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Performance of the Model for End stage Liver Disease (MELD) for mortality prediction and potential role of etiology

--Manuscript Draft--

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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.
Response to Reviewers:	

To the Editor, Journal of Hepatology.

We would be very pleased if you could consider for publication our revised article “Performance of the Model for End stage Liver Disease (MELD) and changing etiology of cirrhosis”. The article has been modified according to the reviewers’ suggestions. In doing this, we have also followed the Editor’s specific indications. The main change in the article is the proposal for a MELD updating for prediction of post TIPS mortality, for which the need for a full external validation has been also underlined. The updated model is reported in the results and the full development in the supplementary material as requested by the Editor. Post-TIPS PPG % reduction has been included in table 1 and in prognostic analyses (supplementary material) although it failed to reach statistical significance. As in revision 1 of the article, results presentation has been balanced between the main text and supporting material in order to comply with the editorial requirements for original articles and to provide the reader with all the needed material supporting the presented results and interpretation.

The study now provides a perspective for a model updating including also age, albumin and indication to TIPS, partially confirming the results reported by Bettinger et al, in their FIPS study.

All the authors have seen and approved the article. The article, neither parts of the article or related papers, have been submitted for publication to any other journal.

Looking forward to your decision,

Sincerely,

The corresponding author

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Below, provide the page number(s) or figure legend(s) where the information can be located. Please make sure that all the information requested below is present in the manuscript.

		Completed, or reported on page(s) or figure legend(s):
1)	**Submission**	
a)	Title page: COI, Financial support, Authors' contributions, keywords.	2,
b)	Structured abstract and lay summary	5-6
c)	All tables and figures included, numbered correctly, with legends (p value and statistical test)	Tables 1-3, pages 24-28 Figure legends page 29
d)	Supplementary data included in a single, separate word file	Y
e)	A detailed point by point response to reviewers comments and changes highlighted in text	y
f)	All authors to complete and upload an ICMJE conflict of interest form.	y
g)	Graphical abstract	Y
2)	**Materials and methods**	
a)	Completed the CTAT form for all reagents and resource to be added to supplementary material	NA
b)	Identify the source and authentication of cell lines	NA
c)	Identify animal species, number of animals used, strain, sex and age.	NA
d)	For animal studies include a statement of compliance with ethical regulations and identify the committee(s) approving the experiments.	NA
e)	For qPCR data provide information according to the Minimum Information for Publication of Quantitative Real-Time PCR Experiments (MIQE) guidelines	NA
3)	**Human subjects**	
a)	Identify the committee(s) approving the study protocol.	Pages 8-9
b)	Include a statement confirming that informed consent was obtained from all subjects.	Pages 8-9

c) For randomized studies report the clinical trial registration number (at ClinicalTrials.gov or equivalent).

d) For phase II and III randomized controlled trials:

I. Please refer to the CONSORT statement and submit the CONSORT checklist with your submission. — NA

II. Include all version of the study protocol and statistical plan (to be published as supplementary information) — NA

e) Identify the inclusion/exclusion criteria in the selection process for the patients included in the study — Page 8

4) Statistics

a) State what statistical tests were completed and why — Pages 11-12

b) Explain the sample size and how this size provides an adequate power to detect a pre-specified effect size. — NA

5) Data deposition (Provide accession codes for deposited data)

a) When using public databases:

I. Identify the source and include a valid link — NA

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Deposition is strongly recommended for many other datasets for which structured public repositories exist — Data available on reasonable request

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1.1 Antibodies

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Name	Sequence	Supplier

1.5 Biological samples

Description	Source	Identifier

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Name of repository	Identifier	Link

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Software name	Manufacturer	Version
STATA	StataCorp 4905 Lakeway Drive- College Station, Texas 77845 USA	16.1

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2.0 Please confirm for randomised controlled trials all versions of the clinical protocol are included in the submission. These will be published online as supplementary information.

