Model for End-Stage Liver Disease (Meld) Score, As a Prognostic Factor for Cirrhotic Patients, Undergoing Hepatectomy for Hepatocellular Carcinoma

Abstract

Background/Aims: To evaluate the ability of the model for end-stage liver disease (MELD) in predicting the post-hepatectomy outcome for hepatocellular carcinoma (HCC).

Methods: between the periods from January 2007 to June 2010 in National liver Institute (NLI) - Menoufiya University 60 cirrhotic patients with HCC underwent hepatectomy and the results were retrospectively analysed. MELD score was associated with post-operative mortality and morbidity, hospital stay and 3-year survival.

Results: Eleven major and 49 minor resections were performed. Thirty-day mortality rate was 8.3%. MELD ≤ 9 was associated with 2.6% peri-operative mortality vs. 20% when MELD > 9 ($P < 0.05$). Overall morbidity rate was 53.3%; 36.6% when MELD > 9 vs. 16.6% when MELD ≤ 9 ($P < 0.05$). Median hospital stay was 18 days [12 days, when MELD ≤ 9 and 22 days when MELD > 9 ($P = 0.05$)]. Three-year survival reached 51% (66% when MELD ≤ 9; 29% when MELD > 9 ($P < 0.01$).

Conclusion: MELD score seems to predict outcome of cirrhotic patients with HCC, after hepatectomy.

Keywords: Hepatocellular carcinoma; MELD score; Hepatectomy; Cirrhosis; Liver resection outcome

Research Article

Volume 2 Issue 3 - 2015

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Received: January 15, 2015| **Published:** June 25, 2015

Abbreviations: MELD: Model for End-Stage Liver Disease; HCC: Hepatocellular Carcinoma; CUSA: Cavitron Ultrasonic Surgical Aspirator; INR: International Normalized Ratio; CPT: Child-Pugh-Turcotte; Cr: Creatinine; TBil: Total Bilirubin; AFP: A-Fetoprotein

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Its incidence is 1:500000 and it is strongly correlated with cirrhosis [1]. The mainstay of treatment, in patients with solitary HCC and good liver function, is hepatic resection [2]. Evolution in surgical techniques and peri-operative care have improved post-operative outcome, in patients with severe under-lying liver disease undergoing hepatectomy. The risk of hepatic failure in a cirrhotic patient undergoing hepatectomy still remains high, as a result of compromised function of the liver remnant [3,4]. Therefore, a thorough evaluation of the hepatic function reserve is necessary prior to surgical intervention, in order to select the best candidates for hepatic resection among cirrhotic patients, with reasonable post-operative morbidity and mortality.

Child-Pugh-Turcotte (CPT) classification was the first systematic approach used to determine the severity of cirrhosis and select those patients who could tolerate hepatic resection [5]. CPT class C is considered an absolute contraindication for surgical treatment, whereas only few hepatectomies are performed in class B cirrhosis [5-7]. CPT class A patients are generally considered good candidates for hepatic resection and good post-operative outcome is expected. More refined evaluation of the liver function reserve is often needed, as a result of limitations in the discriminatory ability of the CPT system, as it uses subjective parameters, such as ascites and encephalopathy [8-11]. The model for end-stage liver disease (MELD) score was recently introduced to evaluate hepatic function reserve in cirrhotic patients [12-15]. It has the advantage of using three objective and easily measured parameters: creatinine levels, international normalized ratio (INR) and total bilirubin. MELD score is used for survival prediction in cirrhotic patients receiving a transjugular intrahepatic portosystemic shunt [12]. It has also been used to determine priority on waiting lists for liver transplantation [13] and in predicting post-operative outcome of cirrhotic patients, undergoing surgical procedures [14,15]. The aim of this study was to examine whether the pre-operative MELD score can predict post-operative mortality, morbidity, hospital stay and 3-year survival in cirrhotic class A patients undergoing hepatectomy for HCC. An effort to subcategorize the low-from the high-risk class A patients is provided.

