Original Article

Change of Plasma Renin-Aldosterone and Paracentesis-Induced Circulatory Dysfunction after Non Large-Volume Paracentesis in Different MELD Cirrhotic Patients

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Background: Therapeutic abdominal paracentesis is associated with the occurrence of paracentesis induced circulatory dysfunction (PICD), manifested by a marked increase of plasma renin activity. Previous studies were performed either before model for end-stage liver disease (MELD) allocation or done in patients with low MELD scores. The aim of study was to characterize the change of plasma renin activity-aldosterone concentration and investigate the clinical importance of PICD after non-large volume paracentesis with differences in the MELD cirrhotic ascites.

Materials and Methods: Cirrhotic patients with tense ascites were divided in two groups by MELD calculation: MELD ≤15 and MELD >15. Changes in plasma renin, aldosterone and other laboratory tests were assessed before and 6 days after modest volume paracentesis (less than 5 liters). PICD was defined as an increase in plasma renin activity on the sixth day after paracentesis of more than 50% of baseline value to a level >4 ng/mL/hr. After paracentesis, complications were also assessed within 90 days of follow-up periods. Factors associated with death were determined using Cox proportional hazards models.

Results: Sixteen patients with MELD ≤15 and 14 patients with MELD greater than 15, the high meld group, were included in the present study. A significant increase in the median change of plasma renin but not plasma aldosterone between the groups of MELD >15 and MELD ≤15 were 54.7% (10.8 to 1,800) vs. 17.6% (0 to 536.4) (p = 0.01) and 15.2% (3.3 to 59.1) vs. 11.6% (0 to 200) (p = 0.55), respectively. Notably, 35.7% of patients, all of whom were in the high MELD group, had PICD events with the Kaplan-Meier survival analysis demonstrating a short median survival of 28 days. High MELD patients had more acute kidney injury consequence (28.6% vs. 0%; p = 0.04) and a significantly increased 90 days mortality as compared to low MELD patients (71.4% vs. 6.3%, p<0.01). Multivariate Cox regression analysis indicated that only high MELD but not PICD can predict mortality with 10.73 times higher risk of death after paracentesis than low MELD patients (adjusted hazard ratio 10.73, 95% CI 1.24 to 92.98, p = 0.03).

Conclusion: Non-large volume paracentesis in high MELD cirrhotic patients causes a significant increase in plasma renin activity. PICD occurred only in high MELD patients and was associated with an increasing risk of acute kidney injury and mortality. An elevated MELD score in advanced cirrhotic patients should be considered as an increased risk for development of circulatory dysfunction, more complications and a short survival even after non-large volume paracentesis without albumin replacement.

Keywords: Ascites, Model for end-stage liver disease, Paracentesis induced circulatory dysfunction, Renin

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Therapeutic abdominal paracentesis, the current first-line treatment for cirrhotic patients with tense and refractory ascites, may associate with paracentesis induced circulatory dysfunction (PICD). PICD was defined as an increase in plasma renin activity on the sixth day after paracentesis of more than 50% of the baseline value to a level >4 ng/mL/hr. PICD is associated with a higher rate of recurrence of the ascites, dilutional hyponatremia, renal impairment, hospital readmission, and inferior survival rates. Most PICD events occurred after large volume paracentesis (LVP). As standard guideline, when less than 5 L of ascites are removed, the incidence of PICD is low and do not need albumin infusion. Human albumin can be used if there are concerns regarding the administration of crystalloids or synthetic colloids (volume overload, renal failure, coagulopathy) with a moderate of evidence. The patient characteristics established in previous studies were not corroborated by the Model for End Stage Liver Disease (MELD) assessment in the effect of hemodynamic and hormonal change after paracentesis. The aim of this study is to characterize the change of plasma renin activity-aldosterone level and investigate the clinical importance of PICD after non-large volume paracentesis (non-LVP) without

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albumin infusion in patients with different MELD scores.

