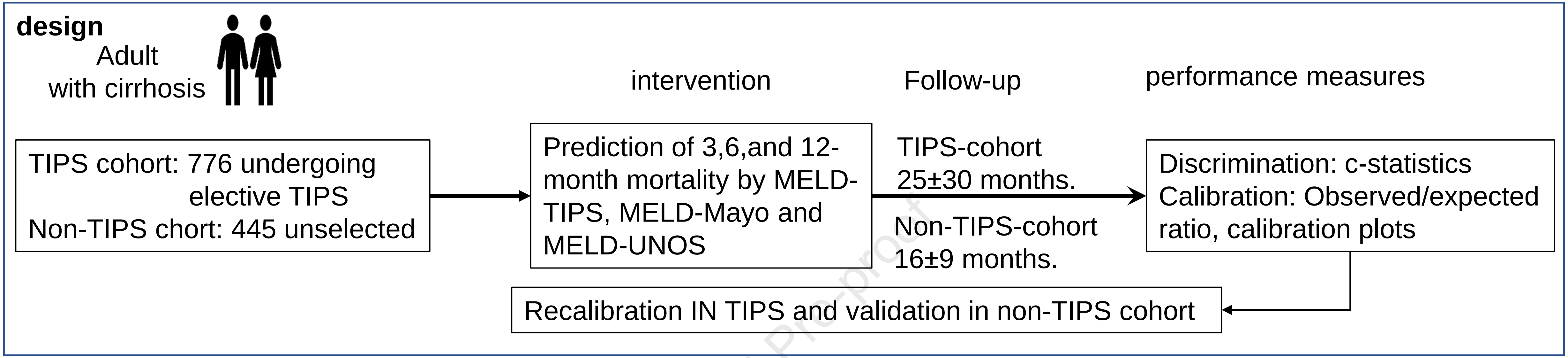
Revised Date: 2 July 2021

Accepted Date: 16 July 2021

Please cite this article as: D’Amico G, Maruzzelli L, Airoldi A, Petridis I, Tosetti G, Rampoldi A, D’Amico M, Miraglia R, De Nicola S, La Mura V, Solcia M, Volpes R, Perricone G, Sgrazzutti C, Vanzulli A, Primignani M, Luca A, Malizia G, Federico A, Dallio M, Andriulli A, Iacobellis A, Addario L, Garcovich M, Gasbarrini A, Chessa L, Salerno F, Gobbo G, Merli M, Ridola L, Baroni GS, Tarantino G, Caporaso N, Morisco F, Pozzoni P, Colli A, Belli LS, Performance of the model for end-stage liver disease score for mortality prediction and the potential role of etiology, *Journal of Hepatology* (2021), doi: https://doi.org/10.1016/j.jhep.2021.07.018.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of

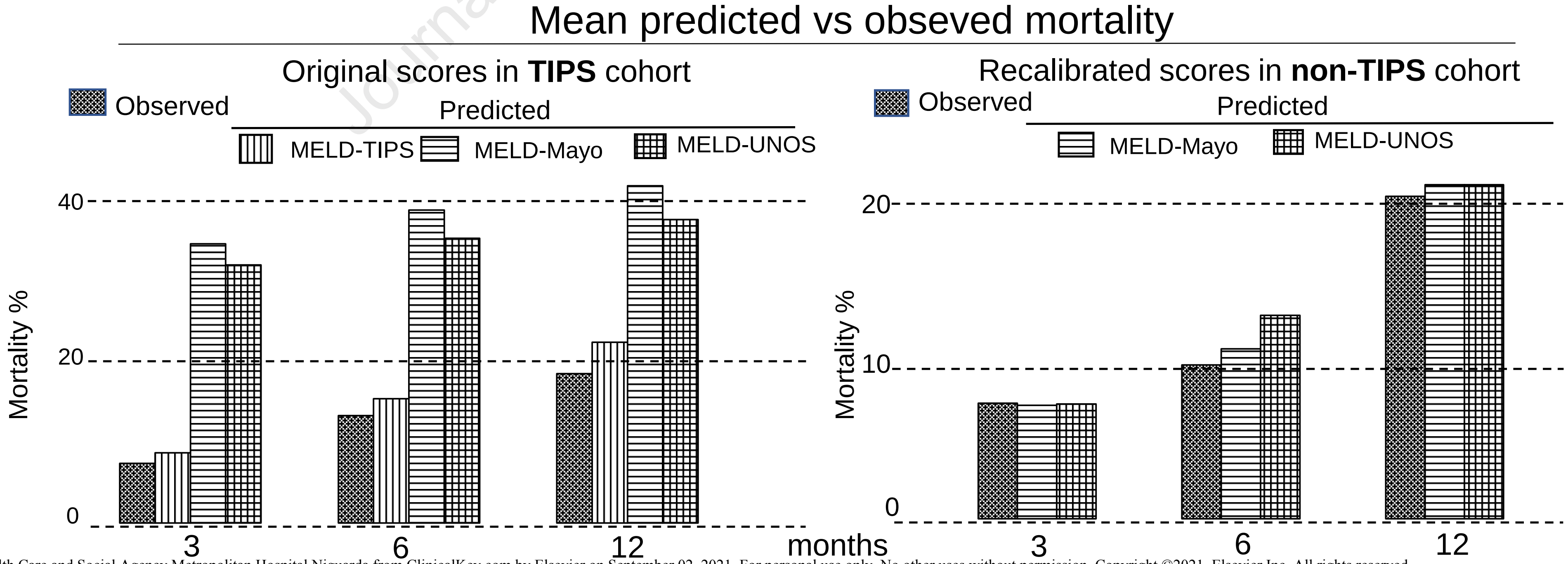
Validation of the model for end stage liver disease (MELD) to predict mortality



findings

C-statistics range for 3,6 and12 months predictions

score	TIPS cohort	Non-TIPS cohort
MELD-TIPS	0.68-0.70	0.66-0.71
MELD-Mayo	0.69-0.72	0.67-0.72
MELD-UNOS	0.68-0.72	0.65-0.76



Title

Performance of the model for end-stage liver disease score for mortality prediction and the potential role of etiology

Short title

MELD performance

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Key words: MELD; clinical prediction rule; cirrhosis;TIPS.

Word count 6342 including abstract, text, references, tables, figure legends (not included: lay summary, abbreviations, aknowledgements)

Number of figures and tables: 3 tables and 5 figures

Conflict of interest: all the authors declare that they have nothing to disclose.

Financial support: none

Data availability statement: data supporting the results of present study are available upon request

Authors contribution

Gennaro D’Amico: study concept and design, analysis and interpretation of data, drafting of the manuscript; study supervision

Luigi Maruzzelli: protocol revision, TIPS placement, data collection,

Aldo Airoldi: protocol revision, patient follow-up

Ioannis Petridis: patient follow-up

Giulia Tosetti: data collection, patient follow-up

Antonio Rampoldi: TIPS placement

Mario D'Amico: TIPS placement, data collection

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Agostino Colli: protocol revision, results interpretation, critical revision of the manuscript for important intellectual content

Luca Saverio Belli: protocol revision, results interpretation, critical revision of the manuscript for important intellectual content

Abstract

Bakground & aims: Although discrimination of the model for end stage liver disease (MELD) is generally considered acceptable, its calibration is still unclear. In a validation study, we assessed the discrimination and calibration performance of 3 versions of the model: original MELD-TIPS, used to predict survival after transjugular intra-hepatic portosystemic shunt (TIPS); classic MELD-Mayo; MELD-UNOS, used by United Network for Organ Sharing (UNOS). Recalibration and model updating were also explored. **Methods:** 776 patients submitted to elective TIPS (TIPS cohort), and 445 unselected patients (non-TIPS cohort) were included. Three, 6 and 12-month mortality predictions were calculated by the 3 MELD versions: discrimination was assessed by c-statistics and calibration by comparing deciles of predicted and observed risks. Cox and Fine and Grey models were used for recalibration and prognostic analyses. **Results:** Major patient characteristics in TIPS/non-TIPS cohorts were: viral etiology 402/188, alcoholic 185/130, NASH 65/33; mean follow-up± SD 25±9/19±21months; 3-6-12 month mortality were respectively, 57-102-142/31-47-99. C-statistics ranged from 0.66 to 0.72 in TIPS and 0.66 to 0.76 in non-TIPS cohorts across prediction times and scores. A post-hoc analysis revealed worse c-statistics in non-viral cirrhosis with more pronounced and significant worsening in non-TIPS cohort. Calibration was acceptable with MELD-TIPS but largely unsatisfactory with MELD-Mayo and -UNOS whose performance improved much after recalibration. A prognostic analysis showed that age, albumin, and TIPS indication might be used for a MELD updating. **Conclusions:** In this validation study the MELD performance was largely unsatisfactory, particularly in non-viral cirrhosis. MELD recalibration and candidate variables for a MELD updating are proposed.

Lay summary

While discrimination performance of the Model for End Stage Liver Disease (MELD) is credited to be fair to good, its calibration, the correspondence of observed to predicted mortality, is still unsettled. We found that application of 3 different versions of the MELD in two independent cirrhosis cohorts yielded largely imprecise mortality predictions particularly in non-viral cirrhosis and propose a validated model recalibration. Candidate variables for a MELD updating are proposed.

