Prognostic Importance of Combined Use of MELD Scores and SII in Hepatic Visceral Crisis in Patients with Solid Tumours

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ABSTRACT

Objective: To determine the sensitivity of combining the model for end-stage liver disease (MELD) scoring with new inflammatory indexes in determining the priority for liver transplantation and demonstrating its potential usability in solid tumour visceral crisis.

Study Design: Descriptive study.

Place and Duration of the Study: Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Turkiye, from June 2017 to June 2022.

Methodology: Patients hospitalised in the medical oncology clinic for hepatic dysfunction were included. The MELD scores of these patients were calculated, and the predictive contribution of the systemic immune-inflammatory index (SII) to prognosis and mortality was evaluated.

Results: A total of 295 patients (158 (53.6%) men and 137 (46.4%) women) were included. When compared for primary tumour types, colorectal cancers were the most common with 55 (18.6%) cases, followed by breast cancers at 52 (17.6%), pancreatic carcinoma at 50 (16.9%), and stomach cancers at 40 (13.6%) cases. In the survival analyses of all three MELD scores (MELD-Original, MELD-Na, and MELD 3.0) between <20 groups and ≥20 groups, the median Overall Survival (OS) for MELD-Original was 1.44 *vs.* 0.88 months (p<0.001), for MELD- Na it was 1.64 *vs.* 0.85 months (p<0.001), and for MELD 3.0 it was 2.16 *vs.* 1.28 months (p=0.039). In the ROC analysis, the SII parameter cut-off was ≥626.28 for the estimation of mortality, SII sensitivity was 78.7%, and specificity was 100% (p=0.013).

Conclusion: Combined use of MELD and SII scores in patients with solid tumours with hepatic visceral crises will be practical, cost-effective, and easy to access, eliminate gender-based disparities, and contribute to clinical follow-ups with objective data.

Key Words: *Malignant neoplasm, MELD score, MELD-Na, MELD 3.0, SII.*

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INTRODUCTION

Prognostic models determine disease severity, survival probability, treatment trends, and patients' treatment orientation. The model for end-stage liver disease (MELD) score is a prospective chronic liver disease severity scoring system calculated using serum bilirubin, creatinine, and international normalised ratio (INR). It is a prognostic assessment score to predict 90-day survival after transjugular intrahepatic portosystemic shunt (TIPS) to determine transplant priority in patients awaiting liver transplantation.[1]

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The MELD score was revised by adding serum sodium values, and the MELD-Na score was developed. This scoring has been a prognostic indicator in determining the order of transplantation since 2016.[2,3] Therefore, the MELD-Na score is mainly used to evaluate cadaver donors.[4]

Serum creatinine being detected lower in women than men might cause MELD scores to be underestimated. As a result of this lower mortality risk estimation, MELD Original and MELD Na values may lead to gender-based disparities in women.[5] Thus, considering they were outdated,[6] the MELD 3.0 score was created based entirely on laboratory data, including albumin, and gender parameters. In the Child Turcott Pugg classification, clinical evaluation findings were preferred less because they included subjective data.[7,8]

The interaction between systemic inflammation and the local immune response is accepted as the seventh feature of cancer and is shown to play a role in the development of various malignancies and in the progression of existing cancer.[9,10] Cancer-related inflammation creates an immune response depending on

tumour-derived and host-derived mediators and initiates some inflammatory processes.[11,12] These inflammation markers are practical in many solid tumours. However, there are also publications on SII being a robust prognostic marker for patients with hepatocellular and colorectal carcinoma.[13,14]

Evaluating MELD scores in combination with SII will enhance the sensitivity and specificity of MELD scoring. The aim of this study was to demonstrate the clinical practicability of inexpensive and easily accessible new biomarkers that can be used in conjunction with prognostic MELD scoring, commonly employed for determining organ transplantation priority, with a higher sensitivity and specificity rate. These scoring systems can be utilised by clinicians not only for prioritising organ transplantation but also for effectively managing visceral crisis during organ failure, displaying high sensitivity and specificity.

The objective of this study was to determine the sensitivity of combining MELD scoring with new inflammatory indexes in determining the priority for liver transplantation, demonstrating its potential usability in solid tumour visceral crisis.

METHODOLOGY

The study was designed as a descriptive comparative study. All patients, who were admitted and treated for liver dysfunction in the Medical Oncology Service of Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, between June 2017 and June 2022, were evaluated. Data were retrospectively collected by scanning the hospital database. In addition to MELD scoring, traditional liver function tests such as transaminase levels, serum direct-indirect bilirubin, and INR parameters were used to assess liver dysfunction. Grading was performed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Patients requiring hospitalisation of Grade 3 or higher were included in the evaluation. MELD scores ≥20 were considered high.[15] Patients were categorised based on their descriptive characteristics and primary cancer diagnoses. A total of 295 patients aged 18 and above who met the inclusion criteria were included in the study. Patients with liver cirrhosis without a cancer diagnosis and those with pre-existing liver dysfunction were not included in the study.

