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Utility of MELD scoring system for assessing the prognosis of acute fatty liver of pregnancy

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ABSTRACT

Objective: To evaluate the value of Model for end-stage liver disease (MELD) in assessing the prognosis of acute fatty liver of pregnancy (AFLP).
Study design: This was a retrospective study. From January 2010 to July 2018, data of 53 women diagnosed with AFLP in the third affiliated hospital of Sun Yat-Sen University were collected. Blood samples were collected on admission and MELD score was calculated. The MELD score was calculated by using the original MELD formula as shown: 9.57 log (creatinine) + 3.78 log (bilirubin) + 11.20 log (international normalized ratio, INR) + 6.43. The perinatal outcomes were documented.
Results: Nine women were excluded as they were transfered to our hospital after delivery in other hospitals. The remaining 44 women had average age of 28.8 ± 5.2 years. The MELD score showed good performance in predicting most of the perinatal complications of AFLP with all the area under the receiver operating characteristic (ROC) curves (AUC) > 0.8, including ascites (AUC: 0.91, 95% CI: 0.78–0.98), wound seroma (AUC: 0.91, 95% CI: 0.78–0.93), hepatic encephalopathy (AUC: 0.93, 95% CI: 0.82–0.99), DIC (AUC: 0.87, 95% CI: 0.74–0.95), sepsis (AUC: 0.93, 95% CI: 0.82–0.99), renal insufficiency (AUC: 0.94, 95% CI: 0.82–0.99) and stillbirth (AUC: 0.85, 95% CI: 0.71–0.94). Nearly all the maternal complications were more frequently happened in MELD score ≥30 group ($P < 0.05$).
Conclusion: MELD scoring system may be a suitable method for assessing the prognosis of AFLP.

Introduction

Acute fatty liver of pregnancy (AFLP) is a rare disease with an incidence about 1 case per 7270–13,000 deliveries [1]. The cause of AFLP remains unclear at present. Certain inheritance patterns in mother and fetus, such as long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, are linked to fetal fatty oxidation defects that may lead to AFLP [2]. Several risk factors have been identified for AFLP, including primigravida, twin pregnancy, and male sex of fetus [3,4]. The symptoms of AFLP are non-specific. Most women start with symptoms of nausea, asthenia, abdominal pain and jaundice, then rapidly progress to have hepatic dysfunction, coagulation disturbance and renal insufficiency [5,6].

AFLP is often fatal to both mother and fetus. Identification of this disease severity and appropriate interventions are likely to improve pregnancy outcome [6,7]. Varied prognostic scoring systems have been developed to predict the severity of liver failure and guide the decision-making, including Child-Turcotte-Pugh (CTP) [8], Model for end-stage liver disease (MELD) [9], Acute physiology and chronic health evaluation (APACHE) [10] and Sequential organ failure assessment (SOFA) [11]. However, none of a prognostic scoring system has been formed to assess the prognosis of AFLP as the rare condition and complicated peripartum physiological changes make it difficult to study.

MELD is one of the most widely used scoring system for assessing the prognosis of liver diseases due to its objective and quantitative variables that are serum total bilirubin (TBIL), serum creatinine, and international normalized ratio (INR) [12]. MELD has originally been used as a screening criterion for liver transplantation in adults [13]. Thereafter, many studies found its ability in predicting the short-term prognosis of patients with acute liver

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failure and also pregnancy-specific liver diseases [14–17]. However, rare study investigated the MELD scoring system in predicting the outcome of AFLP. The purpose of our study is to evaluate the value of MELD in assessing the prognosis of AFLP which is critical for the treatments.

Subjects and methods

A total of 53 women were diagnosed with AFLP from January 2010 to July 2018 in the third affiliated hospital of Sun Yat-Sen University and 9 women were excluded as they were sent to our hospital after delivery in other hospitals. The "Swansea Criteria" proposed by Ch'ng et al. was used for AFLP diagnosis, requiring at least 6 of the following signs/symptoms: nausea, abdominal pain, polydipsia/polyuria, encephalopathy, hypoglycemia, hyperuricemia, leukocytosis, ascites, increased aminotransferase and bilirubin, increased ammonia, renal failure, coagulopathy, metabolic acidosis, pancreatitis, and a liver biopsy demonstrating microvesicular steatosis [18]. The study was approved by the Human Research Ethics Committee of the third affiliated hospital of Sun Yat-Sen University.