Introduction.

The Model for End-stage Liver Disease (MELD) is used worldwide to predict the risk of mortality in patients with liver cirrhosis and to prioritize patients for orthotopic liver transplant (OLT). The original MELD was developed using Cox regression to predict survival after elective trans-jugular intrahepatic portosystemic shunt (TIPS) in patients with cirrhosis[1]. It included disease etiology, bilirubin, creatinine and international normalized ratio (INR), as predictors. We will refer to this score as the MELD-TIPS. Subsequently, MELD-TIPS was adapted by removing the predictor "etiology" and multiplying the predictors' coefficients by 10[2]. This is the classic MELD and is commonly adopted to predict mortality in a broader range of patients with advanced liver disease. We will refer to this as the MELD-Mayo score.

The MELD-Mayo score was later modified by the United Network for Organ Sharing (UNOS) in 2002 to restrict the range of possible predictions[3], and in 2016 to account for hyponatremia[4]. This modified score, which we will refer to as the MELD-UNOS, is commonly used for organ allocation priority for OLT.

Therefore, three different versions of the MELD have entered clinical practice and online calculators are available for each of them[5-7], while it is not always clear which one should be used.

Several studies have investigated the performance of the MELD (mostly MELD-Mayo) models, reporting promising discrimination with concordance statistic ranging from 0.66 to 0.83[8-9]. However, some studies have identified unsatisfactory performance in several patient subgroups, which prompted exceptions to the MELD and model revisions[10-11]. Moreover, studies of the correspondence between observed and expected mortality (calibration) at defined observation times are lacking [9].

Therefore, while the MELD helps physicians in ranking patients according to risk, it is hardly applicable when mortality probability is a key for clinical decisions or simply to inform the patient on his expected survival.

In the present study we assessed the discrimination and calibration performance of mortality predictions by the afore-mentioned three MELD scores in two independent cohorts of patient with cirrhosis. Recalibration and model updating are also explored.

METHODS

Study participants.

Two independent patient cohorts were included.

TIPS-cohort. A total of 776 patients with cirrhosis from any etiology consecutively submitted to elective TIPS for refractory variceal bleeding or refractory ascites from July 1,1999 to May 31, 2020 were included. Since the study was planned in January 2017, 234 patients were included prospectively and 542 retrospectively. Inclusion criteria were the same as in the MELD derivation study[1]. Therefore, patients with other indications (n=199), including emergency, early or rescue TIPS (n=83), were not included.

Patients still alive at inclusion gave oral informed consent to participate in the study. Those already deceased had previously given informed consent to use their collected data for clinical research.

Non-TIPS cohort. This cohort was enrolled in a prospective multicenter study of the clinical course of cirrhosis promoted by the Italian Association of the Study of the Liver (AISF) and designed in 2009. Inclusion criteria were: newly diagnosed cirrhosis from any etiology or first decompensation of cirrhosis. Exclusion criteria were: hepato-cellular carcinoma (HCC); previously known cirrhosis; previous decompensation; age <18 years. The study was approved by the local Ethics Committee at each participating center. A total of 445 consecutive participants were prospectively included after informed consent, between March 1, 2009 and June 30, 2015 at 11 centers.

For both cohorts, recorded patient information included demographic and clinical data, MELD and Child-Pugh[12] scores at the time of inclusion. Occurrence of any clinical event was recorded during follow-up. Patient records were converted to anonymous files before inclusion in the study dataset.

The study conduct complied with the ethical principles reported in the Declaration of Helsinki[13]. Patient flow across the study phases is shown in supplementary figure 1.

Follow-up and outcomes.

Follow-up was retrospective in 432 patients and prospective in 344 in the TIPS cohort, until October 20, 2020, and was prospective for all the patients in the non-TIPS cohort with study end set at January 2018. In both cohorts all the included patients underwent scheduled control visits at 6-month intervals or as clinically required up to the study end.

The outcome of interest was any-cause death at 3,6 and12 months. When missing, the date of death was ascertained by direct contact with patient relatives or family physician. As in the derivation study[1], OLT was a censoring event to achieve a comparable outcome estimation. However, since censoring OLT may result in biased death risk estimation we also assessed the cumulative incidence function (CIF) of death with OLT as a competing risk[14].

Prediction models.

The three MELD versions were calculated using component variables values obtained at the time of inclusion in the study (supplementary table 1). The three linear predictors were calculated according to the published formulas [1,2,4]:

- MELD-TIPS = 0.378 x $\log_e$ (bilirubin mg/dL) + 1.120 x $\log_e$ (INR) + 0.957 x $\log_e$ (creatinine mg/dL) + 0.643 x (cause of cirrhosis)
- MELD-Mayo = 3.8*$\log_e$(serum bilirubin [mg/dL]) + 11.2*$\log_e$(INR) + 9.6*$\log_e$(serum creatinine [mg/dL]) + 6.4
- MELD-UNOS (i) = [0.378 x $\log_e$ (bilirubin mg/dL) + 1.120 x $\log_e$ (INR) + 0.957 x $\log_e$ (creatinine mg/dL) + 0.643]x10. Bilirubin, creatinine or INR values <1.0 are set to 1 in this formula and the maximum score is set at 40. Creatinine values >4 mg/dL are set to 4 as

well as creatinine values of patients who underwent two or more dialysis treatments in the prior 7 days or who received 24 hours of continuous veno-venous hemodialysis in the prior 7 days. According to the UNOS/OPTN policy 9.1[7], in patients with MELD-UNOS(i) >11, the score was recalculated as follows:

MELD-UNOS= MELD-UNOS(i)+ 1.32 * (137-Na) - [0.033*MELD * (137-Na)]. For this calculation sodium values < 125 mmol/L were set to 125, and values > 137 mmol/L to 137.

Prediction time

Time zero was the date of TIPS placement or of inclusion for the non-TIPS-cohort and times of death prediction were 3, 6 and12 months.

Outcome prediction

Individual patient survival probability was calculated according to the Cox model[15], as reported by Malinchoc[1]:

$S(t)=S_0(t)^{exp(R - R_0)}$ where:

S(t) is the probability of survival at each of the times of interest; *R* is the score value in the individual patient in the present cohorts; R_0 is the score of the average patient in the derivation study[1], 1.127; $S_0(t)$ is the underlying survival probability for an average patient undergoing elective TIPS in the derivation study (table 5, ref 1): S_0 *(3 months)*=0.707; S_0*(6 months)*=0.621; S_0*(12 months)*=0.551. Mortality prediction at the relevant times was calculated as 1-*S(t)*.

However, for comparison, we also calculated the individual patient outcome probability by using S_0 and R_0 from the present cohorts. For MELD-Mayo and MELD-UNOS we used S_0 and R_0 only from our study cohorts because no corresponding data from derivation studies are available. Moreover, to account for any potential bias derived from censoring OLT, we also calculated mortality predictions by the competing risks analysis, according to the formula:

$CIF(t) = 1-(1- CIF_0(t))^{exp(R - R\,0)}$, where CIF(t) is the expected probability of death at time (t), and $CIF_0(t)$ is the baseline cumulative incidence of mortality[16] .

Statistical analysis

Case mix analysis was based on the MELD distribution and on the membership analysis[17] (supplementary material). An explorative analysis by the Cox model[15] was also performed to assess the prognostic value of the individual MELD components in the validation cohorts.

Overall MELD performance (discrimination and calibration) was assessed by the Nagelkerke's R^2 and by the rescaled Brier score [18].

Discrimination has been assessed by the c-statistics[19] and by the Yates slope[18], the difference between the mean death risk predicted in patients who remained alive and in those who died.

Calibration has been assessed by plots showing the relationship of the mean predicted death probability versus the mean observed mortality in deciles of patients with increasing values of the predicted probability. Plots were drawn by a *loess smoother* algorithm[18], to allow more insight in calibration analysis. Differences between predicted probability and observed mortality were assessed by the Hosmer-Lemeshow test[20].

Calibration–in–the-large (Observed/Expected ratio, O/E) and calibration slope were assessed by logistic regression models and differences from their ideal values (0 and 1, respectively) were tested by the Wald test[18].

In a post-hoc analysis of potential factors influencing MELD performance, we assessed c-statistics and calibration-in-the-large according to the type of received stent, period of TIPS placement, type of indication to TIPS and etiology.

For the Meld versions with predictions beyond the 95% CI of observed rates in > 5 deciles, a model recalibration was performed by a proportional hazards model for competing risks[21] with MELD as the only covariate, mortality as the outcome of interest and OLT as a competing risk. The recalibration coefficient was derived in the TIPS-cohort and validated in the non-TIPS cohort. Predicted mortality was estimated according to the proportional hazard model for competing risks as follows[16]:

$CIF_{(t)} = 1\text{-}(1\text{-} CIF_{0(t)})^{exp(MELD_r - MELD_{r0})}$, where $CIF_{(t)}$ is the expected probability of death at time (t), $CIF_{0(t)}$ is the baseline mortality cumulative incidence, $MELD_r$ is the recalibrated MELD and $MELD_{r0}$ is the mean recalibrated MELD in the TIPS-cohort or, respectively in the non-TIPS validation cohort.