Authors have partially answered the questions but the message of the paper remains poor though there's an improvement gap looking at their results (mainly relegated to Supplementary Material, which is disappointing). The message remains the same: MELD has poor predictions after TIPS placement though authors now apply a constant value in front of its value to "improve" the calibration (observed-predicted values). However, this strategy does not essentially change the original model so discrimination (ability to individually rank patients according to their severity) remains exactly the same (poor) and selection cut-offs are not provided. My comments, along with the first review:

- **If variables other than MELD are found to be related with prognosis they must be entered along with MELD (or MELD-UNOS) to propose a new prognostic model: in Suppl Tables 5 and 6 ALBUMIN, AGE AND ASCITES INDICATON are clearly associated with prognosis.** So, combine MELD-UNOS (I would choose these model since hepatologists trust it and it is universally accepted for organ allocation) and these variables (Fine-Gray or Cox, whatever) and you'll have a new prognostic model for elective TIPS. Then provide its discrimination (AUC, C-statistic) and it will probably be well calibrated since developed in your own cohort; the external validation must become from an external cohort. Ascites indication could be included in the analysis probably as a stratifying variable, depending on the relationship with other variables... Authors should chose the best option.

Response: As suggested, we have repeated the prognostic analysis. We used the Fine and Grey model as we did for the model recalibration. Age, albumin and ascites as an indication for TIPS, were the only significant variables at multivariable analysis together with MELD-TIPS. Based on this final model we have proposed an updated MELD-TIPS, as requested by rhe Editor, to be externally validated. As expected, the model has a good calibration in our derivation sample even if the c-statistics improvement is not statistically significant. We have correspondingly changed the abstract, methods, results and discussion. Following the Editor's instructions we have included the results in the main manuscript and the full analysis and calibration plots in the supplementary material.

- **PPG change: authors provide pre and post PPG values but not the relative change caused by TIPS.** Please provide this value and study as a potential modifier of the clinical course; it could be proposed as a later variable in the model, after TIPS placement (Pre-TIPS model, post-TIPS model).

Response: the post-TIPS relative change of PPG has been added in table 1 and it has been included in the prognostic analysis as a covariate (supplementary material).

- **Cox: again, I would consider death and transplantation as the same endpoint and analyze transplant-free survival.** I am not clear to censor OLT. In fact, I would only develop the new model with the coefficients given by the CR analysis taking into account the high proportion of patients undergoing transplantation.

Response: the proposed updated model has been developed by considering OLT as a competing event. For MELD validation, the same outcome used in the derivation study (Malinchoc 2000) has been used.

- **Keywords: please remove "clinical prediction rule"** because authors are not providing any CPR to place or not a TIPS depending on a concrete cut-off. I think they can do it if finally develop a specific prognostic model for TIPS based on MELD and other variables.

Response: The Key word "clinical prediction rule" refers to the MELD, the clinical prediction rule of interest for our validation study.

- **I understand that R1 asked for a non-TIPS cohort though I cannot find the sense to it.** The study is on prognostic variables for elective TIPS, the only thing that this non-TIPS cohort adds is confusion. It is only my opinion.

Response: The study is a validation study. The second cohort provides further validation.

- **Viral etiology:** authors continue to show differences in the performance by etiology, but if I have correctly understood, at MV analysis it is not associated with prognosis (suppl T 6 and 7). If I am right, please remove etiology, it not, please analyze accordingly and enter the variable in the model along with all significant variables.

Response: etiology, as rated by Malinchoc, was significant in his original study and therefore is part of the MELD. What we have shown in our study is that with the recently ongoing change of etiology (reduction of viral and increase of non-viral) the performance of the MELD is changing. We have included etiology in prognostic analyses because it is obviously an important variable even if not significant at multivariable analyses. However, in the prognostic analysis for model updating it is not included to avoid redundancy, because it is part of the model to be updated (Malichoc).

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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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]:

$CIF_{(t)} = 1-(1- CIF_{0(t)})^{exp(MELD_r - MELD_{r0})}$, 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_ecreatinine, log_e bilirubin and log_eINR, but not etiology were significantly associated with the risk of death in the TIPS cohort, while only log_ebilirubin 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_ebilirubin being significant in both cohorts and log_ecreatinine 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

