Int J Clin Exp Med 2015;8(8):13464-13472
www.ijcem.com /ISSN:1940-5901/IJCEM0010964

Original Article

Predictive accuracy comparison of MELD and Child-Turcotte-Pugh scores for survival in patients underwent TIPS placement: a systematic meta-analytic review

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Received June 1, 2015; Accepted July 21, 2015; Epub August 15, 2015; Published August 30, 2015

Abstract: Background: Child-Turcotte-Pugh (CTP) and the model for end-stage liver disease (MELD) scores have been used commonly to predict the survival in the patients with liver diseases underwent transjugular intrahepatic portosystemic shunt (TIPS). However, a debate has continued for years whether CTP could be replaced by MELD score. We performed a systematic meta-analytic review to compare the prediction capability of both scores in survival among patients with TIPS. Methods: Retrospective cohort studies among patients with TIPS were published as of May 2013 were identified by systematically searching four electronic literature database, such as Ovid Medline, PubMed, EMBASE, and ISI Web of Science. The difference of standardized mean difference (SMD) of c-statistics for the predictive accuracy of 1-, 3-, 6-, and 12-month survival for both MELD and CP scores, defined as effect size (ES), was calculated for each individual study and then pooled across studies using standard meta-analyses with a random effects model. Publication bias was evaluated using funnel plots and Kendall's rank correlation tests. Results: 174 researches articles or conference abstracts were searched and reviewed using the combination of relevant terms in the articles. Finally, 11 articles were defined as eligible studies to evaluate simultaneously the predictive accuracy of MELD and CTP scores. In the meta-analyses, MELD score was superior to CP score in predicting 3-month survival after TIPS (mean ES, 0.63; 95% confidence interval [CI], 0.13-1.14; P=0.01), but the predictive capability in 1-month, 6-month, and 12-month survival was not significant (1-month: mean ES, 0.79; 95% CI, -0.24-1.83; P=0.13; 6-month: mean ES, 0.46; 95% CI, -2.46-3.37; P=0.76; 12-month: mean ES, 0.36; 95% CI, -0.25-0.96; P=0.25). Conclusions: No enough evidence are confirmed so far that MELD score is better than CTP score to assess the overall prognosis after TIPS, especially long-term predictions, but 3-month predictive capability of MELD score significantly outperform CTP score.

Keywords: Transjugular intrahepatic portosystemic shunt (TIPS), the model for end-stage liver disease (MELD) score, Child-Turcotte-Pugh (CTP) score, systematic review, meta-analysis

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) has been demonstrated as an effective procedure to treat esophageal variceal hemorrhage and refractory ascites due to portal hypertension [1, 2], compared with medical treatment and endoscopic treatment. The patient prognosis of TIPS placement was improved significantly along with the development from bare stents to covered stents, such as the FLUENCY expanded, polytetrafluoroethylene (PTFE) -covered stents in the past two decades [3-5]. However, TIPS techniques were not perfect because of its potential dysfunction and costs of re-intervention [6, 7]. Hence, careful selection of patients is crucial to increase the success rate and cost-effectiveness of TIPS replacement.

Several scoring systems have been developed to identify suitable patients for TIPS [8, 9]. Of these, Child-Turcotte-Pugh (CTP) and the model of end-stage liver diseases (MELD) scores were the most common to predict the survival in patients underwent TIPS, which were validated

using several individual studies across US, Europe and Asia [8-19]. Child and Turcotte [20] first proposed a score to assess and classify the risk in cirrhotic patients in 1964, which were modified by Pugh and his colleagues in 1973 [21]. Subsequently, this classification was defined as Child-Turcotte-Pugh (CTP) score, which was more and more to be used to predict the outcome of cirrhosis patients with or without surgery due to its convenience and reliable classification, including liver-transplantation and TIPS [22-24]. Because of its reproducibility and objectivity, MELD score was reported as a novel and better prognostic score superior to the CTP score in some studies, especially short-term survival [10, 11, 14, 15, 17].