Statistical Package for the Social Sciences program was used for analyses [SPSS for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA)]. Continuous variables were reported using median (interquartile range, IQR) and mean (standard deviation, SD). The authors analysed mortality rates *via* the Cox regression model. In the univariate analysis, a multivariate analysis with significant parameters was created. A Forest plot graph was created using Excel under the Cox regression multivariate model. Survival graphics were obtained using the Kaplan Meier survival graphics and log-rank test. Finally, ROC analysis was performed to determine the cut-off for SII. A p-value of <0.05 was considered significant in all statistical tests.

RESULTS

A total of 295 patients comprising of 158 (53.6%) men and 137 (46.4%) women were included in the study. Most patients (72.2%, n: 213) were over 50 years old. In the group with MELD <20, MELD-Original was 80.7%, MELD-Na was 61.1%, and MELD-3.0 was 11.9%. According to primary tumour types, the top four tumours diagnosed with failure were colorectal cancers at 55 (18.6%) patients, breast cancers at 52 (17.6%), pancreatic carcinoma at 50 (16.9%), and stomach cancers at 40 (13.6%) patients. In most patients, the cause of liver failure was metastases. Liver metastases were present in 249 (84.4%) patients, and 16 (5.42%) underwent metastasectomy. In these patients, the MELD-Original median value was 16.0 (10.0-27.0), the MELD-Na median was 17.5 (10-26), and the MELD 3.0 median was 22.0 (17.0-30.0, Table I).

Table I: Demographic and clinical features of the patients.

Gender			
Female	137 (46.4%)		
Male	158 (53.6%)		
Age			
≤50	82 (27.8%)		
>50	213 (72.2)		
ECOG PS*			
1	42 (14.2%)		
2	134 (45.4%)		
3	102 (34.6%)		
4	17 (5.8%)		
MELD Score**	**MELD- Original**	**MELD-Na**	**MELD- 3.0**
<20	238 (80.7%)	181 (61.1%)	35 (11.9%)
≥20	57 (19.3%)	114 (38.6%)	260 (88.1%)
Primary Cancer (n=295)			
Colorectal	55 (18.6%)		
Breast	52 (17.6%)		
Pancreas	50 (16.9%)		
Stomach	40 (13.6%)		
Lung	23 (7.8%)		
Unknown Primary	23 (7.8%)		
Biliary Tract	14 (4.7%)		
Ovarian	8 (2.7%)		
Hepatocellular Carcinoma (HCC)	7 (2.4%)		
Other	23 (7.8%)		
Liver Metastasis			
Yes	249 (84.4%)		
No	46 (15.6%)		
Chronic Viral Hepatitis B infection	19 (6.4%)		
Chronic Viral Hepatitis C infection	3 (1%)		
Liver Metastasectomy			
Yes	16 (5.4%)		
No	279 (94.6%)		
Hepatosteatosis			
No	144 (48.8%)		
Grade 1	125 (42.4%)		
Grade 2	21 (7.1%)		
Grade 3	5 (1.7%)		

*ECOG *: Eastern Cooperative Oncology Group; MELD**: Model for End-Stage Liver Disease.*

Survival analyses of the patients were based on the date after developing hepatic dysfunction. In the Cox regression analysis, MELD-Na ≥20, anaemia, encephalopathy, and neutropenia negatively affected survival, while biliary dilatation and percutaneous transhepatic cholangiography (PTC) procedure positively affected survival. Survival rates were 2.41 (1.78-3.27) times worse in patients with MELD-Na score ≥20 and 2.30 (1.47-3.61) times worse in the group with encephalopathy (Table II and Figure 1).

The SII parameter estimation was significant in distinguishing the development of mortality (p=0.013). The area under the ROC curve (AUC) for detecting the development of SII mortality is 0.862 (95% CI, 0.795-0.928). Therefore, the sensitivity of SII at a cut-off value of ≥626.28 for the mortality prediction sensitivity is 78.7%, and the specificity is 100%.