To explore the potential for a score updating, a multivariable analysis by the Fine and Grey model[21] has been performed in the TIPS cohort by including the following variables together with MELD-TIPS: gender, age, serum-albumin, serum-sodium, ascites, hepatic encephalopathy, previous variceal bleeding, portal pressure gradient (PPG) before TIPS placement, PPG after TIPS, post TIPS %PPG reduction, bleeding as indication to TIPS, ascites as indication to TIPS, and type of TIPS (covered/uncovered). Quantitative variables were transformed to their natural logarithm to lessen the influence of extreme laboratory values, where appropriate. Single components of the MELD, as well as the Child-Pugh score, were not included to avoid redundancy.

All the performance and prognostic analyses were based on complete cases because missing data were very rare (table1).

RESULTS

Case mix analysis showed significant difference between the derivation and the two validation cohorts (supplementary material), indicating suitability of this study for a score generalizability assessment.

Kaplan Meyer (KM) survival plots censoring OLT, and cumulative incidence function (CIF) of death and OLT by competing risks analysis are reported in figure 1 and 3-6 and 12 month figures in table 1. OLT was significantly more frequent in TIPS-cohort, enrolled at transplant centers, than in non-TIPS cohort (143/776 vs 13/432; p<0.0001).

Cox model analysis showed that among MELD variables, $\log_e$creatinine, $\log_e$ bilirubin and $\log_e$INR, but not etiology were significantly associated with the risk of death in the TIPS cohort, while only $\log_e$bilirubin was significant in the non-TIPS cohort. Of note, MELD components coeffiicients were appreciably and variously different in the two validation cohorts compared with derivation cohort[1] The Fine-Gray model showed only $\log_e$bilirubin being significant in both cohorts and $\log_e$creatinine in TIPS cohort. Details in supplementary material.

Performance of the MELD scores

TIPS-cohort.

The median MELD-TIPS[1] in the 767 patients included in this analysis was 0.874 (range -1.558 to 2.896). C-statistics (95%CI) for 3-, 6- and 12-month mortality were respectively 0.70 (0.62-0.78), 0.70 (0.64-0.75) and 0.68 (0.63-0.73). Other performance estimations (table 2) including calibration-in-the-large were far from satisfactory. Calibration plots showed largely overestimated mortality probability when using S_0 and R_0 from the derivation study across all the assessed prediction times. However, when using S_0 and R_0 from the present cohorts, calibration improved much (panels A- B: figure 2 and supplementary figures 3-4; supplementary table 8).

MELD-Mayo score[2] was assessed in 768 patients. The median score was 10.2 (range from -9.2 to 29.0). C-statistics (95% CI) for 3-, 6- and 12months mortality were respectively 0.72 (0.65-0.80), 0.71 (0.66-0.77), 0.69 (0.64-0.74) and other performance measures were mostly unsatisfactory (table2) except for calibration slope. Calibration plots showed extreme over- and underestimation of expected mortality (panel C: figure 2 and supplementary figures 3-4; supplementary table 9).

MELD-UNOS[4] performance was assessed in 765 patients. The median score was 11.96 (range 6.43-30.01). C-statistics (95%CI) for 3-, 6- and 12-month mortality were respectively 0.72 (0.64-

0.79), 0.70 (0.64-0.75) and 0.68 (0.63-0.73), slightly better than with the MELD-TIPS (table 2). Other performance measures were generally unsatisfactory except for calibration slope. Mortality predictions were largely mis-calibrated (panel D: figure 2 and supplementary figures 3-4; supplementary table 10), with the best O/E ratio (95%CI) being 0.21(0.17-0.27) across all the prediction times (table 2).

Expected mortality computed with OLT as a competing event did not change appreciably (supplementary tables 8-10). Therefore, calibration plots (not shown) were almost overlapping with those shown in figure 2 and supplementary figures 3-4; calibration-in-the-large is shown in table 2.

Explorative analyses of factors potentially influencing MELD performance are shown in table 3. No significant influence was found for covered or uncovered stent, time period of TIPS placement, type of indication to TIPS and etiology. Calibration-in-the-large was better (supplementary table), although still largely unsatisfactory, when indication to TIPS was refractory ascites than bleeding for 6-month prediction with MELD-Mayo and MELD-UNOS. Of note, an important worsening of c-statistics was consistently observed in the last 5 years and in patients with nonviral etiology (table 3). This worsening, seemingly parallels the reduction of hepatitis B or C from 65% to 35% and the increase of alcohol and NASH from 18% to 49% in patients enrolled in this period compared to before ($p<0.0001$). C-statistics were almost always lower in *non-viral* than in *viral* etiology, although not significantly, and in non-viral etiology always ≤0.70 (table 3); a similar trend was observed for O/E ratio (supplementary table 13).

Non-TIPS cohort.

There were overall 433 patients with complete data for performance assessment of MELD-TIPS and MELD-UNOS and 434 for MELD-Mayo (table 2). Median (and range) score values were: MELD-TIPS 0.68(-1.01 to 3.85), MELD-Mayo 9.16(-3.76 to 38.51) and MELD-UNOS 10.79(3.56 to 39.02). C-statistics ranged from 0.65(0.59-0.72) to 0.76(0.67-0.85) across the different prediction times and scores.

With OLT censored, calibration in the large ranged from 0.07(0.04-0.12) to 0.55(0.39-0.79) and also the other performance measures were almost unsatisfactory (table 2). Calibration plots are shown in figure 3 and supplementary figures 5-6 and corresponding data in supplementary tables 10-11. When OLT was considered a competing event, calibration did not change appreciably because only 13 patients were transplanted in this cohort (supplementary table10); calibration in the large is reported in table 2 (calibration plots, almost coincident with those with OLT censored, are not shown).

The reduction of discrimination performance in non-viral etiology was confirmed in non-TIPS cohort and was significant at 12 months with all the 3 scores (figure 4; supplementary table 14); a similar trend was observed for O/E with MELD-Mayo and MELD-UNOS.

MELD recalibration and exploratory updating.

We performed recalibration for MELD-Mayo and MELD-UNOS (details in supplementary material), while considered that the calibration performance of the MELD-TIPS was overall acceptable with mortality predictions always within the 95%CI of observed mortality rates. The Fine and Grey model[21] in the TIPS cohort yielded the following formulas: recalibrated MELD-Mayo=0.0745*(MELD-Mayo); recalibrated MELD-UNOS= 0.0716*(MELD-UNOS). Recalibration appreciably improved the performance of both scores in the TIPS-cohort and even more in the non-TIPS one here used as an external independent validation cohort (figure 5 and supplementary figures 7-8; supplementary table 15).

The prognostic analysis aimed at MELD-TIPS[1] updating showed that age, albumin and ascites as indication for TIPS, were significant together with MELD-TIPS (supplementary table 16). The updated model was: *(0.383*MELD-TIPS) + (0.037*age) + (-0.451*albumin) + (0.744 if indication for TIPS was ascites).* The c-statistics (95%CI) was 0.72(0.66-0.79) for 3-month survival prediction, 0.73(0.68-0.78) for 6-month and 0.70(0.66-0.75) for 12-month and were not significantly different from the original model. Corresponding figures for calibration-in-the-large (95% CI) were 1,25(0.46-3.37) for 3-month, 1.16(0.66-2.01) for 6-month and 0.83(0.57-1.19) for 12-month predictions, showing a consistent improvement of calibration compared to the original model. Calibration plots are shown in supplementary figure 9. Independent validation is needed to assess the performance and applicability of this explorative model updating.

Discussion

A major result of this study is that in two independent cohorts of patients with cirrhosis, MELD performance was globally unsatisfactory either in terms of discrimination or in terms of calibration. Moreover, importantly, discrimination decreased along time parallel to the relative reduction of viral and increase of alcoholic and NASH etiology. The worst calibration performance was found for the Mayo and UNOS versions of MELD. These results were almost overlapping in the two cohorts which were independently recruited and followed-up at different centers and by different physicians. Recalibration of these two scores allowed to satisfactorily re-align predicted and observed mortality with both scores.

The interpretation of these results is that the MELD may not be used in populations with very different case mix distribution compared to the derivation study,[1] like the two included in the present study. Therefore, its use as a survival predictor seems to be not as generalizable as suggested by the MELD-Mayo proposing study[2].

On the other hand, the different patient case-mix in our TIPS cohort compared to the derivation study is explained by the modification of patient selection criteria for TIPS along time together with the use of covered stents, while the difference for non-TIPS cohort is likely explained by the unselected admission in contrast to the derivation study where only patients with refractory ascites or bleeding were included.

In the present study, calibration was particularly poor with MELD-Mayo and MELD-UNOS, while it was still acceptable for MELD-TIPS if underlying survival (S_0) and mean score (R_0) from the present cohorts were used. Reasons for the large miscalibration with these two versions of the score are hard to detect and may lie in the score modifications without recalibration. It is to note, in this respect, that the MELD-Mayo validation was presented only in terms of discrimination in the proposing study[2] and subsequent calibration studies are scanty and show inconsistent results[22-24].

In our study, the role of etiology in the MELD performance is supported by the temporal analysis showing that both discrimination and calibration of the score worsened in the last 5 years parallel to a significant reduction of viral and increase of alcohol and NASH etiology. Importantly this result was even more marked and statistically significant in the non-TIPS cohort whose recruitment started approximately 10 years later than in the TIPS-cohort.