Maternal baseline characteristics were recorded and blood samples were collected on admission, including maternal age, gestational age, parity, onset time, alanine aminotransferase (ALT), aspartate aminotransferase (AST), TBIL, direct bilirubin (DBIL), glucose prothrombin time (PT), prothrombin activity (PTA), INR, blood urea nitrogen, creatinine, uric acid, hemoglobin, white blood cell, and platelets for basic. The MELD score was calculated by using the original MELD formula as shown: 9.57 log (creatinine) + 3.78 log (bilirubin) + 11.20 log (INR) + 6.43.

Regarding treatment, termination of pregnancy was proceeded once AFLP was diagnosed. After delivery, all the patients were sent to the intensive care unit (ICU) and further therapies were chosen according to patients' condition, including plasma exchange, blood products replenishment and antibiotics use. The recovery time, hospitalization expenses and number of perinatal complications were documented. The maternal outcomes were assessed and documented, including gestational age at delivery, birth method, pulmonary edema, hepatic encephalopathy, disseminated intravascular coagulation (DIC), renal insufficiency, ascites, sepsis, heart failure, wound seroma, maternal death and stillbirth. The neonatal outcomes were including low Apgar score ($\leq$7 at 1 or 5 min), neonatal intracranial hemorrhage and neonatal intensive care unit (NICU) admission rate.

Statistical analysis

Data were presented as mean (SD) for continuous variables, medians (interquartile range) for skewed variables and frequency (percentage) for categorical variables. Difference in continuous variables between groups was tested using Student's *t*-test (assuming a Gaussian distribution) or Mann–Whitney test (assuming a non-Gaussian distribution). Pearson correlation analysis was performed to investigate the association between the continuous variables. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the predictive value of the MELD scoring system for the pregnancy outcomes of AFLP. The AUC > 0.8 was considered as having a very good predictive accuracy. The optimal cut-off point was the point on the ROC curve closest to the (0, 1) point. Survival analysis was used to analyze the difference of perinatal outcomes between the high and low MELD groups. Survival curve was plotted by Kaplan–Meier method and Log-rank test was used for the comparison. $P < 0.05$ was considered statistically significant. SPSS19.0 software (SPSS, Inc., Chicago, IL) was used for analysis.

Results

The clinical characteristics of 44 AFLP women were shown in Table 1. The average maternal age was 28.8(±5.2) years (range: 20–43 years), 25 (56.8%) of them were nulliparous, and 3 (6.8%) of them were twin pregnancies. It mainly presented in the third trimester [mean gestational weeks: 36.2(±2.5) weeks]. Anorexia and fatigue were the most common symptoms (77.3% and 63.6%, respectively). The mean gestational age at delivery was 36.2(±2.5) weeks (31.0–39.7 weeks). More than 80% of women were delivered by cesarean section (81.8%). There was one woman died (2.3%) and three stillbirths (6.8%) occurred. Of the total of 47 fetuses (three sets of twins), two-thirds of them were male (78.7%).

The duration of recovery after delivery ranged from 5 to 29 days and the median was 8 days. The ranges of the MELD scores were from 10 to 45 and the median was 25. Fifteen cases (34%) had MELD scores $\geq$ 30. The AUCs and ROC curves for the MELD score in predicting the perinatal complications of AFLP were showed in Table 2 and Fig. 1. The MELD scores showed good at predicting most of the maternal complications of AFLP with the AUCs > 0.8, including ascites (AUC: 0.91, 95% CI: 0.78–0.98), wound seroma (AUC: 0.91, 95% CI: 0.78–0.93), hepatic encephalopathy (AUC: 0.93, 95% CI: 0.82–0.99), DIC (AUC: 0.87, 95% CI: 0.74–0.95), sepsis (AUC: 0.93, 95% CI: 0.82–0.99), renal insufficiency (AUC: 0.94, 95% CI: 0.82–0.99) and stillbirth (AUC: 0.85, 95% CI: 0.71–0.94). However, MELD scores did not show the predictive value for the neonatal outcomes (AUCs < 0.8).