Materials and Methods

We retrospectively analyzed the clinical records of all patients with HCC, who underwent hepatic resection in our institution between January 2007 and June 2010. HCC was pathologically confirmed in all patients included in the study. We identified 60 patients fulfilling the above criteria. Clinical and pathological features of the patients are reported in (Tables 1 & 2). CPT class was calculated using prothrombin time, albumin, bilirubin and clinical findings of ascitis and encephalopathy [16]. CPT score was stratified as class A (5-6), B (7-9) and C (10-15). Fifty nine patients were classified as CPT class A (89.8%) and one patient as CPT class B, score 7 (10.2%). MELD score was calculated using pre-operative values of three laboratory tests: INR for prothrombin time, serum total bilirubin (TBil) and serum creatinine (Cr). MELD score was calculated using the following formula: MELD = 9.57 ¥ loge(Cr mg/dl) + 3.78 ¥ loge(TBil mg/dl) + 11.20 ¥ loge(INR) + 6.43.12. We used the MELD score of the patient upon admission to our clinic, as it more accurately represents the severity of cirrhosis before surgery. MELD score was calculated to all cases with mean of 7.6 (range, 6-13).

Major hepatic resection was defined as the removal of three or more segments [17]. Tumors were classified accordingly to the sixth edition of AJCC Cancer staging manual [18]. Post-operative mortality was defined as any death occurring within 30 days after surgery. The primary end point of the study was the investigation of the relationship between the pre-operative MELD score and the development of irreversible liver failure after hepatectomy in cirrhotic patients. It was defined as a growing impairment of liver function after resection, which led to the death of the patient or required transplantation. The relationship between the MELD score and post-operative complications (morbidity), length of hospital stay and 3-year patient survival represented secondary end points. Post-operative jaundice was defined as a serum bilirubin level above 5 mg/dL, alteration of coagulation factors was defined as considerable or severe, when a FFP infusion was required in order for these to be corrected, and renal impairment was defined as an increase in blood urea nitrogen above 2 g/l and/or an increase in serum creatinine above 2 mg/dl. Hospital stay was computed from the date of the operation, until discharge at home. Patient survival was computed from the date of the operation, until the most recent follow-up. Controls and patients still alive after the first year after surgery were censored at this time point; patients transplanted for post-operative liver failure were censored the day prior to transplantation, and patients who died from causes not related to liver failure were censored the day prior to the event. Kaplan-Meier survival analysis: used for analysis of cumulative survival of studied subjects (Figure 1). ROC Curve to determine: cut-off value of MELD score at which there is significance to outcome or not. P (probability) value is considered to be of statistical significance if it is less than 0.05. Long-term follow-up included serum a-fetoprotein (AFP) and CT scan of the abdomen every 3 months during the first year after surgery and at 6-month intervals thereafter CT, MRI and PET scan or angiography were performed selectively when recurrence was suspected.

Statistical Analysis

Data will be presented as mean & standard deviation (SD). Data will be analyzed using the SPSS package for Windows, version 18.0, SPSS Inc., and Chicago, Illinois, USA. The following tests will be used: Student (t)-test: to test for significance when comparing the means of two sets of quantitative data. Chi-Square test: to test for significance when comparing the means of two sets of qualitative data.

Table 1: Univariate analysis of peri-operative mortality in patients with cirrhosis with hepatocellular carcinoma.

Variable	No of Patients	Peri-Operative Mortality, n (%)	P-value
Age (years)			0.6
50	19	2	
50	41	3	
Gender			0.7
Male	54	4	
Female	61	1	
CPT Class			0.5
A	59	4	
B	1	1	
Meld Score			0.01
9	43	0	
9	26	5	
Tumour Size			0.05
5	43	3	
5	26	2	
Stage			
1	48	2	
2	10	1	
3	12	2	
Extent of Resection			0.08
Minor	49	2	
Major	11	3	
Co-morbid Disease			<0.05
Yes	19	5	
no	41	0	
Vascular Invasion			0.05
Yes	3	2	
no	57	3	

Table 2: Univariate analysis of clinicopathologic factors associated with survival after hepatectomy for hepatocellular carcinoma in patients with cirrhosis.