However, results from single studies have remained inconclusive and study results have been reported in a very heterogeneous manner. Based on a systematic review published in 2005, MELD scores did not performed better than CTP scores in predicting the survival among patients underwent TIPS, but no meta-analyses were conducted [25]. In addition, several recent studies [8, 9, 15-19] were reported after this systematic review [25]. To our knowledge, this is the first to perform a meta-analysis for assessing the difference of predictive accuracy between MELD and CTP scores in survival among patients after TIPS.

Methods

Literature search and study selection

The PRISMA statement for reporting systematic reviews and meta-analyses of studies was used for our study [26]. A systematic literature search was performed to identify retrospective cohort studies that evaluate the predictive capability of both MELD and CTP scores using c-statistics based on the area under the Receiver Operator Characteristic (ROC) curve in survival among patients underwent TIPS placement. We searched Ovid Medline (Ovid Technologies, Inc., New York, 1946-May 20, 2015), PubMed (National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM), the National Institutes of Health (NIH), up to May 20, 2015), EMBASE (Elsevier, Amsterdam, the Netherlands, 1980-May 19, 2015), ISI Web of Science (Thomson Scientific Technical Support, New York, 1956-May 20, 2008) databases for relevant articles by the following combinations of relevant terms in the article: (Transjugular intrahepatic portosystemic shunt OR TIPS OR transjugular intrahepatic portosystemic stent-shunt OR TIPSS) AND (Child-Pugh OR Child-Turcotte-Pugh) AND (Model For End Stage Liver Disease Score OR MELD). All publications were imported into an Endnote file (Endnote X4, Thomson Reuters, San Francisco, CA), and the duplicates were deleted. Each title and abstract was checked for relevance. The full text was reviewed if the abstract indicated that the article reported predictive values of both MELD and CTP scores for the survival among patients after TIPS. Cross-referencing was employed to complement the study identification process.

Inclusion criteria and data extraction

Studies were defined as eligible if they 1) used prospective or retrospective cohort study design to predict the survival after TIPS replacement; 2) calculated MELD and CTP before TIPS for each patient; 3) reported c-statistics based on the area under the ROC curve for both MELD and CTP and 95% confidence intervals (CI), which are used to calculate effect size (ES) estimates in our meta-analyses; 4) published in all languages.

From eligible studies, at least two authors extracted the following data independently from each study in a standardized manner, and any disagreement was resolved by consensus: authors, publication year, country, enrollment period, characteristics of the study population, duration of follow-up, mean of MELD and CTP scores before TIPS replacement, overall mortality at the end of follow-up, as well as c-statistics and their 95% CI based on areas under the ROC curve at the various follow-up months. If such data were not explicitly reported or were presented in non-English and non-Chinese, they were derived from data provided in the articles or requested from the authors through email contacts, wherever possible [9, 11, 14-16, 19].

CTP and MELD scores

CTP score was calculated using the five following point assignment scheme: 1) bilirubin (assigned <2 mg/dL, 2-3 mg/dL, and >3 mg/dL to 1, 2, and 3 points, respectively); 2) albumin (>3.5 g/dL: 1 point; 3.5-2.8 g/dL: 2 points; <2.8 g/dL: 3 points); 3) prothrombin time (<4 second accounted for 1 points, 4-6 second for 2 points, and >6 second for 3 points); 4) asci-