The laboratory results at admission of the 44 cases were shown in Table 3. Liver dysfunction and coagulation disorder were found in AFLP including elevated serum ALT [329.48(±228.90) U/L], AST [276.91(±192.67) U/L] and DBIL [93.75(±61.09) mol/L], decreased fibrinogen [1.20(±0.70) g/L], prothrombin activity [44.86(±17.17) %], and prolonged PT [20.80(17.98–27.38) s]. Elevated serum creatinine (164.57(±52.23) umol/L) reflected the renal damage. Compared with the MELD < 30 group, MELD $\geq$ 30 group women had more obvious jaundice [TBIL: 190.02(±68.91) *vs* 81.50(50.00–104.60) umol/L, $P = 0.00$; DBIL: 148.44(±54.93) *vs* 53.80(34.20–87.00) umol/L, $P = 0.00$], more severe renal damage [creatinine: 214.87(±41.84) *vs* 135.00(115.00–150.00) umol/L, $P = 0.00$; uric acid: 616.51(±146.11) *vs* 508.68(±105.19) umol/L, $P = 0.01$] and coagulation abnormalities [PT: 27.60(22.40–32.60) *vs* 18.70

Table 1
Clinical characteristics of 44 patients with acute fatty liver of pregnancy.

Variable	Measure
Basic characteristics	
Maternal age (years)*	28.84(±5.24)
Gestational age (weeks)*	36.22(±2.51)
Parity	
Nullipara, n (%)	25(56.8)
Multipara, n (%)	19(43.2)
Twin pregnancy, n (%)	3(6.8)
Birth method	
Vaginal delivery, n (%)	8(18.2)
Cesarean section, n (%)	36(81.8)
Stillbirth, n (%)	3(6.8)
Gender of baby	
Male, n (%)	37(78.7)
Female, n (%)	10(21.3)
Birth weight*	2.66(±0.73)
Death, n (%)	1(2.3)
Symptoms	
Anorexia, n (%)	34(77.3)
Fatigue, n (%)	28(63.6)
Jaundice, n (%)	21(47.7)
Nausea and vomiting, n (%)	14(31.8)
Liver on sonogram (bright), n (%)	13(29.5)
Abdominal pain, n (%)	8(18.2)

* Data are given as mean ± SD (range).

Table 2
Predictive value of the Model for End-Stage Liver Disease (MELD) score on the perinatal complications of acute fatty liver of pregnancy.

Variables	AUC	Standard error	95%CI	Optimal cut-off point	Sensitivity (%)	Specificity (%)	+LR	-LR	PPV	NPV
Maternal complications										
Ascites	0.91	0.05	0.78–0.98	26	92.31	80.65	4.77	0.10	66.70	96.20
Pulmonary edema	0.76	0.09	0.61–0.88	26	81.82	72.73	3.00	0.25	50.00	92.30
Wound seroma	0.91	0.06	0.78–0.93	32	71.43	94.59	13.21	0.30	71.40	94.60
Heart failure	0.76	0.09	0.61–0.88	26	81.82	72.73	3.00	0.25	50.00	92.30
Hepatic encephalopathy	0.93	0.05	0.82–0.99	32	83.33	94.74	15.83	0.18	71.40	97.30
DIC	0.87	0.10	0.74–0.95	32	80.00	92.31	10.40	0.22	57.10	97.30
Sepsis	0.93	0.04	0.82–0.99	31	100.00	87.50	8.00	0.00	44.40	100.00
Renal insufficiency	0.94	0.04	0.82–0.99	32	100.00	92.50	13.33	0.00	57.10	100.00
Stillbirth	0.85	0.07	0.71–0.94	28	10.00	70.73	3.42	0.00	20.00	100.00
Perinatal outcomes										
Low Apgar score	0.52	0.11	0.36–0.68	27	50.00	74.07	1.93	0.68	50.00	74.10
NICU	0.61	0.10	0.45–0.76	27	52.94	79.17	2.54	0.59	64.30	70.40
Intracranial hemorrhage	0.69	0.27	0.53–0.83	32	66.67	92.11	8.44	0.36	40.00	97.20

AUC: area under the curve; +LR, positive likelihood ratio; -LR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; CI, confidence interval; DIC, disseminated intravascular coagulation; NICU, Neonatal intensive care unit.