Materials and Methods

Study design

The study was performed in 30 cirrhotic patients with tense ascites who visited the liver clinic, Department of Medicine, Vajira Hospital in Thailand between January and September 2018. The diagnosis of cirrhosis was based on clinical, laboratory, and ultrasonography. Patients with a serum potassium <3.5 mEq/L, eGFR <15 mL/min/1.73 m^2, a history of recent abdominal paracentesis within the previous 4 weeks, had received plasma expander or blood components within the previous 4 weeks, gastrointestinal hemorrhage within the previous 2 weeks, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, acute kidney injury, hepatocellular carcinoma, a change in dose of diuretics (furosemide/thiazide within the previous 4 weeks, spironolactone within the previous 8 weeks) and angiotensin converting enzyme agents or angiotensin II receptor blocker or beta blocker use within the previous 4 weeks or receiving renal replacement therapy were excluded. All patients gave informed consent to participate in the study, which was approved by the Ethics Committee of Vajira Hospital. Patients received a low sodium diet and diuretics at regular dosage at our liver clinic. The type and dose of medication given to these patients were not adjusted within 14 days before entry. Initial body weight and body weight after paracentesis at day 0 were recorded. We also collected the patients' baseline characteristic data at the day of paracentesis. After patients were in supine position for at least 2 hours, samples of plasma renin activity (PRA) and plasma aldosterone concentration (PAC) measured at day 0. Ascites removal in a single tap was done at the outpatient department without albumin infusion. After paracentesis symptoms and signs were observed and a blood sample was obtained to measure biochemical tests, PRA and PAC, body weight was recorded at the sixth day. The follow-up period started at the end of procedure. Patients visited the outpatient clinic weekly during the first month and monthly for the next 2 months. Patients who rapidly developed ascites re-accumulation during follow-up were treated with paracentesis. We followed-up patients until the first hospitalization with any complication or the event of death.

PRA and PAC measurement

PRA and PAC were measured by the enzyme-linked immunosorbent assay (ELISA) (ELx800™, BioTek®, Belgium) which was made using standard laboratory techniques. The normal reference value for PRA and PAC were a range of 0.2 to 1.6 ng/mL/hr and 1 to 16 ng/dL respectively. The MELD score was calculated according to the United Network for Organ Sharing modifications of the MELD formula using: MELD = 11.2 ln (INR) + 3.78 ln (serum bilirubin [mg/dL]) + 9.57 ln (serum creatinine [mg/dL]) + 6.43. The maximal serum creatinine level considered within MELD score calculation was 4.0 mg/dL.

Definition of complications

PICD was defined as an increase in PRA of >50% of the baseline value to a level >4 ng/mL/hr on the sixth day after paracentesis. Acute kidney injury (AKI) was defined as an increase in serum creatinine ≥50% compared with the baseline value to a level >1.5 mg/dL on the sixth day after paracentesis or an increase in serum creatinine ≥30% compared with the baseline values on the sixth day after paracentesis in patients with a serum creatinine level >1.5 mg/dL at baseline. Hyponatremia was defined as a decrease in serum sodium level >5 mEq/L to a level <130 mEq/L after paracentesis. Patients with a baseline serum sodium level <130 mEq/L, a decrease in level >5 mEq/L at the sixth day after paracentesis were included in the group of patients developing hyponatremia. Orthostatic hypotension was defined as decrease in systolic blood pressure of 20 mmHg or a decrease in diastolic blood pressure of 10 mmHg within three minutes of maintaining a standing position after paracentesis when compared with baseline blood pressure from the supine position.

Statistical analysis

Statistical analysis for the data was performed using the IBM SPSS statistics version 23. The MELD and PICD events were input as the test variable. Baseline clinical and laboratory parameters were compared using an independent t-test or Mann-Whitney U-test and Fisher's exact test for continuous variables while categorical variables were compared using a X^2 test with the appropriate degrees of freedom. Continuous variables are presented as mean ± standard deviation (SD) while categorical variables are presented as percent and frequency over total available. Significance was established at a *p*-value of <0.05. We performed Kaplan-Meier survival analysis. Patients were censored at the time of death or 90 days of follow-up after paracentesis. We calculated statistical significance of difference between survival curves with the log-rank test. We used Cox proportional Hazard model regression analysis for risk of adverse event.