Variable	1-Year Survival	3-Year Survival	P - Value
Age (year)			0.3
50	61	52	
50	69	43	
Gender			0.6
Male	66	47	
Female	64	58	
CPT Class			0.6
A	70	64	
B	100	100	
Meld Score			0.01
9	78	66	
9	63	40	
Tumour Size			0.01
5	77	60	
5	63	40	
Stage			0.6
1	100	94	
2	80	59	
3	85	55	
Extent of Resection			0.06
Minor	76	61	
Major	55	40	
Vascular Invasion			0.05
Yes	60	55	
No	80	60	
Co-morbid Disease			< 0.05
Yes	60	44	
No	77	60	

MELD score	No	%
6	2	3.3
7	18	30.0
8	13	21.7
9	5	8.3
10	15	25.0
11	4	6.7
12	2	3.3
13	1	1.7

Figure 1: Distribution of model for end-stage liver disease (MELD) in patients with cirrhosis.

Results

Surgery consisted of 49 (81.6%) minor hepatic resections and 11 (18.4%) major hepatic resections. Serum AFP was elevated in 50% of patients with a mean level of 469 ± 1364 ng/ml (range 4-9071 ng/ml). Laparoscopic resection was done in only 3 cases (5%) while 57 cases (95%) were done by open technique one of them preceded by Laparoscopic evaluation to extent of tumor. Non anatomical resection was performed in 55 cases (91.6%) while anatomical resection was performed only in 5 cases (8.4%). Minor resection was performed in 49 cases (81.6%) while major resection was performed in 11 cases (18.4%). The mean size of HCC was 6.3 ± 3.5 cm (range 2-24 cm). AJCC stage was I in 48 patients, II in 10 patients and III in 2 patients. All resections were performed with a tumour-free margin of at least 1 cm. Resection was done by Cavitron Ultrasonic Surgical Aspirator (CUSA), Harmonic scalpel and Habib sealer.

There was bleeding in 44 cases (73.3%) with mean volume of blood loss 936.6 cm ± 1395.1 cm (range, 500-6000 cm) and mean operative time of 249.8 ± 46.7min (range 150-350min). Intra-operative ultrasound was performed routinely in patients undergoing hepatectomy and Median operating time was 160 min (range 90 to 295 min).

Cholecystectomy performed in 19 cases (31.6%), RFA performed in 5 cases (8.3%) while alcohol injection performed in 2 cases (3.4%), Two cases (3.3%) died on table from intra-operative bleeding. The 2 cases were child A with mean MELD score of 8 (range 6-10), one of them underwent right hepatectomy for large mass and the other case underwent non-anatomical resection in left lobe seg IV. There were 3 cases (5%) developed liver failure and died within 30 days after surgery. Patients who experienced post-operative liver failure had a mean MELD score of 11.5 ± 1.4 (range 10-13), significantly higher in comparison to patients where this event did not occur mean 7 ± 1.2 (range 6-13); P = (0.01). ROC analysis identified a MELD score above nine as a satisfactory cut-off value for predicting postoperative liver failure [area under the curve (AUC) = 0.92, 95% CI = 0.87-0.96; sensitivity = 93%; specificity = 80%] (Figure 2). Post-operative liver failure included the occurrence of intractable ascites, requiring intensive therapy with diuretics for remission, elevation of INR > 2; 24-h post-surgery requiring a FFP transfusion and elevation of total bilirubin >5 mg/dl. Thirty-two patients (53.3%) experienced at least one post-operative complication. Refractory ascites developed in 14 cases (23.3%), jaundice in 6 cases (10%), and alteration of coagulation factors in 12 cases (20%).