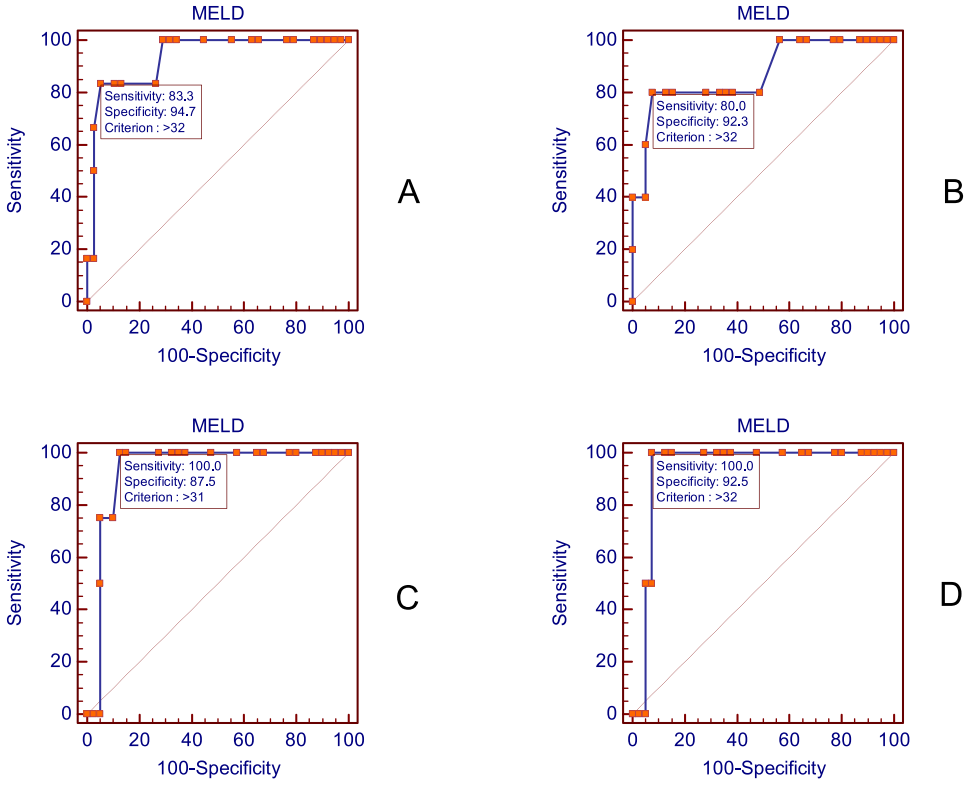

Fig. 1. ROC curves for the Model for End-Stage Liver Disease (MELD) score in predicting the complications of acute fatty liver of pregnancy (A: Hepatic encephalopathy; B: Disseminated intravascular coagulation; C: Sepsis; D: Renal insufficiency).

(17.00–21.10) s, $P = 0.00$; PTA: 30.77(±13.40) *vs* 52.17(±14.17) %, $P = 0.00$; INR: 2.41(±1.08) *vs* 1.56(1.37–1.83), $P = 0.00$; fibrinogen: 0.81(±0.33) *vs* 1.16(0.86–1.75) g/L, $P = 0.00$] (Table 3).

Differences of perinatal complications between MELD scores <30 and ≥30 in 44 patients of AFLP were shown in Table 4. Pearson correlation analysis was used. Nearly all the maternal complications were more frequently happened in MELD ≥ 30 group ($P < 0.05$), except DIC ($\chi^2 = 3.24$, $P = 0.07$), stillbirth ($\chi^2 = 3.47$, $P = 0.06$) and maternal death ($\chi^2 = 0.12$, $P = 0.73$) which were not different between the two groups. There were no differences between the two groups in fetal complications including low Apgar score ($\chi^2 = 1.03$, $P = 0.31$) and neonatal intracranial hemorrhage ($\chi^2 = 0.84$, P = 0.36). There was also no difference in the incidence of NICU admission between the two groups ($\chi^2 = 3.18$, $P = 0.07$).