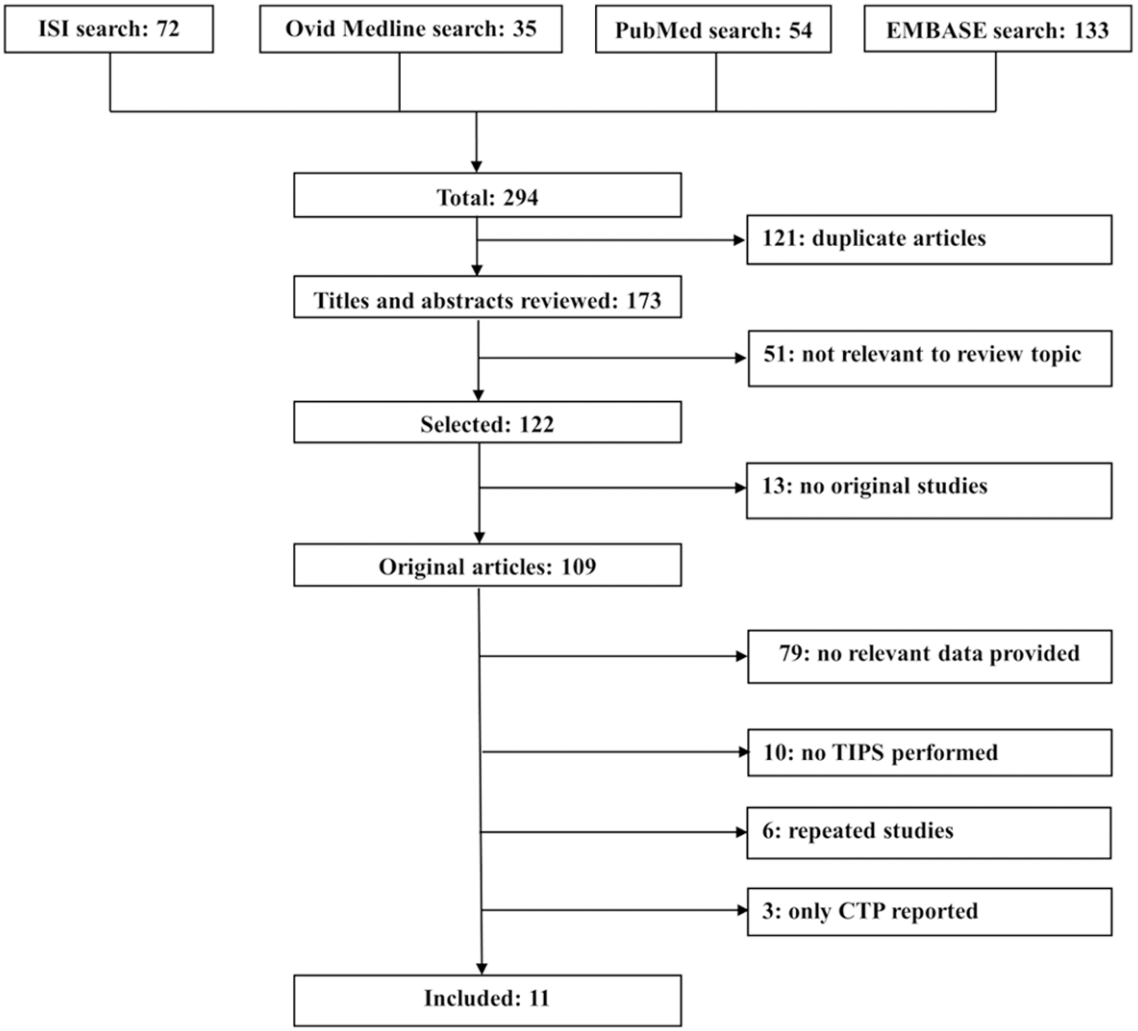

Figure 1. Flow diagram of the literature search process.

tes (absent counted as one point, mild to moderate as two points, and severe or refractory as three points); 5) encephalopathy categorized absent, mild, and severe as 1, 2, 3 points. Five above-mentioned schemes were summed as CTP score. CTP were classified as Class A (5-6 points), Class B (7-9 points), and Class C (10-15 points) [21]. The MELD score was calculated using the total serum bilirubin, serum creatinine and international normalized ratio (INR) as the following formula: 3.78× In (bilirubin [mg/dL]) +11.2× In (INR) +9.57× In (serum creatinine [mg/dL]) +6.43 [27, 28].