It is therefore likely that removing etiology in the MELD-Mayo score[2] without recalibrating the coefficients of the other component predictors may have contributed to worsening the model calibration performance.

Moreover, censoring OLT in the MELD derivation study[1] instead of considering it as a competing event might have contributed to miscalibration by overestimating the risk of death. For this reason, we used a competing risks approach to recalibrate the Mayo and UNOS versions of the MELD in the TIPS cohort with substantial improvement of performance confirmed in the non-TIPS cohort.

A relevant issue raised from our study and also related to case mix, concerns the use of Cox model based prognostic scores in clinical practice. This requires knowing the mean survival probability (S_0) and the mean score value (R_0) in the target population. However, usually physicians do not have at hands these parameters from their own patient population and use the parameters reported in the model derivation study. A typical example of this is the use the Mayo-Clinic calculator[5] or the corresponding nomogram[1] to predict mortality following TIPS. Both the web calculator and the nomogram are based on S_0 and R_0 from the derivation study[1]. However, our study shows how much predicted probabilities can deviate from observed outcomes when the underlying risk and score distribution of the target population are so much different from the corresponding parameters in the derivation study. This finding calls for caution in using such prediction tools when the underlying risk and predictor distribution are not accounted for. In fact, the use of S_0 and R_0 from our cohorts resulted in acceptable calibration of the MELD-TIPS with predictions always in the 95%CI boundaries of the observed rates.

Obviously, the proposed recalibrations for MELD-Mayo and UNOS, do not overcome the problem of S_0 and R_0, which should be derived from the target population whenever possible, but they allow for more reliable mortality predictions. For post-TIPS survival prediction we have also proposed an updated MELD-TIPS based on age, albumin and TIPS indication, together with a recalibrated MELD. Although it requires full external validation, the model is promising with good calibration and maintaining acceptable discrimination. Importantly, both albumin and age were also significant in a recently reported study proposing a new prognostic score for patient selection to TIPS, the FIPS score[25].

Limitations of the present study are the partially retrospective patient enrollment and follow-up, in the TIPS-cohort. However, we are confident that the risk of bias is minimized by consecutive patient inclusion and the prospective nature of data collection even for patients observed before beginning the study. In fact, the very low number of missing information allowed for complete case analysis avoiding data imputation. Moreover, the results in the TIPS-cohort were fully replicated in the independent non-TIPS prospective cohort. A second limitation may be that the separate analyses of the influence of the indication to TIPS, placement date, type of used stent and etiology of cirrhosis was planned after finding the unexpectedly low calibration with MELD-Mayo and -UNOS versions of the score. Rationale for the analysis of TIPS related factors, were the known TIPS technical improvement along time together with changes in indications and superiority of covered stents which almost completely substituted uncoverd stents in early 2000s. The rationale for assessing the influence of etiology was the progressive reduction of viral and corresponding increase of non-viral etiology of cirrhosis in the last years. Although we did not find any statistically significant difference between c-statistics for viral vs non-viral etiology of cirrhosis in the TIPS-cohort, we found that both discrimination and calibration-in-the-large of the three versions of the MELD were systematically lower for non-viral than viral etiology. However, the etiology effect on MELD performance was even more important and statistically significant in the non-TIPS cohort. This finding strengthens our conclusion that the Mayo and UNOS versions of the MELD are not so broadly generalizable as previously suggested, also in the face of the progressive change of cirrhosis etiology.

In conclusion, the present study provides evidence of largely unsatisfactory performance of MELD-Mayo and MELD-UNOS scores to predict mortality either in patients undergoing TIPS or in unselected patients, particularly in those with non-viral, etiology. Performance of MELD-TIPS is acceptable if underlying survival (S_0) and mean score value (R_0) from the target population are accounted for. A recalibration of both the MELD-Mayo and MELD-UNOS is proposed to be used when clinical decision making is based on the expected probability of death, or for patient prognostic information, until a valid MELD updating or a new prognostic score will be available.

Abbreviations:

MELD: model for end stage liver disease

TIPS: transjugular intra-hepatic portosystemic shunt

HCC: hepato-cellular carcinoma

UNOS: United Network for Organ Sharing

OPTN: organ procurement and transplantation network

OLT: orthotopic liver transplant

AISF: Associazione Italiana per lo Studio del Fegato

KM: Kaplan and Meyer

CIF: cumulative incidence function

SD standard deviation

CI: Confidence Interval

O/E: observed/expected ratio

NASH: nonalcoholic steato-hepatitis

AKNOWLEDGMENT

We are most grateful to Dr Thomas Debray for his important conceptual contribute and thorough manuscript revision; to Dr Davide Bernasconi for conceptual contribute to the application of the Fine and Gray proportional model for competing risks and for manuscript revision.

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Table1. Major patient characteristics for the derivation and validation samples

Patient characteristics	Derivation cohort (1)	Validation cohorts in the present study						
		TIPS cohort					**non-TIPS cohort**	
		Total	Ismett	Niguarda	Maggiore	m#	Multicenter	m#
N patients	231	776	590	137	49		445	
Follow-up, mos *	13.2 (1-45.6)	14.3 (1-170)	13.3 (1-170)	14.8 (1-52)	23.1 (2-95)	8	16.6 (1-67)	0
Age ¶	56±12	59± 10	59±10	60± 9	59±9	7	60±11	0
Etiology N(%)						1		22
Viral	24 (10.4)	402 (51.8)	337 (57.1)	46 (33.6)	19 (38.8)	-	188(42.3)	-
Alcohol	142(61.9)	185 (23.8)	108 (18.4)	57 (41.6)	20 (40.8)	-	130 (29.2)	-
NASH	nr	65 (8.4)	46 (7.8)	15 (10.9)	4 (8.2)	-	33(7.4)	-
Cholestatic	23 (10.0)	18 (2.3)	11 (1.9)	4 (2.9)	3 (6.1)	-	12 (2.7)	-
Other or mixed	41 (17.8)	106 (13.7)	88 (14.9)	15 (10.9)	3 (6.1)	-	72 (16.2)	-
Ascites %	183 (79.4)	629 (84.6)	520 (88.2)	72 (63.1)	37 (75.5)	24	261(58.6)	-
Hepatic encephalopathy %	139 (60.1)	224 (31.8)	168 (29.7)	49 (56.3)	6 (12.2)	72	60 (5.8)	
Albumin (g/dL) ¶	2.7±0.6	3.1±0.6	2.9±0.5	3.4±0.5	3.8±0.5	49	3.1±0.7	3
Bilirubin (mg/dL) ¶	3.9±4.6	1.7±1.2	1.8±1.3	1.3±0.8	1.3±1.0	0	2.8±4.3	2
INR ¶	1.6±0.7	1.3±0.2	1.3±0.2	1.3±0.2	1.3±0.2	0	1.4±0.4	
Creatinine (mg/dL) ¶	1.4±1.2	1.1±0.5	1.1±0.5	0.9±0.4	1.0±0.3	0	0.9±0.5	11
Sodium (mEq/L) ¶	NR	136.2±4.8	135.6±4.7	138.4±4.2	137.2±4.2	7	137±7.9	26
Refractory bleeding ˧	58 (25)	233 (30)	171 (29)	50 (36)	12 (25)	-	-	-
Refractory ascites ˧	173 (75)	452(58)	355 (60)	70 (51)	27 (55)	-	-	-
Bleeding and ascites ˧	nr	90 (12)	63 (11)	17 (13)	10 (20)	-	-	-
PPG pre,mmHg¶§	23.5±8.2	18.0±5.4	17.6±5.2	18.0±5.2	23.0±5.8	7	-	-
PPG post,mmHg¶§	11.2±4.5	7.8±3.6	7.2±3.1	10.5±4.0	7.9±3.6	7	-	-
PPG reduction post TIPS, % ¶§		56	59	40	65	12	-	-
Pugh score (N observations)	9.8±2.1	8.2±1.6	8.4±1.5	7.9±1.6	6.9±1.1	35	7.5±2.1	2
Pugh A/B/C %	8/36/56	14/65/21	11/65/24	19/69/12	29/69/2	35	36/45/19	2
MELD score ¶, ǂR_0								
MELD-TIPS	1.127±1.02‖ǂ	0.861±0.6ǂ	0.953±0.6	0.561±0.6	0.588±0.6	1	0.70±0.7	12
MELD-Mayo	--	10.269±5.1ǂ	10.810±5.1	8.395±4.4	8.999±4.2	0	9.96±6.4	11
MELD-UNOS	--	13.365±5.0ǂ	13.888 ± 5.2	11.683±3.8	11.667±3.6	4	13.121±6.6	12
Deaths, N (%)	110 (47)	274 (35.6)	230 (39.0)	31 (23.7)	13(26.5)	6	288	0
3 months	70 (30)	57 (7.4)	49 (8.3)	8 (6.2)	0(0)	-	31(7.0)	-
6 months	89 (38)⊢	102 (13.3)	84 (14.2)	15 (11.6)	3(6.1)	-	47(10.6)	-
12 months	102 (44)⊢	142 (18.5)	115(19.5)	22 (17,1)	5(10.2)	-	99(22.3)	-
OLT, N(%) ¤	28(12.1)	143(18.7)	120(20.4)	12(9.5)	11(22.5)	0	13(2.9)	-
KM survival, ˧ (S_0)						8		0
3 months	0.707 ˧	0.926 ˧	0.917	0.928	0.979	-	0.930	-
6 months	0.621 ˧	0.866 ˧	0.856	0.876	0.936	-	0.894	-
12 months	0.551 ˧	0.801 ˧	0.788	0.813	0.883	-	0.773	-
CIF of death ˧⊢						8		0
3 months	-	0.071	0.079	0.063	0.021	-	0.070	-
6 months	-	0.128	0.136	0.112	0.06 3	-	0.106	-
12 months	-	0.188	0.199	0.168	0.109	-	0.214	-
CIF of OLT ˧⊢						0		0
3 months	-	0.035	0.041	0.023	0.021	-	0.011	-
6 months	-	0.074	0.079	0.048	0.085	-	0.016	-
12 months	-	0.115	0.115	0.079	0.131	-	0.023	-

number of patients with missing information; * median (range); ¶ mean± standard deviation

Ⅎ Indication to TIPS, number of patients

Ͱ since number of deaths observed at 6 and12 months in the derivation study (1) were not reported, this data is derived by the underlying risk reported in table 5 of ref 1.