Survival curves of perinatal complications according to MELD groups are reported in Fig. 2. Significant differences were observed in heart failure (Fig. 2A), hepatic encephalopathy (Fig. 2B), DIC (Fig. 2C), sepsis (Fig. 2D), pulmonary edema (Fig. 2E), and renal insufficiency (Fig. 2F) between the two MELD groups (MELD < 30 and MELD ≥ 30) (all $P < 0.05$).

Discussion

In the present study, MELD score showed good performance in predicting most of the perinatal complications of AFLP and the maternal complications were also more prevalent in subjects with higher MELD scores. Our results suggested that the MELD scoring system might be suitable for assessing the prognosis of AFLP women.

Table 3
Differences of laboratory results between MELD scores <30 and ≥30 in 44 patients with acute fatty liver of pregnancy at admission[a].

Laboratory tests	Total (n = 44)	MELD ≥ 30[b] (n = 15)	MELD < 30 (n = 29)	*P* Value
Alanine aminotransferase (U/L)	329.48(±228.90)	205.27(±105.33)	311.00(191.00–577.00)	0.02
Aspartate aminotransferase (U/L)	276.91(±192.67)	210.48(±78.00)	217.00(147.00–432.00)	0.32
Total bilirubin (umol/L)	122.53(±75.09)	190.02(±68.91)	81.50(50.00–104.60)	<0.01
Direct bilirubin (umol/L)	93.75(±61.09)	148.44(±54.93)	53.80(34.20–87.00)	<0.01
Albumin (g/L)	28.59(±3.16)	28.21(±3.37)	28.73(±3.09)	0.57
Cholinesterase (U/L)	3943.91(±1057.51)	3986.00(3344.00–4550.00)	3799.45(±928.01)	0.61
Glucose (mmmol/L)	3.34(±0.64)	2.96(±0.80)	3.50(3.21-3.76)	0.05
$HCO3^-$ (mmol/L)	16.93(±3.24)	15.37(±3.03)	17.73(±3.10)	0.02
Blood urea nitrogen (umol/L)	6.67(±2.58)	7.74(±3.27)	6.11(±1.98)	0.05
Creatinine (umol/L)	164.57(±52.23)	214.87(±41.84)	135.00(115.00–150.00)	<0.01
Uric acid (umol/l)	545.44(±129.73)	616.51(±146.11)	508.68(±105.19)	0.01
Prothrombin time (s)	20.80(17.98–27.38)	27.60(22.40–32.60)	18.70(17.00–21.10)	<0.01
Prothrombin activity (%)	44.86(±17.17)	30.77(±13.40)	52.17(±14.17)	<0.01
International normalized ratio	1.93(±0.80)	2.41(±1.08)	1.56(1.37–1.83)	<0.01
Fibrinogen (g/L)	1.20(±0.70)	0.81(±0.33)	1.16(0.86–1.75)	<0.01
White blood cell (10^9/L)	15.73(±5.78)	14.06(12.62–16.86)	14.02(12.04–18.20)	0.63
Platelets (10^9/L)	170.09(±70.27)	135.00(109.00–198.00)	168.76(±50.85)	0.54

MELD, Model for end-stage liver disease.
[a] Values are mean (SD) or median (interquartile range).
[b] Compared with the MELD < 30 group.

Table 4
Differences of perinatal complications between MELD scores <30 and ≥30 in 44 patients with acute fatty liver of pregnancy[§].