Patients were divided according to the cut-offs of the MELD scores obtained by ROC analysis in two groups: MELD below or equal to 9 and MELD above 9. MELD score was 9 in 38patients (63.3%) and 9 in 22 patients (36.7%). It was observed that duration of hospital stay significantly higher among patients with MELD score > 9 (22.47±19.47 days) than patients with MELD score ≤ 9 (15.0±6.23 days) (P<0.05)

Patients who experienced post-operative liver failure had a mean MELD score of 11.5 ± 1.4 (range, 10-13), significantly higher in comparison to patients where this event did not occur mean 7± 1.2 (range, 6-13); (P = 0.01). MELD ≤ 9 was associated

with 2.6% peri-operative mortality vs. 20% when MELD > 9 (P < 0.05). Overall morbidity rate was 53.3%; 36.6% when MELD > 9 vs. 16.6% when MELD ≤ 9 (P < 0.05).

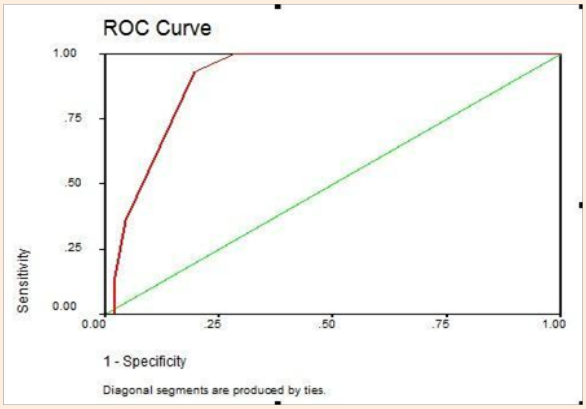

Figure 2: Receiver-operating characteristic (ROC) curve of the model for end-stage liver disease (MELD) score in predicting post-operative liver failure after hepatic resection in patients with cirrhosis (AUC = 0.92, 95% CI = 0.87-0.96).

Discussion

Liver failure after hepatectomy is one of the most severe complications of liver resection. In patients with liver cirrhosis, liver failure after hepatectomy is even more common because of the fact that resection removes functional liver tissue, from an organ that is already functioning marginally. Pre-operative assessment of liver function and prediction of post-operative functional reserve are of paramount importance to minimize surgical risk. CPT is not always a reliable indicator of hepatic reserve and has a limited role in predicting post-operative outcome [19]. The MELD score seems to have the ability to categorize cirrhotic patients more accurately [20]. A cirrhotic patient eligible for resection on the basis of CTP score may not be resectable on the basis of MELD. Such patients should be referred to non-surgical approaches such as radiofrequency ablation or transarterial chemoembolization. In our study most patients were class A (59 out of 60 patients: 98.3%) according to the CPT system and only one patient was class B (1.7%). Mean value of MELD score in all patients was (8.6 ± 1.65) range (6-13). However, MELD classification managed to identify pre-operatively those class A patients with a higher 30-day mortality rate, greater risk of developing a post-hepatectomy complication and having a longer hospital stay and poorer long-term outcome.