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REFERENCES

1. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871.
2. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.
3. Freeman RB, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E. The new liver allocation system: moving towards evidence based transplantation policy. Liver Transplantation 2002;8:851-858
4. OPTN policy 9. https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf . Page 167. Accessed on October 22nd 2020.
5. https://www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/probability-of-mortality-following-transjugular-intrahepatic-portosystemic-shunts/itt-20434720 (accessed on june the 12th 2020)
6. https://www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/meld-model/itt-20434705 (accessed on june the 12th 2020)
7. https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/ (accessed on june the 12th 2020)
8. Kamath PS, Kim WR. The Model for End-Stage Liver Disease (MELD). Hepatology 2007;45:797–805.
9. Cholangitas E, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, Burroughs AK. A systematic review of the performance of the Model for End-Stage Liver Disease (MELD) in the setting of liver transplantation. Liv Transplant 2006;12:1049-1061
10. Freeman RB Jr., Gish GR, Harper A, Davis GL, Vierling J, Lieblein L et al. model for end-stage liver disease (MELD) exception guidelines: results and recommendations from the MELD exception study group and conference (MESSAGE) for the approval of patients who

need liver transplantation with diseases not considered by the standard MELD formula. Liver Transplantation 2006;12:S128-S136

11. Luca A, Angermayr B, Bertolini G, Koenig F, Vizzini G, Ploner M, et al. An integrated MELD model including serum sodium and age improves the prediction of early mortality in patients with cirrhosis. Liver Transpl 2007;13:1174–1180.
12. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the esophagus for bleeding oesophageal varices. Br J Surg 1973;60:646-649
13. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053
14. Pintile M. Competing risks. A practical perspective.John Wiley & Sons. Chichester 2006
15. Cox DR. Regression models and life-tables (with discussion). J. R. Statist. Soc. B.1972; 34:187–220
16. Austin P, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Statistics in Medicine 2017;36:4991-4400.
17. Debray TP, Vergouwe Y, Koffijberg H, Nieboer D, Steyerberg EW, Moons KG. A new framework to enhance the interpretation of external validation studies of clinical prediction models. *J Clin Epidemiol*. 2015;68(3):279-289. doi:10.1016/j.jclinepi.2014.06.018
18. Steyerberger EW. Clinical prediction models. A practical approach to development, validation and updating. Second edition. © Springer Nature Switzerland AG 2019
19. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29 –36.
20. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. Stat Med. 1997; 16(9):965–80.
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of competing risk. J Am Stat Ass 1999;94:496–509

22. Finkenstedt A, Dorn L, Edlinger M, Prokop W, Risch L, Griesmacher A, et al. Cystatin C is a strong predictor of survival in patients with cirrhosis: is a cystatin C-based MELD better? Liver Int. 2012 Sep;32(8):1211-6.

23. Vilar Gomez E, Bertot LC, Oramas BG, Soler EA, Navarro RL, Elias JD, et al. Application of a biochemical and clinical model to predict individual survival in patients with end-stage liver disease. World J Gastroenterol. 2009 Jun 14;15(22):2768-77.

24. Renfrew PD, Quan H, Doig CJ, Dixon E, Molinari M. The Model for End-stage Liver Disease accurately predicts 90-day liver transplant wait-list mortality in Atlantic Canada. Can J Gastroenterol. 2011 Jul;25(7):359-64

25. Bettinger D, Sturm L, Plaff L, Hahn F, Kloekner R, Volkwein L, et al. Refining prediction of survival after TIPS with the novel Freiburg index of post-TTIPS survival. J Hepatol 2021. doi: 10.1016/j.jhep.2021.05.042.

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 ǂ	58 (25)	233 (30)	171 (29)	50 (36)	12 (25)	-	-	-
Refractory ascites ǂ	173 (75)	452(58)	355 (60)	70 (51)	27 (55)	-	-	-
Bleeding and ascites ǂ	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 ¶, ǂ								
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)ŀ	102 (13.3)	84 (14.2)	15 (11.6)	3(6.1)	-	47(10.6)	-
12 months	102 (44)ŀ	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, ǂ (S_0)						8		0
3 months	0.707 ǂ	0.926 ǂ	0.917	0.928	0.979	-	0.930	-
6 months	0.621 ǂ	0.866 ǂ	0.856	0.876	0.936	-	0.894	-
12 months	0.551 ǂ	0.801 ǂ	0.788	0.813	0.883	-	0.773	-
CIF of death ǂŀ						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 ǂŀ						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

ɬ Indication to TIPS, number of patients

⊢ 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

ɬ 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

ɬ⊢ 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.