Table II: Overall survival analysis in all patient groups.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Hepatosteatosis	0.9 (0.76-1.06)	0.207	0.92 (0.77-1.10)	0.389
INR ≥1.5	1.59 (1.18-2.14)	0.002	0.85 (0.60-1.19)	0.340
Biliary Dilatation	0.46 (0.35-0.59)	<0.001	0.60 (0.36-0.99)	0.046
PTC	0.47 (0.36-0.61)	<0.001	0.62 (0.36-1.06)	0.085
Ascites	0.92 (0.79-1.06)	0.250	0.90 (0.78-1.05)	0.200
Hemoglobin	0.93 (0.89-0.98)	0.011	0.93 (0.88-0.98)	0.007
Encephalopathy	1.97 (1.32-2.94)	0.001	2.30 (1.47-3.61)	<0.001
Neutrophil	1.00 (1.00-1.00)	0.001	1.00 (1.00-1.00)	0.006
Creatinine	1.67 (1.23-2.27)	0.001	1.02 (0.72-1.46)	0.870

**Cox regression, PTC: Percutaneous Transhepatic Cholangiography, INR: International Normalised Ratio,*

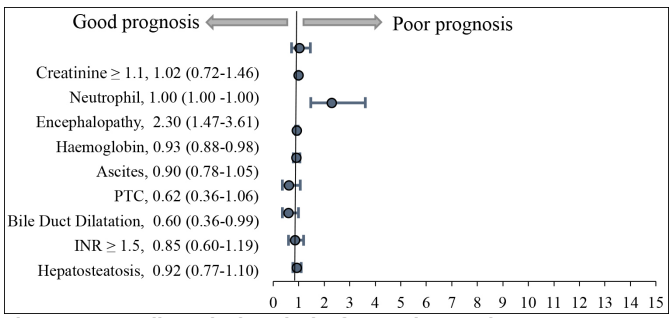

Figure 1: Overall survival analysis, forest plot graph.

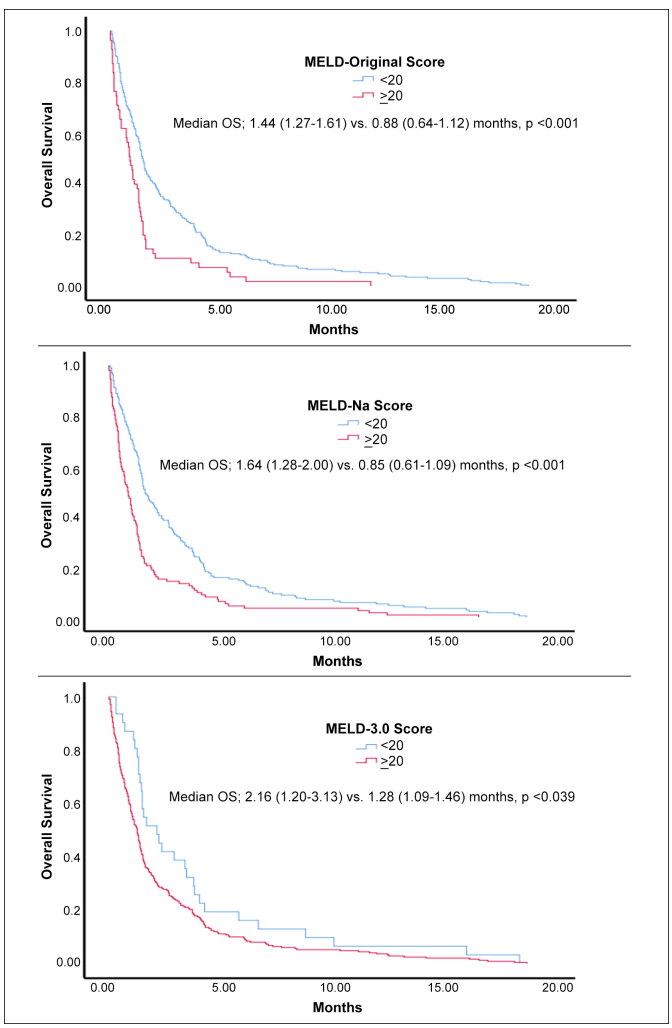

Figure 2: MELD scores mortality analyses.

A nearly two-fold difference was present in the Kaplan Meier survival analyses of all three MELD scores (MELD-Original, MELD-Na, and MELD 3.0) between the <20 groups and ≥20 groups. The median OS for MELD-Original was 1.44 *vs.* 0.88 months (p<0.001), for MELD- Na, it was 1.64 *vs.* 0.85 months (p<0.001), and for MELD 3.0 it was 2.16 *vs.* 1.28 months (p=0.039) (Figure 2).