Rigor score

The rigor of study quality for retrospective cohort studies was evaluated using a 6-item scale and one point awarded for each of the following items: 1) follow-up rate of 80% or more after excluding death cases; 2) sample size of 200 or more; 3) means of both MELD and CTP scores before TIPS reported; 4) median duration after TIPS of 6 months or longer; 5) c-statistics and 95% CI for both MELD and CTP scores reported; 6) socio-demographic characteristics of patients before TIPS described. If any above-mentioned items were not presented in original articles or obtained via personal contacts, 0 was counted.

Statistical methods

All cohort studies that were included in our meta-analyses had the c-statistics for MELD and CTP scores at least one follow-up time

Table 1. General information of included retrospective cohort studies at study enrollment

Authors (year)	No. of patients	Country	Enrollment period	Months of follow-up	Mean patient age	Patient male %	Mean MELD	Mean CTP	Mortality (%)	Rigor score
Salerno et al. [10], 2002	140	Italy	1993-2000	23.7 (0.3-93)	60.5	64.3	0.9	8.0	39.2	5
Angermayr et al. [11], 2003	475	Austria	1991-2001	62.4 (0.04-116.4)	56.0	n/a	7.0	8.7	48.4	3
Schepke et al. [13], 2003	162	Germany	1992-2001	30.7±26.4	57.0	64.2	6.7	8.1	50.0	5
Ferral et al. [14], 2004	166	USA	1999-2002	11.0 (0.1-42.8)	52.5	62.7	15.3	9.3	71.8	4
Fejfar et al. [15], 2006	110	Czech	1992-2003	n/a	55.0	n/a	n/a	n/a	n/a	0
Stewart et al. [16], 2007	223	USA	1994-1999	11.9 (0-46.1)	56.0	n/a	15.0	10.0	49.3	3
Tzeng et al. [17], 2009	107	China	1995-2006	36	55.5	69.2	n/a	n/a	76.6	3
Zipprich et al. [18], 2010	74	Germany	1995-2004	39 (0.5-129)	51.0	62.0	11.9	8.0	62.0	4
Chen et al. [19], 2013	210	China	2010-2013	12	47.2	69.5	9.9	7.0	18.1	4
Gaba et al. [9], 2013	211	USA	1999-2011	3	54.0	62.0	17.0	9.0	29.0	3
Zhang et al. [8], 2014	159	China	2008-2013	21 (1-65)	52.0	71.1	8.9	6.8	10.7	6

Note: TIPS, transjugular intrahepatic portosystemic shunt; CTP, Child-Turcotte-Pugh; MELD, the model for end-stage liver diseases; n/a, not available.

point after TIPS replacement. Stratified analyses at the different follow-up time points were used to evaluate the difference of predictive accuracy between MELD and CTP scores in the short-term and long-term survival after TIPS replacement. Standard mean differences (SMD) of c-statistics between MELD and CTP scores, defined as effect size (ES), was calculated for each study and then pooled across studies using standard meta-analysis with a random effects model [29], which allow for variation of true effects across studies, were taken as "main results" [30]. Random effects estimates were derived using the DerSimonian-Laird method [31, 32]. A negative value of SMD indicates that CTP score is superior to MELD, and vice versa. Standardized deleted residuals analysis was done to identify outliers. The robustness of results to this predictive difference was assessed in sensitivity analyses that removed outlier studies. Heterogeneity was additionally assessed by the I^2 statistic. The funnel plot, and Begg and Mazumdar rank correlation tests were employed to assess indications of publication bias [33]. All meta-analyses were performed in the R/S plus software, version 3.2.1 [34].