Results

Table 1 shows baseline characteristics of patients at study inclusion. A total of 30 patients, were divided in 2 groups according to MELD score (≤15 or >15), 16 patients were in the lower MELD group and the others were in the high MELD group. Most of them were male and etiology of alcoholic cirrhosis. The mean ages were significantly higher in the low MELD group as compared to the other (63.3 vs. 52.3 years, $p = 0.009$). Ninety-three percent in the high MELD group were Child-Pugh score C and most of the patients with lower MELD were in Child-Pugh score B. Baseline of mean arterial pressure, serum creatinine, serum sodium were not significantly different between the two groups. A higher initial plasma renin and aldosterone were seen in the high MELD group (4.1 vs. 0.8 ng/mL/hr, $p = 0.038$ and 28 vs. 16 ng/dL, $p = 0.002$).

Table 2 shows hemodynamics and laboratory

parameter before and sixth days after paracentesis according to MELD group. After non-LVP in all 30 patients, none of them developed orthostatic hypotension. A significant decrease in MAP was observed at the sixth day of paracentesis. Figure 1 shows a median increase of plasma renin and plasma aldosterone compared at day 0 and day 6 was demonstrated in both MELD groups (0.8 to 1.4 ng/mL/h, $p = 0.003$ and 4.1 to 16.1 ng/mL/h, $p = 0.001$) and (16 to 17.5 ng/dL, $p = 0.001$ and 28 to 31 ng/dL, $p<0.001$). A significant increase in serum creatinine was observed only in the high MELD group (1.3 to 1.5 mg/dL, $p = 0.017$). Both groups had no significant change in serum sodium.

Table 3 shows volume of ascites removal, percent change in PRA, PAC, hemoglobin, body weight and

Table 1. Baseline characteristics of 30 patients according to MELD score

Characteristics	MELD ≤15	MELD >15	*p*-value
Age (years), mean (SD)	63.3 (11.4)	52.4 (9.8)	0.009
Male, n (%)	12 (75)	9 (64.3)	0.404
Etiology of cirrhosis, n (%)			
Alcohol	8 (50)	9 (64.3)	0.484
Hepatitis B virus	0 (0)	1 (7.1)	0.467
Hepatitis C virus	4 (25)	0 (0)	0.103
Other causes	4 (25)	4 (28.6)	1
Child-Pugh score, n (%)			
A	0	0	NA
B	15 (93.8)	1 (7.1)	<0.001
C	1 (6.3)	13 (92.9)	<0.001
Mean arterial pressure (mmHg), mean (SD)	88.8 (13.3)	94.7 (13)	0.227
Liver biochemistries tests			
Total billirubin (mg/dL), mean (SD)	1.3 (0.6)	4.1 (1.5)	<0.001
Direct billirubin, (mg/dL), mean (SD)	0.7 (0.4)	3.1 (1.5)	<0.001
Aspartate aminotransferase (U/L), median (IQR)	49.5 (17 to 89)	93.5 (28 to 195)	0.081
Alanine aminotransferase (U/L), median (IQR)	22.5 (9 to 55)	36 (10 to 77)	0.118
Alkaline phosphatase (U/L), mean (SD)	118.7 (42.6)	136.9 (46.4)	0.271
Albumin (g/dL), mean (SD)	2.5 (0.7)	2 (0.6)	0.058
Globulin (g/dL), mean (SD)	5 (1.2)	4.6 (1.2)	0.303
Serum creatinine (mg/dL), mean (SD)	1.1 (0.4)	1.3 (0.7)	0.485
INR, mean (SD)	1.3 (0.2)	1.9 (0.6)	0.001
MELD score, mean (SD)	11.5 (2.4)	21.2 (5.4)	<0.001
Serum sodium (mmol/L), mean (SD)	137.8 (4.2)	135.6 (5.9)	0.25
Serum potassium (mmol/L), mean (SD)	4.1 (0.5)	3.9 (0.5)	0.509
PRA (ng/ml/hr), median (IQR)	0.8 (0.2 to 10.1)	4.1 (0.1 to 22.2)	0.038
PAC (ng/dL), median (IQR)	16 (2 to 52)	28 (17 to 60)	0.002

INR = international normalized ratio, IQR = interquatile range, MELD = model for end-stage liver disease, PAC = plasma aldosterone concentration, PRA = plasma renin activity, SD = standard deviation