ǁ standard deviation for the derivation sample estimated by normal distribution

§ PPG= Portal pressure gradient. PPG pre= before TIPS; PPG post= post TIPS; PPG reduction post TIPS % is calculated as: [(PPG pre – PPG post) / PPG pre]*100

ǂR_0 is the mean value of the score used for calculations of expected survival probability

Ⱶ KM survival is the Kaplan Meyer survival probability, which is the underlying survival probability (S_0) at the times of interest used for calculations of expected survival probability

¤ OLT, orthotopic liver transplant

ⱶͰ Cumulative incidence by competing risks analysis with death and OLT as competing events

Table 2. Performance of the 3 assessed scores

Performance measure	MELD-TIPS		MELD-Mayo	MELD-UNOS
	‡	¶		
	TIPS cohort			
N patients	767		768	765
Score, median (range)	0.874(-1.558 to 2.896)		10.2 (-9.2 to 29.0)	11.96 (6.43-30.01)
	3-month prediction			
R^2 Nagelkerke, %	9.2		11.2	11.0
Brier scaled %	5.4		6.4	6.1
c-statistics	0.70 (0.62-0.78)		0.72 (0.65-0.80)	0.72 (0.64-0.79)
Discrimination slope (95%CI)	0.11 (0.08-0.15)	0.05 (0.03-0.06)	0.32 (0.21-0.44)	0.34 (0.23-0.45)
O/E ratio (OLT censored) #	0.21 (0.14-0.31)	1.316 (0.484-3.582)	0.062 (0.043-0.089)	0.072(0.050-0.103)
O/E ratio (OLT competing) *		1.400 (0.503-3.899)	0.060(0.042-0.087)	0.071(0.049-0.101)
	6-month prediction			
R^2 Nagelkerke, %	10.4		11.7	10.5
Brier scaled %	7.0		7.5	6.6
c-statistics	0.70 (0.64-0.75)		0.71 (0.66-0.77)	0.70 (0.64-0.75)
Discrimination slope (95%CI)	0.12 (0.09-0.15)	0.07 (0.05-0.09)	0.30 (0.21-0.39)	0.30 (0.21-0.39)
O/E ratio (OLT censored) #	0.26 (0.21-0.34)	0.986 (0.560-1.734)	0.119 (0.091-0.156)	0.153 (0.118-0.199)
O/E ratio (OLT competing) *		1.057(0.589-1.890)	0.120(0.092-0.157)	0.154 (0.118-0.200)
	12-month prediction			
R^2 Nagelkerke, %	9.3		10.5	10.3
Brier scaled %	6.8		7.2	7.0
c-statistics	0.68 (0.63-0.73)		0.69 (0.64-0.74)	0.68 (0.63-0.73)
Discrimination slope (95%CI)	0.11 (0.08-0.14)	0.08 (0.06-0.10)	0.25 (0.17-0.33)	0.28 (0.20-0.36)
O/E ratio (OLT censored) #	0.30 (0.24-0.36)	0.714 (0.495-1.030)	0.180 (0.144-0.228)	0.211 (0.167-0.266)
O/E ratio (OLT competing) *	-	0.774(0.525-1.139)	0.181 (0.144-0.228)	0.215(0.170-0.272)
	Non-TIPS cohort			
N Patients	433		434	433
Score, median (range)	0.68(-1.01 to 3.85)		9.16(-3.76 to 38.51)	10.79(3.56 to 39.02)
	3-month prediction			
R^2 Nagelkerke, %	8.9		9.5	11.9
Brier scaled %	6.5		6.4	6.7
c-statistics	0.71(0.61-0.81)		0.72(0.63-0.82)	0.76(0.67-0.85)
Discrimination slope (95%CI)	0.13(0.07-0.18)	0.06(0.03-0.09)	0.30(0.14-0.45)	0.41(0.26-0.56)
O/E ratio (OLT censored) #	0.14(0.09-0.23)	0.51(0.19-1.35)	0.07(0.04-0.12)	0.08 (0.05-0.14)
O/E ratio (OLT competing) *	-	0.52(0.20-1.38)	0.08(0.05-0.13)	0.09(0.05-0.15)
	6-month prediction			
R^2 Nagelkerke, %	8.2		9.3	10.0
Brier scaled %	9.1		9.1	9.3
c-statistics	0.69(0.61-0.78)		0.72(0.64-0.80)	0.72(0.64-0.80)
Discrimination slope (95%CI)	0.12(0.07-0.18)	0.068(0.035-0.102)	0.30(0.17-0.43)	0.35(0.22-0.48)
O/E ratio (OLT censored) #	0.16(0.11-0.23)	0.44(0.22-0.89)	0.10(0.07-0.16)	0.11(0.07-0.17)
O/E ratio (OLT competing) *	-	0.44(0.22-0.88)	0.10(0.06-0.15)	0.11(0.07-0.017)
	12-month prediction			
R^2 Nagelkerke, %	9.1		9.1	6.7
Brier scaled %	17		17	17
c-statistics	0.66(0.59-0.72)		0.67(0.61-0.73)	0.65(0.59-0.72)

Continues over leaf

Discrimination slope (95%CI)	0.12(0.08-0.16)	0.10(0.07-0.14)	0.27(0.18-0.37)	0.25(0.16-0.35)
O/E ratio (OLT censored) #	0.38(0.29-0.49)	0.55(0.39-0.79)	0.22(0.16-0.30)	0.31(0.22-0.43)
O/E ratio (OLT competing) *	-	0.59(0.40-0.85)	0.23(0.17-0.31)	0.32(0.23-0.44)

‡ S_0 and R_0 from the derivation study; ¶ S_0 and R_0 from the validation study

O/E ratio= calibration-in-the-large computed with underlying survival function obtained by censoring OLT

* O/E ratio= calibration-in-the-large computed with underlying survival obtained considering OLT as a competing event with death

Table 3. C-statistics for the 3 assessed scores in patient subgroups according to type of TIPS, date of placement, type of indication to TIPS and viral etiology.

Patient group *	Prediction time	MELD-TIPS (n=767)	MELD-Mayo (n=768)	MELD-UNOS (n=765)
		c-statistics (95% CI)		
Type of stent				
Uncovered	3 months	0.66(0.51-0.81)	0.69(0.53-0.84)	0.80(0.66-0.93)
Covered		0.70(0.62-0.79)	0.73(0.64-0.81)	0.70(0.62-0.79)
Uncovered	6 months	0.72(0.58-0.85)	0.73(0.60-0.87)	0.78(0.66-0.91)
Covered		0.70(0.64-0.76)	0.71(0.66-0.77)	0.69(0.63-0.65)
Uncovered	12 months	0.65(0.52-0.79)	0.64(0.50-0.78)	0.66(0.51-0.81)
Covered		0.68(0.63-0.74)	0.70(0.64-0.75)	0.69(0.64-0.74)
TIPS date				
Before 2009	3 months	0.69(0.57-0.81)	0.69(0.56-0.82)	0.69(0.57-0.82)
2009-2015		0.73(0.62-0.85)	0.75(0.63-0.86)	0.72(0.61-0.84)
From 2016 on		0.57(0.37-0.78)	0.68(0.53-0.83)	0.69(0.53-0.85)
Before 2009	6 months	0.69(0.60-0.78)	0.71(0.61-0.80)	0.70(0.62-0.79)
2009-2015		0.76(0.66-0.85)	0.75(0.66-0.85)	0.73(0.63-0.82)
From 2016 on		0.62(0.51-0.74)	0.66(0.57-0.76)	0.64(0.54-0.74)
Before 2009	12 months	0.69(0.62-0.77)	0.69(0.71-0.77)	0.68(0.60-0.76)
2009-2015		0.69(0.60-0.78)	0.70(0.62-0.79)	0.70(0.62-0.78)
From 2016 on		0.61(0.51-0.71)	0.65(0.55-0.74)	0.63(0.54-0.72)
Type of indication				
Bleeding	3 months	0.61(0.27-0.94)	0.69(0.38-1.0)	0.74(0.45-1.0)
Ascites		0.67(0.58-0.75)	0.68(0.60-0.77)	0.65(0.57-0.74)
Ascites+bleeding		0.75(0.47-1.0)	0.73(0.44-1.0)	0.79(0.48-1.0)
Bleeding	6 months	0.63(0.38-0.87)	0.66(0.42-0.89)	0.72(0.52-0.91)
Ascites		0.67(0.60-0.73)	0.68(0.61-0.74)	0.63(0.57-0.70)
Ascites+bleeding		0.72(0.52-0.92)	0.71(0.52-0.91)	0.75(0.55-0.93)
Bleeding	12 months	0.64(0.49-0.80)	0.69(0.55-0.83)	0.69(0.54-0.83)
Ascites		0.64(0.58-0.70)	0.64(0.58-0-70)	0.63(0.57-0.68)
Ascites+bleeding		0.73(0.58-0.89)	0.71(0.56-0.86)	0.73(0.56-0.89)
Etiology				
Viral	3 months	0.74(0.66-0.83)	0.74(0.66-0.83)	0.72(0.63-0.81)
Non-viral		0.63(0.50-0.76)	0.67(0.54-0.81)	0.70(0.56-0.83)
Viral	6 months	0.75(0.69-0.82)	0.75(0.69-0.82)	0.72(0.65-0.78)
Non-viral		0.64(0.55-0.73)	0.66(0.57-0.75)	0.66(0.57-0.76)
Viral	12 months	0.70(0.64-0.77)	0.70(0.64-0.77)	0.67(0.61-0.74)
Non-viral		0.64(0.56-0.72)	0.66(0.58-0.74)	0.69(0.61-0.76)