Results

Results of literature search

A flow diagram of the search process is provided in **Figure 1**. Total searches from four electronic literature databases using targeting term combination yielded 294 entries. After excluding 121 duplicates, 173 titles and abstracts were reviewed and 122 studies appeared to be potentially relevant to our topic. 110 articles or conference abstracts were deleted due to the following reasons: no original studies but editorials, comments, reviews or meta-analyses (n=13), no relevant data were provided (n=79), no TIPS performed (n=10), repeated studies with included studies in our meta-analyses [22, 35-39] (n=6), and no c-statistics for CTP were reported 40-42 (n=3). Finally, the remaining 11 studies were included in our meta-analytic review [8-11, 13-19].

Characterization of Individual studies

Details on the respective study design, the study populations and the study results are shown in **Table 1**. Among these 11 eligible studies involving 2037 patients with TIPS replacements during 1991-2013, 5 studies were from European countries [10, 11, 13, 15, 18], three from USA [9, 14, 16], and three from China [8, 17, 19]. Overall mortality at the end of follow-up ranged from 10%-80%. Five studies reported the predictive capability of both MELD and CTP scores in 1-month survival among patients after TIPS replacement [9, 11, 14, 15, 17], seven reported for 3-month survival [9-11, 13-16], two for 6-month survival [10, 14], nine for 12-month survival [8, 10, 11, 13, 15-19], and one for 24-month 8 and one for 36-month survival [13]. Rigor scores were obtained, ranging from 0 to 6, with a mean of 3.6. Only one study had a full score of 6.

Results of meta-analyses

The forest plots of meta-analyses on the respective difference of predictive accuracy for