Table 2. Mean arterial pressure, serum creatinine, serum sodium, plasma renin activity and plasma aldosterone at day 0 and day 6 after paracentesis according to MELD score

	MELD ≤15 (n = 16)			MELD >15 (n = 14)		
	Day 0	Day 6	*p*-value	Day 0	Day 6	*p*-value
MAP (mmHg), mean (SD)	88.8 (13.4)	80.2 (14.9)	0.002	94.7 (13.0)	86.2 (16.9)	<0.001
Serum creatinine (mg/dL), mean (SD)	1.1 (0.4)	1.1 (0.3)	0.550	1.3 (0.7)	1.5 (0.8)	0.017
Serum sodium (mmol/L), mean (SD)	137.8 (4.3)	138.6 (4.3)	0.414	135.6 (5.9)	133.5 (5.2)	0.165
PRA (ng/ml/hr), median (IQR)	0.8 (0.1 to 10.1)	1.4 (0.2 to 11.4)	0.003	4.1 (0.1 to 22.2)	16.1 (0.3 to 34.4)	0.001
PAC (ng/dL), median (IQR)	16 (2 to 52)	17.5 (6 to 64)	0.001	28 (17 to 60)	31 (23 to 70)	0.001

IQR = interquatile range, MAP = mean arterial pressure, MELD = model for end-stage liver disease, PRA = plasma renin activity, PAC = plasma aldosterone concentration

complications during the study period from day 0 to day 6 according to MELD group. The mean volume of ascites removed between both MELD groups were not different (2.6 vs. 2.9 L, p = 0.305) and median percent change of increase plasma renin but not plasma aldosterone were significantly higher in MELD >15 (54.7% vs. 17.6%, p = 0.01), (15.2% vs. 11.6%, p = 0.55). With measurements of PRA before and 6th days after non-LVP, 13 of 30 patients (43.3%) had significant increases in plasma renin and/or developed PICD. Nine of 14 high MELD patients (64.28%) had increased plasma renin more than 50% from baseline as compared to 4 of 16 (25%) in the low MELD group (p = 0.03). A greater increase in body weight after procedure was seen in the high MELD although insignificant.

Five of 30 patients (16.6%) developed PICD. All were in Child C status with MELD >15 and mean MELD of 21. An occurrence of PICD was significantly higher in the group of MELD >15 (35.7 vs. 0%; p = 0.014). The mean volume of ascites removed in the PICD group was not different from the non-PICD. Table 4 shows hemodynamics and laboratory parameter before and sixth days after paracentesis according to PICD group. Mean SBP before paracentesis in the PICD group was 92.6 mmHg and these patients had significant changes in MAP after paracentesis (92.6 vs. 87.6 mmHg, p = 0.017). Figure 1 shows a significant increase in PRA and PAC in PICD patients was observed at sixth days after treatment as compared to baseline (2.5 to 14.1 ng/ml/hr, p = 0.043), (22 to 29 ng/dL, p = 0.043). An increase in plasma creatinine and a reduction in plasma sodium were observed in the PICD group (1.2 to 1.7 mg/dL, p = 0.046, 138 to 135 mmol/L, p = 0.023 respectively). Three of 5 PICD patients developed AKI after non-LVP. Ascites reaccumulation defined as a mean change of body weight after procedure at day 0 and day 6 were 1.9 kg, a greater change was seen in the PICD group (4.7 vs. 1.4 kg, p = 0.02).

Table 5 shows complications after paracentesis during the 90-day follow-up period. After procedure, we found 13 patients (43.3%) had complications during the first admission with a median time to first readmission of 42 days (20 to 90). Most of them (92.3%) were in the high MELD group irrespective of PICD. Most common complications were sepsis (64.3%) followed by hepatic encephalopathy (50%), acute kidney injury (28.6%) and GI bleeding (21.4%). Nearly half of sepsis occurrences were caused by spontaneous bacterial peritonitis. Four of 30 patients (13.3%) developed AKI and all AKI patients were in the high MELD group with an incidence of 4/14 (28.6%). All of them did not survive. An occurrence of hyponatremia was documented in only 2 patients. And only one non-survivor in the low MELD died