*Number of patients in the shown analyses were as follows: uncovered stent 101, covered stent 675; TIPS before 2009, n=252; from 2009 to 2015, n=219; from 2016 on, n=305; viral etiology, n=402; non-viral etiology n=374.
‡ S_0 and R_0 from the derivation study; ¶ S_0 and R_0 from the validation study
# O/E ratio (mean observed to mean expected outcome events) = calibration-in-the-large,
CI = confidence interval

Figure legends

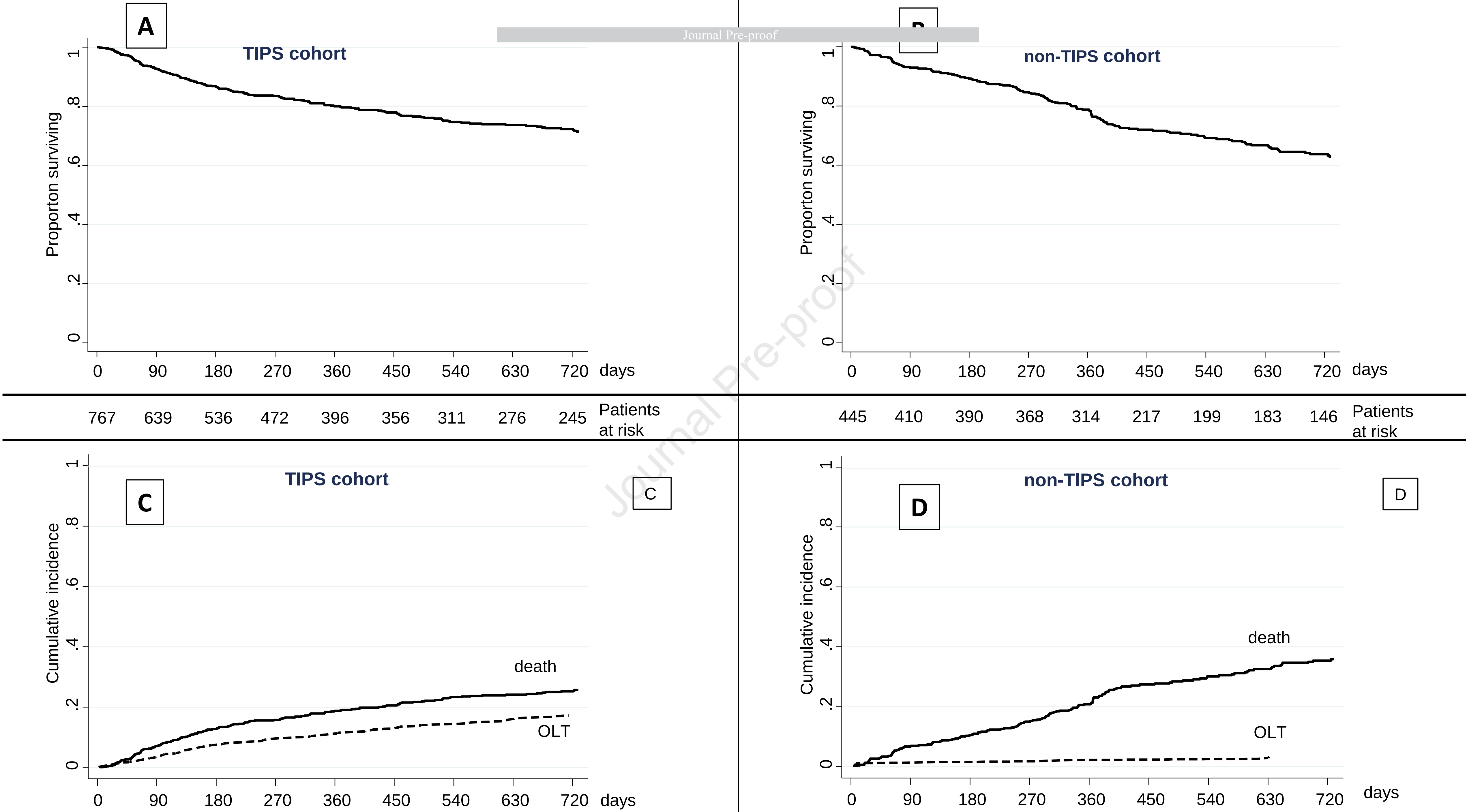
Figure 1. **Survival analysis.** Panels A and B: Kaplan-Meier plots of survival analysis with OLT censored: Panels C and D: competing risks plots of death and OLT cumulative incidences. Numbers between upper and lower panels are patients at risk

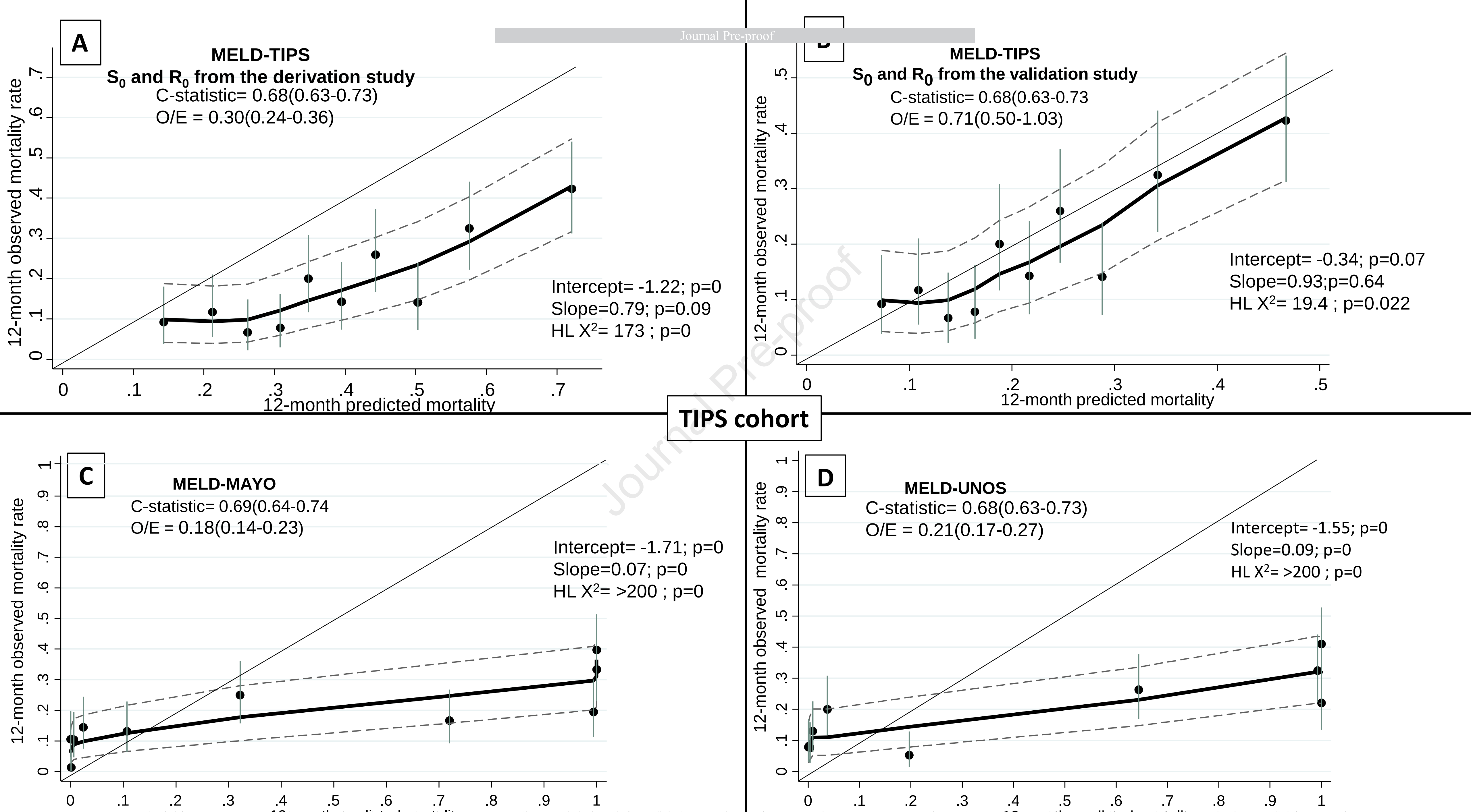
Figure 2. Calibration plots for 12-month mortality prediction in TIPS cohort. Smoothed (loess) calibration plots with 95% confidence bounds (dashed lines) in deciles of patients ordered according to increasing predicted probability of death by the assessed scores. A) MELD-TIPS with S_0 and R_0 from the derivation study; B) MELD-TIPS, C) MELD-Mayo, D) MELD-UNOS; S_0 and R_0 from our TIPS cohort in B-C-D. Vertical bars indicate the 95% confidence intervals of observed mortality rates; the diagonal lines indicate the ideal line of perfect correspondence of predicted to observed mortality. P values for intercept and slope are from Wald test. HL: Hosmer-Lemeshow test.