Our study showed that patients who underwent hepatectomy with a pre-operative MELD score > 9, had elevated 30-day mortality rate (18.2% vs. 2.6%), Long term mortality (59.1% vs. 2.6%) high incidence of post-operative complications (80% vs. 26%), longer hospital stay (22.4 vs. 15 days) and worse 3-year survival (29% vs. 66%) in comparison to patients with a MELD score ≤9. Conversely, patients with MELD scores below or equal to 9, who represent the (63.3%) of cirrhotic patients in the present study, showed only (13.6%) post-operative liver failure, as well as low morbidity, shorter hospital stays and a (66%) survival rate, proving that a good outcome can be achieved in these patients through hepatic resection. Several reports from different groups consider partial hepatectomy as a good option in well-compensated CPT class A patients [21-24]. In addition, liver resection has been considered as a bridge to liver transplantation in order to reduce the dropout rate in patients with HCC on cirrhosis on the waiting list [25]. In a study of Spiros G et al. [6] patients who underwent hepatectomy, with a pre-operative MELD score > 9, had elevated 30-day mortality rate (19% vs. 0%), high incidence of post-operative complications (48% vs. 25%), longer hospital stay (15.6 vs. 8.8 days) and worse 3-year survival (32% vs. 66%) in comparison to patients with a MELD score ≤9. The results of our study when compared to results of Spiros G et al. [6] are nearly the same as the number of cases (60 cases vs. 69 cases) and the number of peri-operative mortality are the same but the cause is different in our study 3 cases died from early hepatic failure and 2 cases died intra-operative from bleeding but the 5 cases in Spiros G et al. [6] study died from early hepatic failure. Patients who experienced post-operative liver failure had a mean MELD score of 11.5 ± 1.4 (range 10-13), significantly higher in comparison to patients where this event did not occur median 7 ± 1.2 (range, 6-13); P = 0.01). In our study the percent of post-operative complications (80% vs. 48%) and hospital stay (22 days vs. 15 days) were higher in comparison to Spiros G. study, this may contributed to the use of ASA (American Society of Anesthesiologists) assessment before surgery and high infection control in their study. In our study the percent of cases that develop infection about (40%) in cases with MELD score > 9 either from chest infection (30%) or from wound infection (10%). Regarding incidence of recurrence it was found significantly higher among patients with MELD score > 9 (63.6%) than among patients with MELD ≤9 (36.8%) (P<0.05) and regarding to timing of recurrence it was found that no significant difference between patients with MELD score >9 and patients with ≤9. The high recurrence rate in patients with higher MELD scores can be explained by the different immunological status of these patients (cytokines) [26].

Regarding survival analysis, it was significantly higher among patients with MELD score ≤9 (66%) than among patients with >9 (29%) (P<0.05) also survival was significantly higher among patients underwent minor resection (60%) rather than who underwent major resection (20%) (P<0.05). In a study of Spiros G et al. [6] the survival for the entire cohort reached 49%. The 3-year survival was (66%) when MELD < 9 and (32%) when MELD > 9 (P < 0.01). Several reports from different groups, consider partial hepatectomy as a good option in well-compensated CPT class A patients. In addition, liver resection has been considered as a bridge to liver transplantation in order to reduce the dropout rate in patients with HCC on cirrhosis on the waiting list [25]. Merion et al. showed that a threshold score of (11) patients in whom, independent of HCC, transplantation is justified (above 11) or futile (below 11); in particular, cirrhotic patients with a MELD score between 6 and 11, were shown to have a post-transplant mortality significantly higher than waiting list mortality. Therefore, the results from recent studies may give support to a systematic transplantation policy in small HCC patients with a MELD score exceeding (11) as well as partial hepatectomy in patients with lower MELD scores [27]. In our study, all patients had histological proved cirrhosis. The

MELD score's reliability in predicting morbidity and mortality after elective liver resection has been criticized in patients with minimal or no evidence of liver disease [28]. It is worth noting that there are number of patients who, in spite of a low MELD score, have advanced liver disease using clinical evaluation and CTP score and therefore cannot be candidates for resection. These are patients with intractable ascites, who are malnourished and with encephalopathy, who have a very low MELD score, but clearly in whom surgery would be too dangerous. CPT stage and clinical evaluation should always be the initial consideration that precedes the MELD calculations. We must remember that only CPT class A and B patients should be considered for resection in the first place.

Conclusion

MELD score can accurately predict mortality, morbidity and long-term survival in patients with HCC and cirrhosis, undergoing hepatic resection. Cirrhotic patients with a high MELD score have an increased risk of post-operative liver failure and complications; they are expected to have poorer long-term survival after liver resection and should be referred for other treatments. Cirrhotic patients with a low MELD score treated with minor hepatic resections achieve zero 30-day mortality and low morbidity rates, whereas expected long-term survival is promising. Application of a MELD score in the pre-operative assessment of liver function prior to hepatic resection is recommended, as it facilitates identification of high-risk class A patients prior to hepatic resection and selection of the best candidates for hepatectomy. A multi-institutional study is required to better define the selection criteria for hepatic resection in HCC patients with cirrhosis.

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