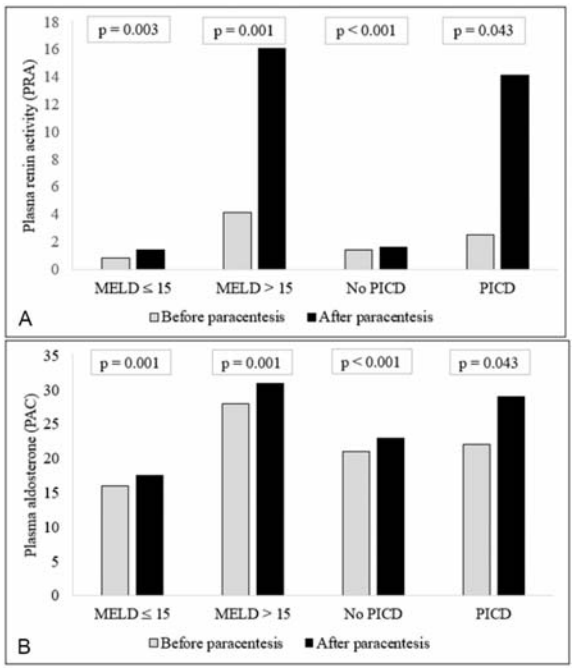

Figure 1. Plasma renin activity, plasma aldosterone at baseline and 6th day and percent change according to MELD and PICD. A) Plasma renin activity (PRA), B) Plasma aldosterone concentration (PAC)

Table 3. Volume of ascites removal, percent change in plasma renin activity, plasma aldosterone, hemoglobin, body weight and complication after paracentesis separated by level of MELD score

Percent change measured at day 0 and day 6	MELD ≤15 (n = 16)	MELD >15 (n = 14)	p-value
Volume of ascites removal (L), mean (SD)	2.6 (0.9)	2.9 (0.8)	0.305
Change of PRA (%)	17.6 (0 to 536.36)	54.7 (10.81 to 1,800)	0.014
Change of PAC (%)	11.6 (0 to 200)	15.2 (3.33 to 59.1)	0.546
No. of patients with increase PRA >50% (%)	4 (25)	9 (64.28)	0.030
Change of hemoglobin (%), mean (SD)	- 4.2 (8.8)	-5.9 (19.9)	0.770
Change of body weight (%), mean (SD)	1.6 (2.2)	5.9 (7.4)	0.054
No. of patients with PICD (%)	0	5 (35.7)	0.014
No. of patients with AKI (%)	0	4 (28.6)	0.037

AKI = acute kidney injury, MELD = model for end-stage liver disease, PRA = plasma renin activity, PAC = plasma aldosterone concentration, PICD = paracentesis induced circulatory dysfunction

Table 4. Mean arterial pressure, serum creatinine, serum sodium, plasma renin activity, plasma aldosterone concentration at day 0 and day 6 after paracentesis according to PICD

	Non PICD (n = 25)			PICD (n = 5)		
	Day 0	Day 6	*p*-value	Day 0	Day 6	*p*-value
MAP (mmHg), mean (SD)	91.3 (14.3)	82.1 (16.9)	<0.001	92.6 (7.8)	87.6 (9.5)	0.017
Serum creatinine (mg/dL), mean (SD)	1.2 (0.5)	1.2 (0.6)	0.134	1.2 (0.6)	1.7 (0.8)	0.046
Serum sodium (mmol/L), mean (SD)	136.5 (5.2)	136.4 (5.3)	0.935	138 (5.3)	135 (5.9)	0.023
PRA (ng/ml/hr), median (IQR)	1.4 (0.1 to 22.2)	1.6 (0.2 to 34.4)	<0.001	2.5 (0.7 to 19)	14.1 (5.7 to 28.9)	0.043
PAC (ng/dL), median (IQR)	21 (2 to 60)	23 (6 to 70)	<0.001	22 (17 to 30)	29 (26 to 35)	0.043

MAP = mean arterial pressure, PRA = plasma renin activity, PAC = plasma aldosterone concentration

Table 5. Complications after paracentesis during the follow up period according to MELD score