Figure 1

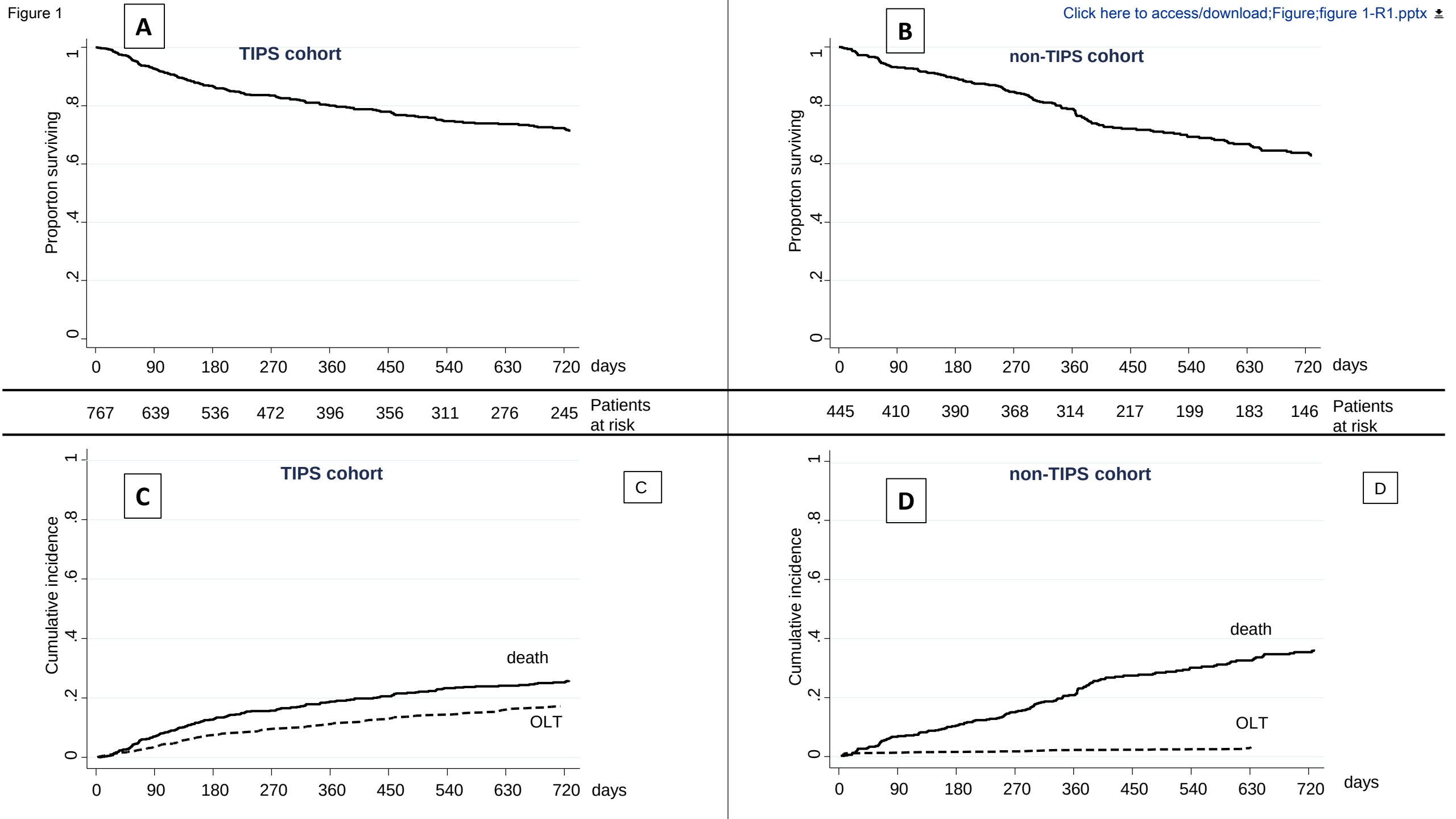


Figure 2