Variables	MELD ≥ 30 n = 15 (%)	MELD < 30 n = 29 (%)	χ^2	*P*
Maternal complications				
Ascites	10(66.7)	3(10.3)	12.48	<0.01
Pulmonary edema	7(46.7)	4(13.8)	4.08	0.04
Wound seroma	6(40.0)	1(3.4)	7.33	0.01
Heart failure	6(40.0)	2(6.9)	5.23	0.02
Hepatic encephalopathy	5(33.3)	1(3.4)	5.18	0.02
Sepsis	4(26.7)	0(0)	5.59	0.02
Renal insufficiency	4(26.7)	0(0)	5.59	0.02
DIC	4(26.7)	1(3.4)	3.24	0.07
Maternal death	1(6.7)	0(0)	0.12	0.73
Stillbirth	3(20.0)	0(0)	3.47	0.06
Perinatal outcomes				
Low Apgar score	6(50.0)*	10(31.3)**	1.33	0.25
NICU	8(66.7)*	10(31.3)**	3.18	0.07
Intracranial hemorrhage	2(16.7)*	1(3.1)**	0.84	0.36

MELD, Model for end-stage liver disease; DIC, Disseminated intravascular coagulation; NICU, Neonatal intensive care unit.
[§] Chi-square test was used.
* n = 12 (3 stillbirth in this group).
** n = 32 (3 twin pregnancy in this group).

Earlier recognition of AFLP is one of the most important factors that can improve the perinatal outcomes [5,6]. Primigravida, twin pregnancy, male sex of fetus and mainly occurring in the third trimester are the common risk factors that can help us for the early recognition [3,4]. In our study, we had the same risk factors. In AFLP, hepatic dysfunction, renal insufficiency, and impaired procoagulant synthesis are the three most prominent organ system derangements [19]. Therefore, typical laboratory findings, including elevated serum ALT, creatinine, bilirubin, PT, hypoglycemia, and hypoalbuminemia, are the key indices for the early diagnosis [20]. The similar laboratory changes were also observed in our study.

MELD score is excellent in predicting the short-term prognosis of patients with acute liver failure [21] and the optimal cutoff value was 30 [22,23]. However, limited data were found for its application in pregnancy women. In Murali's study, MELD was shown to be a reliable method for predicting the short-term mortality among women with pregnancy-specific liver diseases (the AUC was 0.83) [15]. In Yang's study, MELD showed good predictive value for the prognosis of patients with fulminant viral hepatitis in late pregnancy (the AUC 0.89 and the optimal cut-point was 32) [14]. In Deng's study, MELD scoring system showed the extraordinary predicting value for the short-term prognosis of pregnancy complicating fulminant hepatitis [23]. The AUC was 0.82 and the optimal cut-point was 30. In our study, we evaluated the predictive value of MELD for other perinatal complications of AFLP, including ascites, hepatic encephalopathy, sepsis, and renal insufficiency. Our results showed that MELD was a good predictor for all complications (with all AUCs > 0.8) and the optimal cut-off values were close to 30. While comparing with MELD scores < 30, the maternal complications were more prevalent in mothers with MELD scores ≥ 30. The laboratory results also showed that MELD ≥ 30 women had more obvious jaundice, more severe renal damage and coagulation abnormalities. These results suggested that MELD could be used as a suitable tool for predicting the complications of AFLP and MELD score ≥ 30 might be used for identifying the prognosis of AFLP.

There are also some limitations in our research. First, it was a single-center and small sample study which might reduce the general applicability of our findings. Secondly, due to the small number of the maternal death, it was difficult to evaluate the predictive value of the MELD scoring system for the mortality of AFLP. Third, we did not do the liver biopsy. Although it is the gold standard for the diagnosis of AFLP, this is rarely necessary and