Complications	MELD ≤15	MELD >15	*p*-value
No. of patients with complication	1 (6.3)	12 (85.7)	0.005
No. of complication (n = 27)	1 (3.7)	26 (96.3)	<0.001
Acute kidney injury	0	4 (28.6)	0.037
Hyponatremia	0	2 (14.3)	0.209
Orthostatic hypotension	0	0	NA
Gastrointestinal bleeding	0	3 (21.4)	0.090
Hepatic encephalopathy	0	7 (50)	0.002
Sepsis	0	9 (64.3)	<0.001
Spontaneous bacterial peritonitis	0	4 (28.6)	0.037
Others	0	5 (35.7)	0.014
Acute coronary syndrome	1 (6.3)	1 (7.1)	0.724
Death within 90 days	1 (6.3)	10 (71.4)	<0.001

Value presented as n (%)
MELD = model for end-stage liver disease

from non-liver related complication.

Eleven of 30 patients (36.6%) died, and all death events occurred within 3 months. Almost all of the non-survivors (90.9%) were in the high MELD group with an average time after paracentesis to death of 59 days. The most common cause of death (81.8%) was due to sepsis. Two of 11 died with acute coronary syndrome (ACS). The cause of death in 6 patients who did not develop PICD was sepsis (5 patients) and ACS (1 patient). In the PICD group, sepsis occurred in 4 patients and ACS occurred in 1 patient. More than one third of non-survivors (4 of 11; 36.4%) died within 1 month after paracentesis. Of the 4 short-survival patients, 3 of them (75%) develop PICD even though the PICD patients had a non-significantly shorter time to first readmission compared to those who did not develop this event (28 vs. 43 days, $p = 0.1$).

Figure 2 shows survival analysis according to PICD. The Kaplan-Meier analysis showed that all PICD patients died with a short median survival of 28 days (95% CI 23.7 to 32.3), while there was no median survival time in the non PICD group. During 90 days of follow-up, none of the PICD patients survived as compared to 80% survivors of the non PICD patients. The log rank test indicated that there was a statistically significant difference between the two survival rates ($p<0.001$). Most of the PICD patients (80%) died from sepsis.

Figure 3 shows survival analysis according to MELD score. Survival analysis according to MELD group demonstrated that the median survival in the high MELD group was 42 days, (95% CI 32.2 to 51.8), while there was no median survival time in the low MELD group. After 90 days of follow-up, less than one-third (21.4%) of high MELD patients survived as compared to a high proportion (93.8%) in the low MELD group ($p = 0.0003$).

We had 8 additional patients who had significant percent changes in PRA but did not develop PICD by a definition of absolute level of plasma renin at day 6. However, 9 out of 13 (69.2%) patients with significantly increased changes in PRA irrespective of PICD occurred in high MELD cirrhotic ascites patients with a mean change of 221%, (52.1 to 1,800).

Table 6 shows Cox regression analysis for death events. In the univariate analysis, the following 3 variables were significantly associated with increased death events;

MELD >15 (hazard ratio (HR) 16.5, 95% CI 2.1 to 130.4), PICD (HR 11.9, 95% CI 3.2 to 44.2), AKI (HR 6.7, 95% CI 1.85 to 24.3). After multivariate analysis, only the high MELD group was at a 10.73 times higher risk of death than the low MELD group (adjusted HR 10.73, 95% CI 1.24 to 92.98, $p = 0.03$).

Discussion

Therapeutic abdominal paracentesis is an effective standard of care treatment for tense ascites. Mobilization of ascites by paracentesis initially increases venous return and cardiac output. However, this may be followed by decreased systemic vascular resistance caused by activated renin angiotensin aldosterone systems, salt and water retention and re-accumulation of ascites[1,2]. In LVP, the PICD incidence is reduced to 15 to 35% when volume expanders are used especially when albumin infusion, an incidence of PICD is less than 20%[3-6]. Previous reported incidences of PICD after less than 5 liters of ascites was removed with plasma expander was 5 to 16%[6-8]. Current knowledge suggests limiting the volume of ascites removed to less than 5 liter is the concept to prevent PICD.