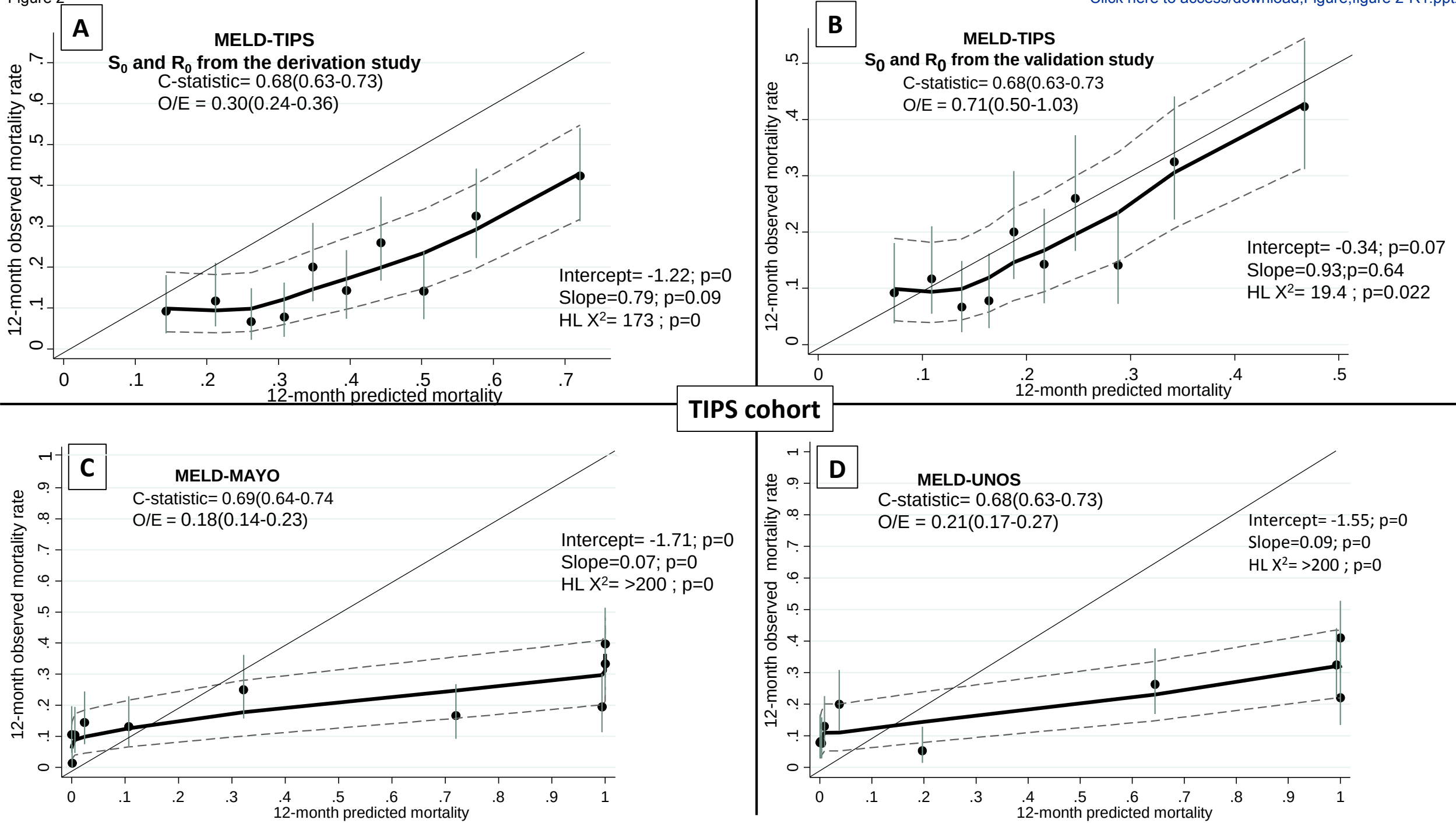


Figure 3

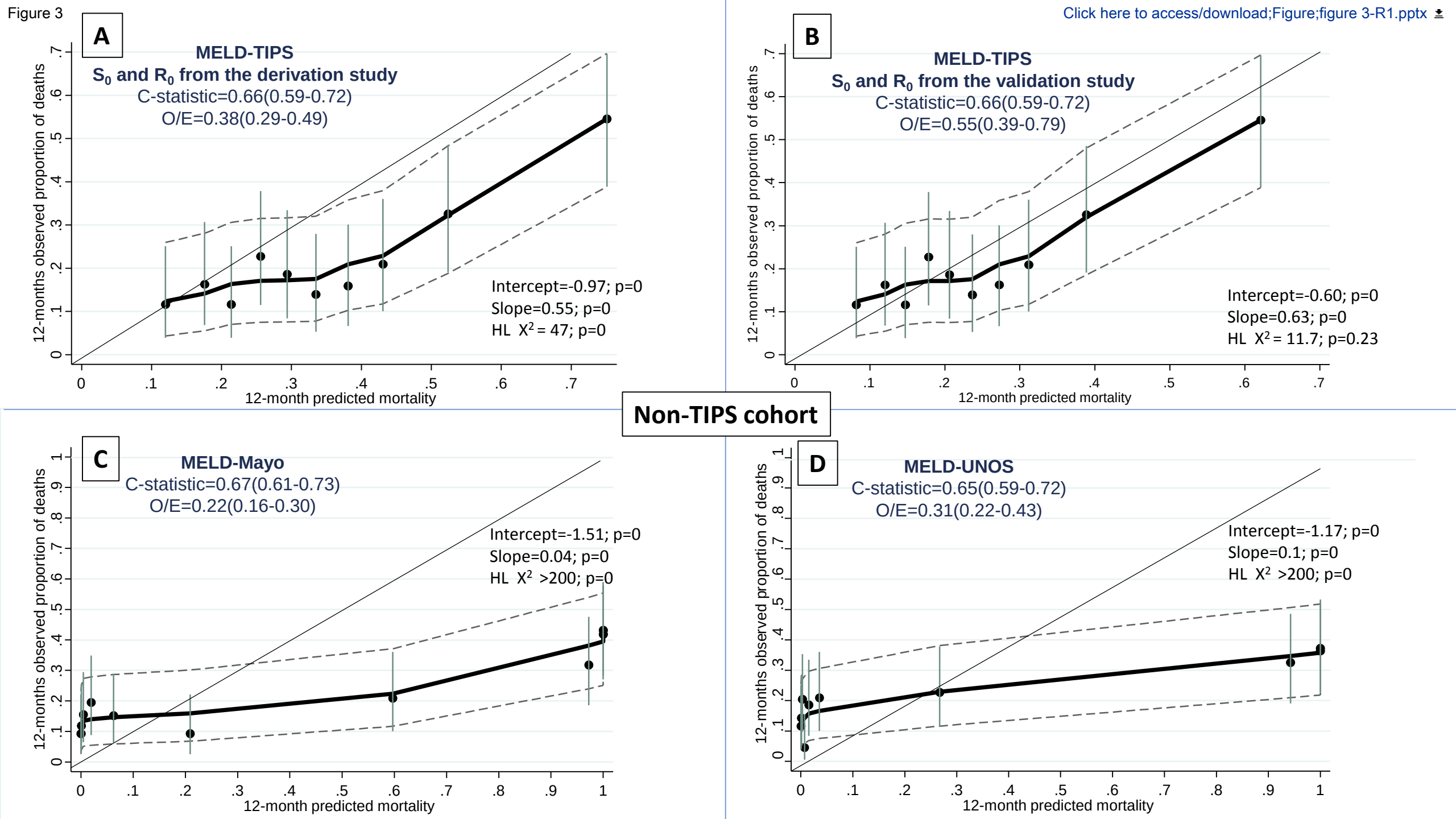