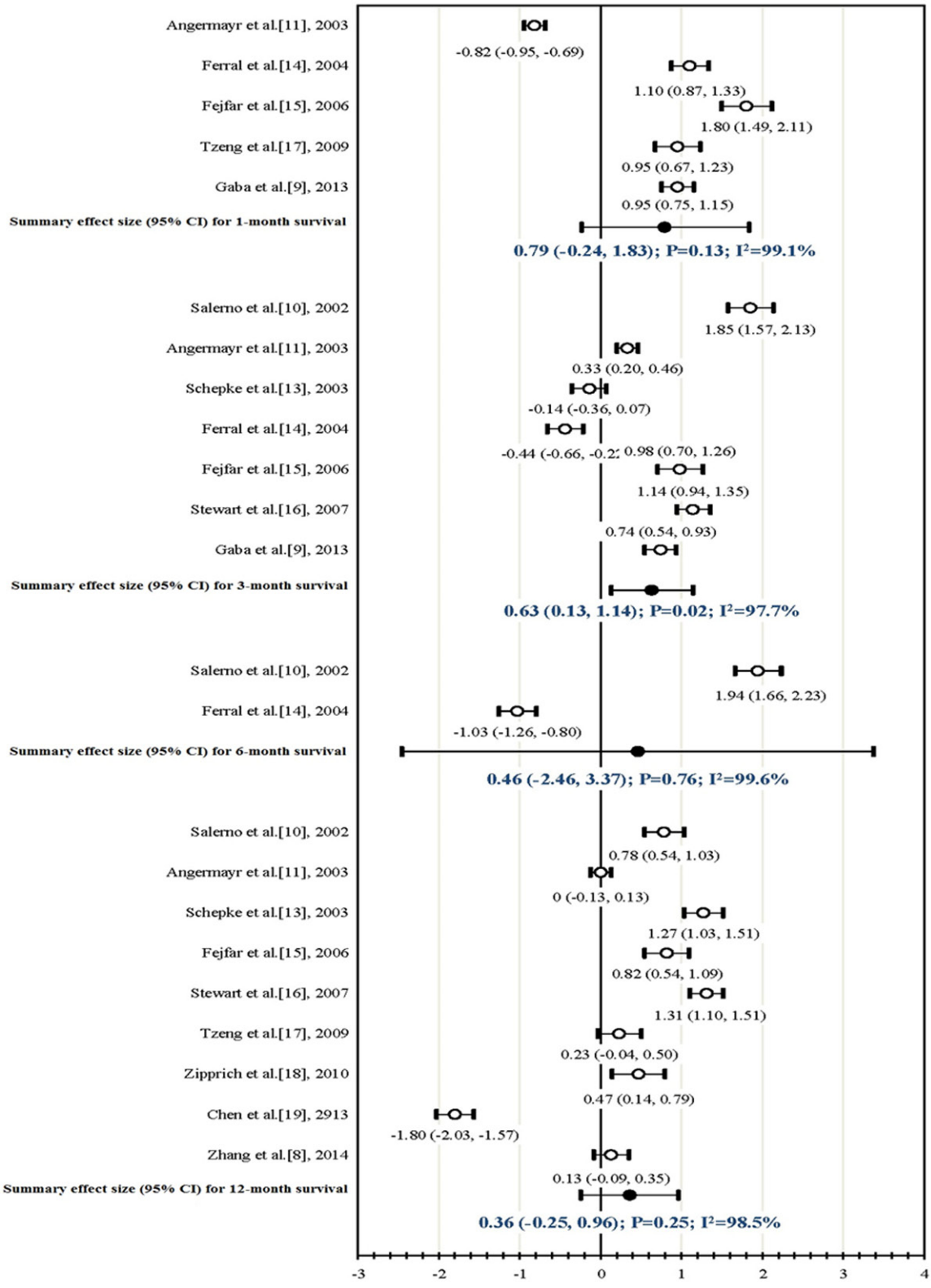

Figure 2. Forest plots of the comparison for the predictive accuracy of MELD and CTP scores in 1-month, 3-month, 6-month, and 12-month survival among patients underwent TIPS replacement.

MELD vs. CTP scores in 1-month, 3-month, 6-month, 12-month survival among patients after TIPS replacements are shown in **Figure 2**. Among five individual studies reporting 1-month

survival, only one study [11] reported a negative value of SMD for MELD vs. CTP scores, and other four studies indicated MELD score were superior to CTP score. A positive results was observed in pooled analyses using a random effects model, but it did not reach to statistical significance (mean ES, 0.79; 95% CI, -0.24-1.83; P=0.13). Large statistical heterogeneity among these 5 included studies was observed (I^2=99.1%; P<0.01). The funnel plot did not show evidence of publication bias (Kendall's tau=0.60; P=0.23). In standardized deleted residuals analysis, the study by Angermayr et al. [11] was identified as an outlier (Standardized deleted residual=-5.35). After excluding this study [11], the predictive accuracy of MELD score was much better than CTP score (mean ES, 1.19; 95% CI, 0.84-1.53; P<0.01) with large heterogeneity (I^2=86.5%; P<0.01).

Regarding 3-month survival, seven studies were used to perform a meta-analysis comparing the predictive capability of MELD and CTP scores [9-11, 13-16]. Two studies observed a better predictive ability for CTP score [13, 14] and other five [9-11, 15, 16] reported MELD outperformed. In the meta-analyses, a positive summary ES was shown (mean ES, 0.63; 95% CI, 0.13-1.14; P=0.01), and the I^2 statistic indicated large statistical heterogeneity across the seven studies (I^2=97.7%; P<0.01). No publication bias was found in the funnel plot (Kendall's tau=0.24; P=0.56). One study [10] was identified as an outlier in standardized deleted residuals analysis (Standardized deleted residual=2.26). No significant difference was observed between MELD and CTP scores for predictive capability in survival among patients underwent TIPS after deleting this outlier study [10] (mean ES, 0.43; 95% CI, -0.03-0.89; P=0.06). Large heterogeneity still was obtained (I^2=96.9%; P<0.01).