Child-Pugh scores evaluation has some parameters which limited discriminate ability. Not only impairment of synthetic liver function and the presence of ascites but subclinical decrease in renal function were independently associated with 6 months mortality in cirrhosis. Additional application of MELD score has been used as a prognostic tool as a good predictor of short-term mortality in cirrhotic

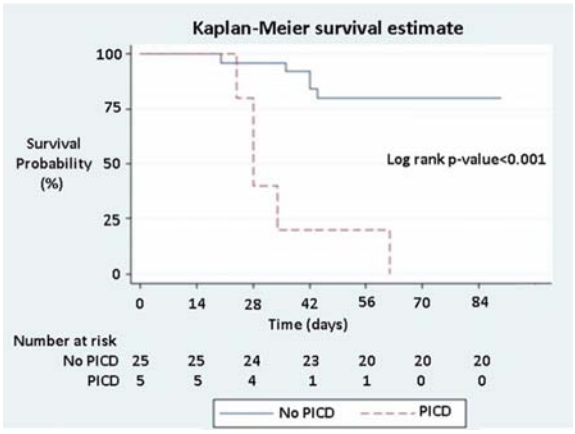

Figure 2. Survival analysis according to paracentesis induced circulatory dysfunction.

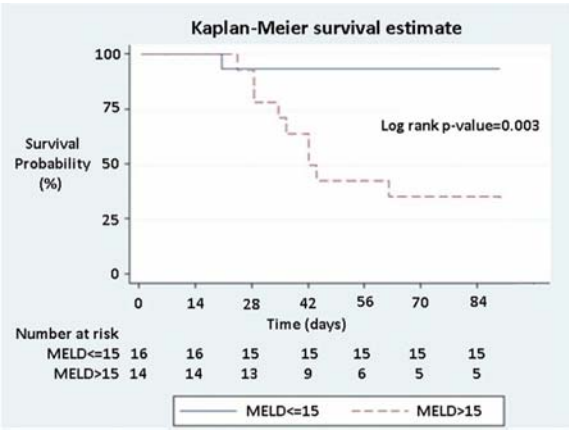

Figure 3. Survival analysis according to MELD.

Table 6. Univariates and Multivariate Cox regression for death

Variables	Univariate analysis		Multivariate analysis	
	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Male	0.79 (0.2, 2.7)	0.71	-	-
Age	0.98 (0.9, 1.0)	0.35	-	-
Etiology				
Alcohol	Reference	1	-	-
HBV	0 (0, 1)	0.99		
HCV	0 (0, 1)	0.98		
Other	1.83 (0.56, 6.0)	0.32		
Child-Pugh score				
B	Reference	1	-	-
C	16.5 (2.1, 130.3)	0.008		
MELD >15	16.5 (2.1, 130.4)	0.008	10.73 (1.24, 92.9)	0.031
% change of PRA	1.01 (1, 1.02)	0.077	-	-
PICD	11.94 (3.2, 44.2)	<0.001	5.46 (0.79, 37.73)	0.086
AKI	6.7 (1.85, 24.3)	0.004	0.87 (0.13, 5.82)	0.884

AKI = acute kidney injury, HBV = hepatitis B virus, HCV = hepatitis C virus, HR = hazard ratio, MELD = model for end-stage liver disease, PRA = plasma renin activity, PICD = paracentesis induced circulatory dysfunction

patient because it takes into consideration serum creatinine, the international normalized ratio and bilirubin levels and is reported as continuous value which has shown significant correlations with Child-Pugh scores. Combined score were more precise for predicting short and medium survival in cirrhotic patients[9,10]. Study of Roth et al identified a cut off MELD scores of more than 15 was positively associated with in-hospital mortality and co-morbidities of hospitalized patients[11]. Current recommendation based upon hemodynamic and hormonal change after LVP was conducted before the inception of MELD scoring system. The mean MELD score in previous PICD studies was less than 15 and does not mention the clinical significance of MELD score application[12]. We hypothesized that in the same level of Child-Pugh classification but more severity in terms of higher MELD score may impact differently in circulatory dysfunction after non-LVP.