Figure 4

Click here to access/download;Figure;figure 4-R1.pptx

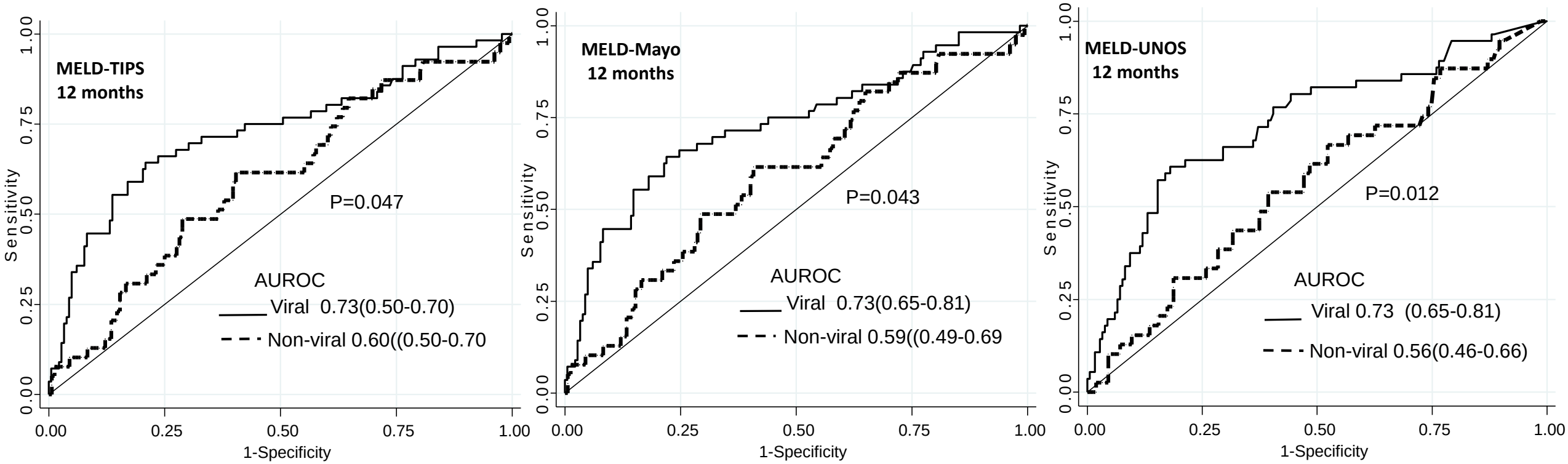
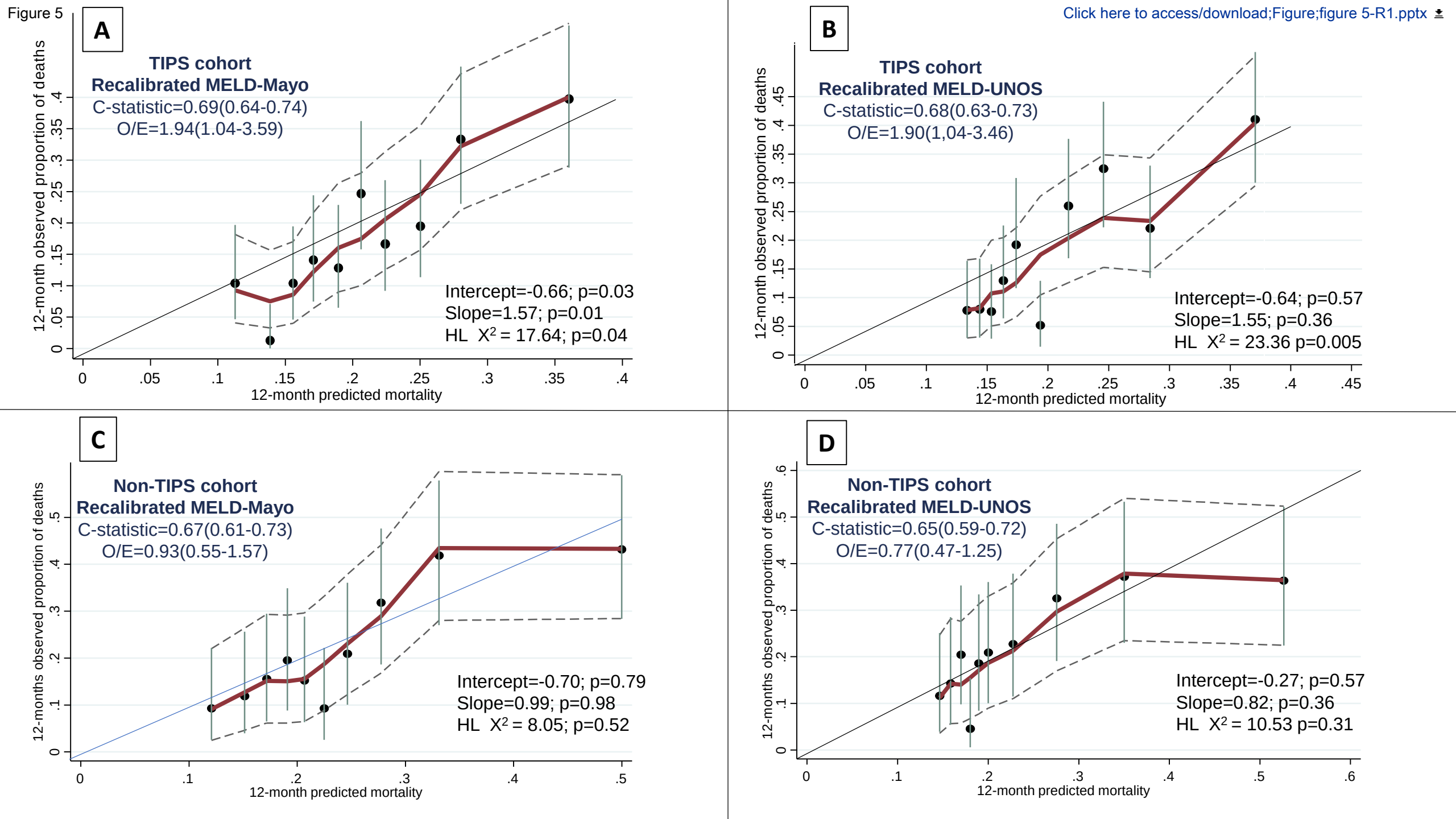