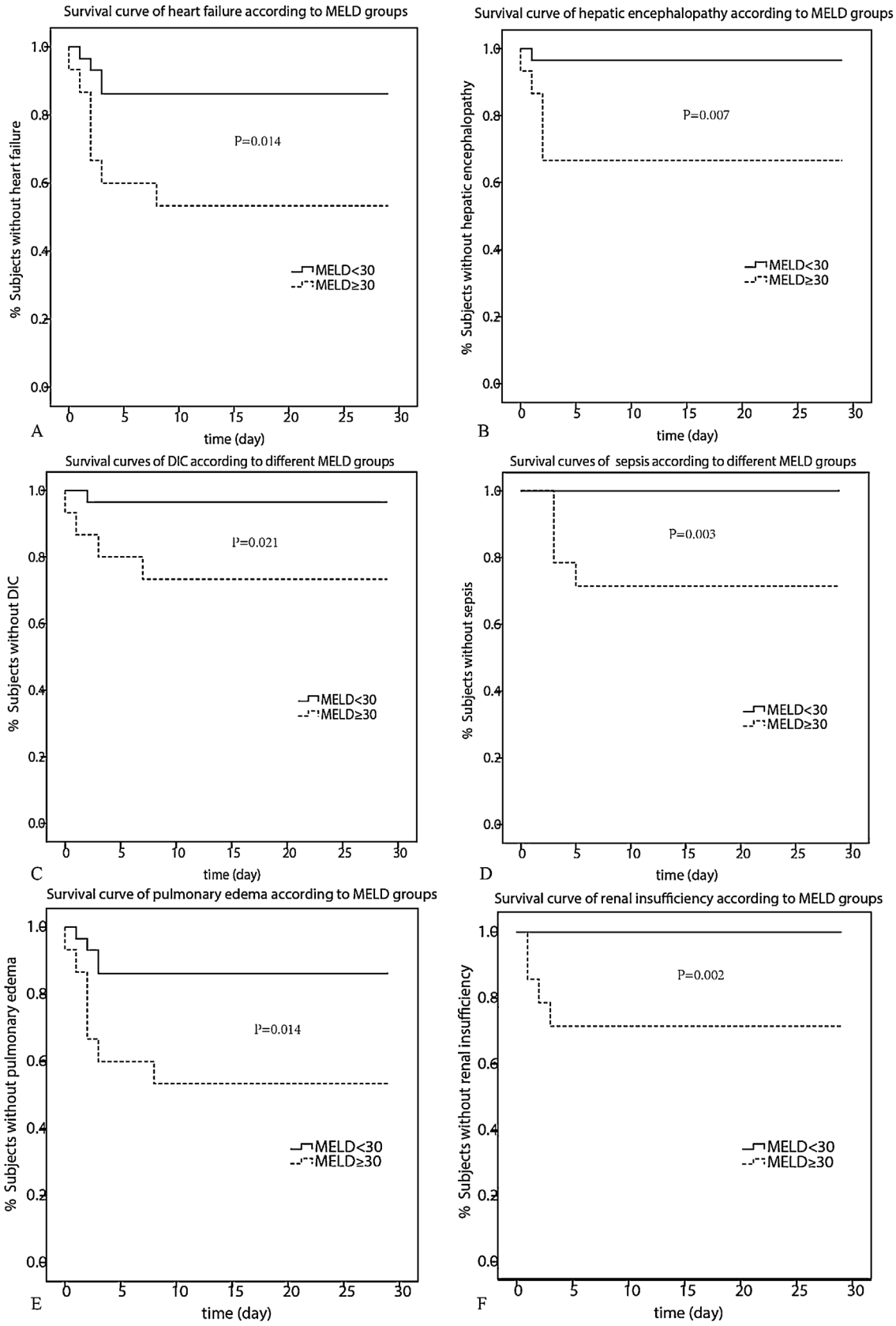

Fig. 2. The difference of the recovery time between MELD scores <30 and ≥30 in 44 patients with acute fatty liver of pregnancy*.
*: Survival analysis was used.
MELD, Model for end-stage liver disease; DIC, Disseminated intravascular coagulation.

should be avoided as the risk of bleeding is high [1]. The Swansea diagnostic criteria are an alternative to liver biopsy [24]. Further studies are needed to explore the accuracy of using MELD score to predict the prognosis of AFLP.

In conclusion, our study showed that the MELD scoring system was useful to predict the maternal complications of AFLP and could provide the clinician a reasonable expectation about AFLP.

Authors' contribution

PL: Project development, Data Collection, Manuscript writing.
SL: Project development, Statistical analysis, Revision.
LL: Data Collection.
JHC: Data Collection.
QQW: Data Collection.
SSZ: Project development.
JHF: Project development, Revision.

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