After paracentesis, there is no reduction in total intravascular volume present shown by non-significant changes of mean hemoglobin in the entire group. But a reduction in effective intravascular volume followed by activated neurohormonal vasoactive systems was demonstrated by impaired renal function. We observed after non-LVP, not only a decrease in MAP but also an increase in serum creatinine significantly occurred only in the high MELD group without significant change in serum sodium. Corresponding with an impact of more advanced liver disease on a change of neurohormonal systems, we saw a significantly higher median percent change of increased PRA in the high MELD group when compared to the other group and also demonstrated that nearly 70% of patients who had a significant increase in PRA and/or developed PICD (n = 9), occurred in high MELD cirrhotic patients. We controlled volume of ascites removed by demonstrating a non-different volume removed between the two MELD groups.

Four of 16 (25%) patients in the low MELD group who had increased plasma renin at levels more than 50% but did not develop PICD or other liver-related complications because these patients had low baseline median PRA (0.39; 0.22 to 0.53 ng/ml/hr) which may have the tendency to increase the percentage changing of level without clinically significant consequences.

Patients with advanced liver disease with high MELD are vulnerable to developing AKI even after non-LVP without colloid replacement as demonstrated in nearly one-third (28.6%) of these events which resulted from a higher level of activated RAA systems. AKI in advanced cirrhosis causes a very high mortality rate as seen in our study where all AKI-developed patients did not survive. Our study has shown that high MELD with occurring PICD events, more than half of them developed AKI and subsequent other complications. After paracentesis, more than one-third of all patients survived less than 3 months; almost all non-survivors (90.9%) were in advanced high MELD score. Almost all causes of death came from liver-related complications. The present study found that spontaneous bacterial peritonitis (SBP) contributed to nearly half of the causes of sepsis, corresponding with previous study which reported increasing MELD score is associated with a greater risk of SBP[13]. Our Cox regression analysis indicated that patients in high MELD were 10.73 times more at risk of death than patients in the other.

In our study, 16.6% of patients developed PICD after non- LVP. The occurrences of PICD were not associated with volume of ascites removed. We cannot identify patients who develop PICD only by a change in mean arterial pressure because of an initial clinical silence, but this condition indicated grave prognoses not only AKI but reaccumulate ascites, hyponatremia results in a short survival of less than one month. Arora et al reported predictor of PICD occurrence was modest volume paracentesis (<5 L) without albumin in ACLF patients and significant develop AKI complication and increase mortality[14]. Although standard guideline and limited resources recommend that albumin infusion is not indicated for non-LVP, we reported all PICD events occurred within high MELD decompensated cirrhosis, future, large scale population is needed to support this result. Our study has shown that using MELD calculation may be beneficial to identify patients who would benefit from albumin infusion during modest volume abdominal paracentesis. Moreover, the significantly high risk of death occurred only in the high MELD group irrespective of PICD events. There were 4 patients who were refractory ascites by intractable to diuretics, all of whom had previous history of resolved acute kidney injury which was the reason why we removed ascites in these patients in only a modest volume.

One limitation in our study was that we did not study the flow rate of fluid extraction during the paracentesis, without volume expander, whether the flow rate significantly impacted PICD incidence is a controversial issue[15-17]. Elsabaawy MM reported that the flow rate of ascites removal of LVP plus albumin does not correlate with PICD development[16]. Secondly, even though most complications were from liver-related causes with AKI exception, these events are commonly seen in decompensated cirrhosis irrespective of paracentesis, so we cannot conclude these complications were all from our procedure. Finally, we did not see a long-term outcome of survivors because of limited times of follow-up.

Conclusion

High MELD score in advanced liver disease was associated with a high mortality rate. A significant increase in plasma renin and/or PICD followed by other complications after paracentesis occurred in a significant proportion of high MELD cirrhotic patients. PICD in these patients was associated with a chance of developing AKI and shortened median survival. Advanced cirrhotic patients with high MELD scores should be considered at risk of developing circulatory dysfunction even after non-LVP without albumin replacement.

What is already known on this topic?

Significant increase in plasma renin and/or PICD

followed by AKI after paracentesis was associated with short median survival in cirrhotic patients.

What this study adds?

High MELD cirrhotic patients should be considered at risk of developing PICD even after non-LVP.

Potential conflicts of interest

The authors declare no conflicts of interest.

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