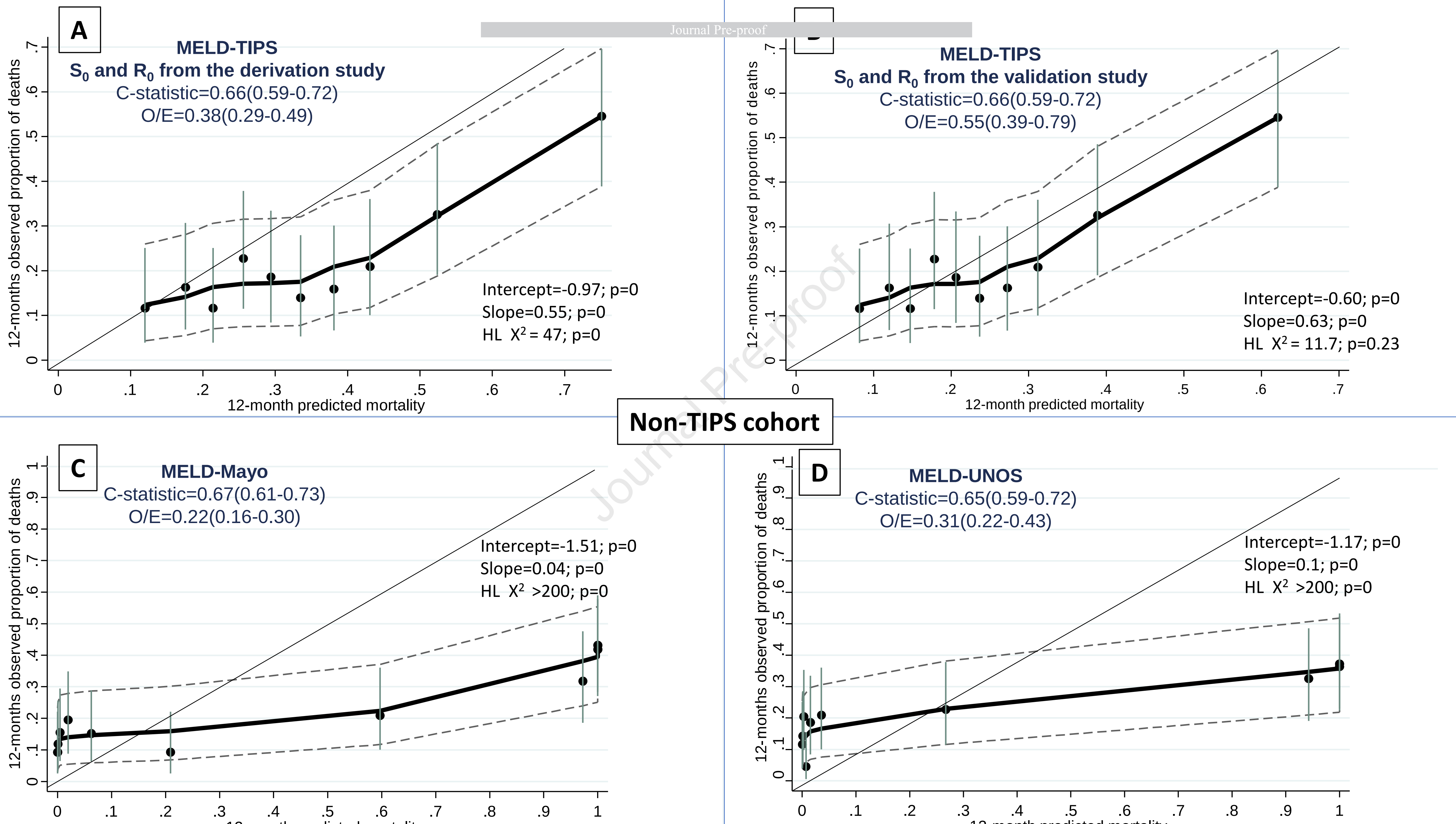
Figure 3. **Calibration plots for 12-month mortality prediction in non-TIPS cohort.** Smoothed (loess) calibration plots with 95% confidence bounds (dashed lines) in deciles of patients ordered according to increasing predicted probability of death by the assessed scores. A) MELD-TIPS with S_0 and R_0 from the derivation study; B) MELD-TIPS, C) MELD-Mayo, D) MELD-UNOS; S_0 and R_0 from our non-TIPS cohort in B-C-D. Vertical bars indicate the 95% confidence intervals of observed mortality rates; the diagonal lines indicate the ideal line of perfect correspondence of predicted to observed mortality. P values for intercept and slope are from Wald test. HL: Hosmer-Lemeshow test.

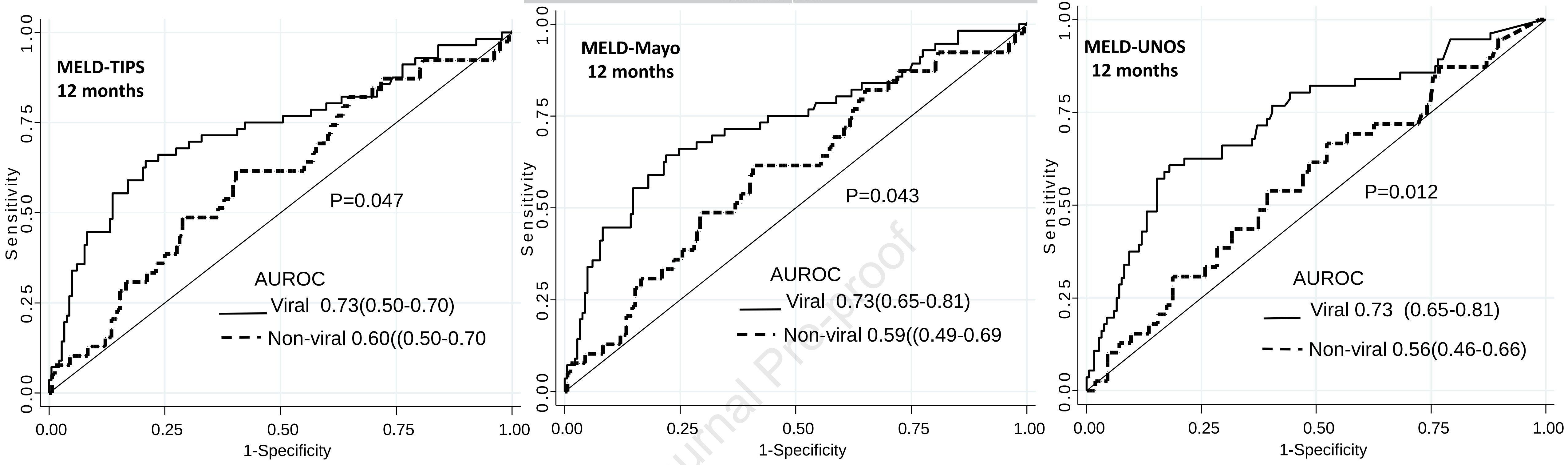
Figure 4. **MELD discrimination performance according to etiology of cirrhosis in non-TIPS cohort.** Receiver Operating Characteristics (ROC) curves for 12- month survival prediction by the 3 assessed scores for patients with viral and non-viral etiology. Differences between curves were assessed by the DeLong test.