Figure 5



Graphical Abstract

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

design

Adult with cirrhosis

intervention

TIPS cohort: 776 undergoing elective TIPS
Non-TIPS chort: 445 unselected

Prediction of 3,6,and 12-month mortality by MELD-TIPS, MELD-Mayo and MELD-UNOS

Follow-up

TIPS-cohort 25±30 months.

Non-TIPS-cohort 16±9 months.

performance measures

Discrimination: c-statistics
Calibration: Observed/expected ratio, calibration plots

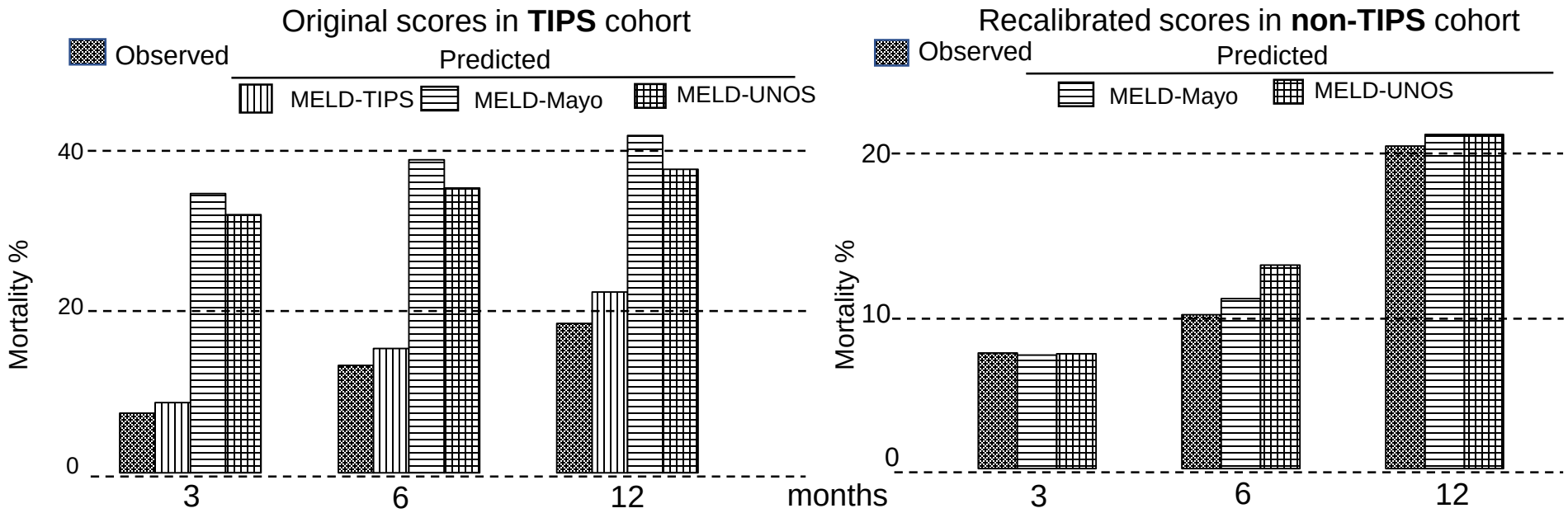
Recalibration IN TIPS and validation in non-TIPS cohort

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

Mean predicted vs obseved 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