Only two studies [10, 14] reported relevant c-statistics in 6-month survival and did not indicate a significant results after combination using meta-analyses (mean ES, 0.46; 95% CI, -2.46-3.37; P=0.76). Among nine studies included in meta-analysis for 12-month survival [8, 10, 11, 13, 15-19], one study reported CTP was better than MELD 19, and one showed zero [11]. The remaining seven studies addressed a positive value, but this difference was significant in five studies [10, 13, 15, 16, 18]. However, the difference was not significant in the random effects model of meta-analysis (mean ES, 0.36; 95% CI, -0.25-0.96; P=0.25), and there were strong indications of statistical heterogeneity across studies (I^2=98.5%; P<0.01). No publication bias was obtained (Kendall's tau=0.06; P=0.92). We found an outlier study [19] in standardized deleted residuals analysis (Standardized deleted residual=-3.96). MELD score was superior to CTP score in predicting 12-month survival using sensitivity analysis without this study [19] (mean ES, 0.63; 95% CI, 0.22-1.03; P<0.01), but large heterogeneity was observed (I^2=96.2; P<0.01).

Discussion

To our knowledge, this is the first meta-analytic review summarizing eleven individual studies and evaluating the difference of predictive accuracy for both MELD and CTP scores in survival among 2037 patients undergoing TIPS replacement. Like previous systematic reviews [23, 25, 43, 44], no confirmatory evidence is shown that MELD score is superior to CTP score in predicting overall survival based on current data, though MELD score is proved 63% better in predicting 3-month survival. However, these results were not stable in the sensitivity analyses. Few studies were observed for more than one-year survival after TIPS replacement. Further predictive capabilities of MELD and CTP for longer-time survival were needed.

Along with the rapid progress of modern medicine, TIPS were widely conducted for patients with liver diseases to improve the survival and quality of life during waiting for liver transplantation. Using prognostic models or scores to select patients for TIPS became more and more important when determining the most appropriate therapeutic option for patients. Compared with empirical CTP score, MELD score calculates a more objective value using laboratory tests to evaluate the severity of liver diseases. However, ascites and hepatic encephalopathy (HE) were not taken into account into MELD, but they are components of the CTP score [25, 45]. The MELD score might underestimate the risk of death when patients had developed or would develop HE [23, 44]. Hence, some researchers proposed that CTP was used for individual assessment of liver disease in daily clinical practice, and MELD was best in prioritizing candidates for liver transplantation [25]. Additionally, some studies have been reported

better predictive capabilities of modified MELD, such as MELD-Na and Delta MELD [40, 41, 44, 46, 47]. Further predictive evaluation should be performed using systematic meta-analyses.

Most predictive models focus on survival after TIPS replacement as an outcome index, but other end-points might be also important, such as HE, ascites, stent dysfunction, and quality of life. In the light of the covered TIPS combined with variceal embolization, the survival has been increased significantly in recent years [48, 49]. Predictive accuracy of MELD and CTP scores in other outcomes among patients is more valuable in further patient selection for TIPS, though MELD might be powerless to assess quality of life in liver transplant candidates [50]. Accurate MELD classification should be further explored using more individual studies [51].

Our analysis has specific strengths and limitations. Strengths include comprehensive comparison of predictive accuracy using meta-analyses. The c-statistic represents a global estimate of predicting an event, which is derived from area under the ROC curve, ranged from 0 to 1. When a c-statistic is more than 0.8 in a prediction model, the score has strong support to its accuracy [52]. On the other hand, our analyses are limited by the data provided by the individual studies. Firstly, depending on the results reported, 95% CIs of c-statistics had to be used for pooling, but which were not provided in some studies included in our meta-analyses [9, 11, 14-16, 19]. Mean variance of the two scores from available studies was used if authors did not response after personal email contacts, which might lead to calculation bias. Secondly, despite the lack of indication of major publication bias in the formal evaluations employed, potential publication bias is impossible to be excluded completely. Thirdly, although four databases were searched and additive checks by cross-referencing were performed, we cannot promise to have missed a relevant study. Finally, large heterogeneity was observed across individual studies, which might be related to stent types and mean MELD and CTP scores before TIPS replacement. Available articles are still sparse further in-depth subgroup analyses and moderator evaluation should be considered when more relevant studies were reported.

Disclosure of conflict of interest

None.

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