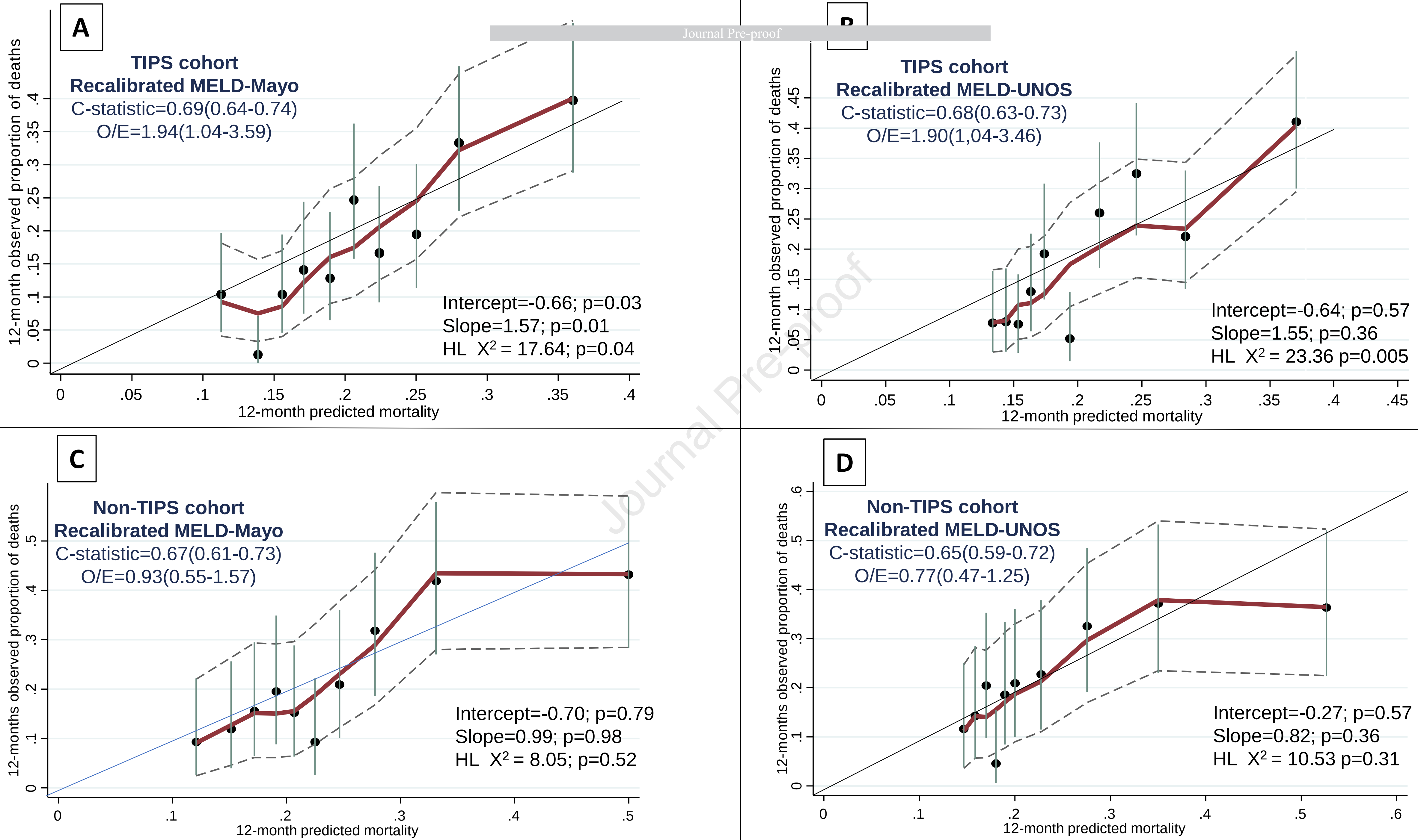
Figure 5. Re-**Calibration plots for 12-month mortality prediction.** Smoothed (loess) calibration plots with 95% confidence bounds (dashed lines) in deciles of patients ordered according to increasing predicted probability of death by the recalibrated MELD-Mayo and MELD-UNOS scores. A-B: TIPS cohort; C-D: non-TIPS validation cohort. Vertical bars indicate the 95% confidence intervals of observed mortality rates; the diagonal lines indicate the ideal line of perfect correspondence of predicted to observed mortality.


A
TIPS cohort
Proporton surviving
0
.2
.4
.6
.8
1
0 90 180 270 360 450 540 630 720 days
767 639 536 472 396 356 311 276 245 Patients at risk
non-TIPS cohort
Proporton surviving
0 90 180 270 360 450 540 630 720 days
445 410 390 368 314 217 199 183 146 Patients at risk
C
TIPS cohort
C
Cumulative incidence
death
OLT
0 90 180 270 360 450 540 630 720 days
D
non-TIPS cohort
D
Cumulative incidence
death
OLT
0 90 180 270 360 450 540 630 720 days


A
MELD-TIPS
S_0 and R_0 from the derivation study
C-statistic= 0.68(0.63-0.73)
O/E = 0.30(0.24-0.36)
Intercept= -1.22; p=0
Slope=0.79; p=0.09
HL X^2= 173 ; p=0
12-month observed mortality rate
12-month predicted mortality
B
MELD-TIPS
S_0 and R_0 from the validation study
C-statistic= 0.68(0.63-0.73
O/E = 0.71(0.50-1.03)
Intercept= -0.34; p=0.07
Slope=0.93;p=0.64
HL X^2= 19.4 ; p=0.022
12-month observed mortality rate
12-month predicted mortality
TIPS cohort
C
MELD-MAYO
C-statistic= 0.69(0.64-0.74
O/E = 0.18(0.14-0.23)
Intercept= -1.71; p=0
Slope=0.07; p=0
HL X^2= >200 ; p=0
12-month observed mortality rate
12-month predicted mortality
D
MELD-UNOS
C-statistic= 0.68(0.63-0.73)
O/E = 0.21(0.17-0.27)
Intercept= -1.55; p=0
Slope=0.09; p=0
HL X^2= >200 ; p=0
12-month observed mortality rate
12-month predicted mortality


A
MELD-TIPS
S_0 and R_0 from the derivation study
C-statistic=0.66(0.59-0.72)
O/E=0.38(0.29-0.49)
Intercept=-0.97; p=0
Slope=0.55; p=0
HL X^2 = 47; p=0
12-months observed proportion of deaths
12-month predicted mortality
MELD-TIPS
S_0 and R_0 from the validation study
C-statistic=0.66(0.59-0.72)
O/E=0.55(0.39-0.79)
Intercept=-0.60; p=0
Slope=0.63; p=0
HL X^2 = 11.7; p=0.23
12-months observed proportion of deaths
12-month predicted mortality
Non-TIPS cohort
C
MELD-Mayo
C-statistic=0.67(0.61-0.73)
O/E=0.22(0.16-0.30)
Intercept=-1.51; p=0
Slope=0.04; p=0
HL X^2 >200; p=0
12-months observed proportion of deaths
12-month predicted mortality
D
MELD-UNOS
C-statistic=0.65(0.59-0.72)
O/E=0.31(0.22-0.43)
Intercept=-1.17; p=0
Slope=0.1; p=0
HL X^2 >200; p=0
12-months observed proportion of deaths
12-month predicted mortality


MELD-TIPS
12 months
P=0.047
AUROC
Viral 0.73(0.50-0.70)
Non-viral 0.60((0.50-0.70
Sensitivity
1-Specificity
0.00
0.25
0.50
0.75
1.00
MELD-Mayo
12 months
P=0.043
AUROC
Viral 0.73(0.65-0.81)
Non-viral 0.59((0.49-0.69
Sensitivity
1-Specificity
MELD-UNOS
12 months
P=0.012
AUROC
Viral 0.73 (0.65-0.81)
Non-viral 0.56(0.46-0.66)
Sensitivity
1-Specificity


A
TIPS cohort
Recalibrated MELD-Mayo
C-statistic=0.69(0.64-0.74)
O/E=1.94(1.04-3.59)
Intercept=-0.66; p=0.03
Slope=1.57; p=0.01
HL X2 = 17.64; p=0.04
12-month observed proportion of deaths
12-month predicted mortality
B
TIPS cohort
Recalibrated MELD-UNOS
C-statistic=0.68(0.63-0.73)
O/E=1.90(1,04-3.46)
Intercept=-0.64; p=0.57
Slope=1.55; p=0.36
HL X2 = 23.36 p=0.005
12-month observed proportion of deaths
12-month predicted mortality
C
Non-TIPS cohort
Recalibrated MELD-Mayo
C-statistic=0.67(0.61-0.73)
O/E=0.93(0.55-1.57)
Intercept=-0.70; p=0.79
Slope=0.99; p=0.98
HL X2 = 8.05; p=0.52
12-months observed proportion of deaths
12-month predicted mortality
D
Non-TIPS cohort
Recalibrated MELD-UNOS
C-statistic=0.65(0.59-0.72)
O/E=0.77(0.47-1.25)
Intercept=-0.27; p=0.57
Slope=0.82; p=0.36
HL X2 = 10.53 p=0.31
12-months observed proportion of deaths
12-month predicted mortality

Highlights

- Discrimination of MELD is widely reported as fair to good, although its calibration is still unclear.
- In two cirrhosis cohorts we found barely acceptable c-statistics, significantly worse in patients with non-viral etiology
- Calibration was largely unsatisfactory with the Mayo and UNOS MELD versions
- Validated recalibrations of MELD-Mayo and UNOS versions are presented which allow reliable predictions for clinical practice.
- Age, albumin and ascites as indication to TIPS are candidate variables for MELD-TIPS updating