DISCUSSION

Prognostic models are important modalities used in clinical practice to gain insight into patient survival, determine treatment approaches, and assess prognosis. MELD scores are a prognostic scoring system used in patients with advanced liver cirrhosis. Obtaining the most accurate prognostic scoring is crucial for patient monitoring and facilitating clinical practice for healthcare professionals. Consequently, MELD scores are updated with new versions to enhance their sensitivity and specificity. However, there is a lack of sufficient studies regarding their applicability in patients with solid tumours. Therefore, there is a need for studies aimed at improving the sensitivity and specificity of MELD scores by combining them with new markers that can be used in conjunction. The authors aimed to demonstrate the utility of these scoring systems for determining the prognosis of solid tumour hepatic visceral crises. The combined use of SII and MELD scores was found to be reliable, cost-effective, and accessible for determining survival in patients with solid tumours.

Ross *et al*. stated that new studies are needed to confirm the relationship between the MELD score and mortality.[16] In light of all these data, there is a need for scoring that can make a meaningful evaluation in terms of survival, determine the prognosis, and predict survival in hepatic failure visceral crisis that develops in patients with solid tumours. In this study, the evaluability of all three MELD scoring systems currently in use in oncological patients and the contribution of SII in determining prognosis and predictive effect on mortality were studied. It was found detected that these scoring systems are usable in primary liver tumours and metastases. In the present analysis, the vast majority of the 295 patients with hepatic visceral crisis had primary cancer originating from a non-liver tumour, and only 7 (2.4%) patients were diagnosed with hepatocellular carcinoma.

Patients with a high MELD score receive less local treatment due to more severe hepatic dysfunction and require liver failure treatment rather than cancer treatment.[15] Since primary liver cancers usually develop from a background of existing liver damage, there are some reports that these cancers have higher MELD scores and higher complications.[17] For example, the contribution of these scores has not been clearly confirmed, as metastatic tumours of the liver have a lower incidence and lower grade of liver dysfunction, according to Frommer *et al*.[17] Additionally, Teh *et al*. claimed that MELD evaluated aside from cirrhosis could not accurately predict results.[18] However, liver dysfunction in cancer patients may develop due to several immunologic factors other than liver metastases.[19] Cancer-induced inflammation elicits an immune response due to tumour-derived and host-derived mediators and is also known to initiate several inflammatory processes. Therefore, to elucidate the visceral crisis of hepatic dysfunction, evaluating the liver alone is insufficient in detecting the disease. Clarifying the hepatic visceral crisis requires a holistic patient evaluation with a systematic and multidisciplinary approach.

In this study, 16 of 295 patients underwent metastasectomy. In these patients, the MELD-Original median value was 16.0 (10.0-27.0), MELD-Na median was 17.5 (10-26), and MELD 3.0 median was 22.0 (17.0-30.0).

In the study by Frommer *et al*., a patient with a MELD score >7.24 had an approximately three-fold increased risk of death within 30 days of metastatic liver resection. This provides additional important mortality markers that are also valuable in preoperative planning and risk stratification. Likewise, the present study demonstrates that in all three MELD scoring systems, the group with MELD ≥20 had an approximately 2-fold increased risk of death.

Chen *et al*. found that the SII value significantly contributed to overall and progression-free survival in patients with colorectal cancer. The limitations of Chen *et al*. study were that it was a single-centre retrospective study, included only patients with colorectal cancer, and did not include patients who had not undergone radical surgery.[14] Consequently, the result obtained from a more extensive and comprehensive evaluation to include all solid tumour patients aroused curiosity. In the present study, the prognostic value of the SII parameter was calculated to meet this curiosity, including all solid cancer patients with hepatic visceral crises. In the ROC analysis with SII value, mortality estimation was highly effective with a cut-off value of ≥626.28.

The findings of this study have to be seen in light of some limitations. The fact that the majority of the patients were 50 years or older brings with it additional comorbid diseases and an increased burden of medical treatment. It should also be kept in mind that hepatic visceral crisis may occur due to the use of multiple therapies. In addition, the study was retrospective, and homogeneity could not be achieved between the patient groups for all these reasons. However, there are not enough relevant studies on these patients. Multicentre prospective studies with larger numbers of patients are needed in this area in future.

CONCLUSION

Calculating MELD scores and SII values in patients with solid tumours who have developed hepatic visceral crisis with practical, low-cost, easy-to-access, and objective evaluations will contribute to clinical follow-ups. In addition, it will eliminate situations such as gender-based disparities that are the subject of mortality estimation.

ETHICAL APPROVAL:
Ethical approval was obtained from the Health Sciences University, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital's Ethical Committee on 08.24.2022 with decision number 2022-08/2019.

PATIENTS' CONSENT:
Patients' consent was waived as this study was conducted retrospectively.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
FT, MB, AOD: Carried out the conception and design of the research, analysis and interpretation of data, and drafted the manuscript.
MB, FT: Performed the statistical analysis and participated in data acquisition.
All the authors have approved the final version of the manuscript to be published.

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