Risk Factors for Maternal and Fetal Mortality in Acute Fatty Liver of Pregnancy and New Predictive Models

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Abstract

Background: Acute fatty liver of pregnancy (AFLP) is a rare but potentially life-threatening hepatic disorder that leads to considerable maternal and fetal mortality. A better understanding of the risk factors of AFLP is required.

Methods: We analyzed demographic characteristics, clinical symptoms, and laboratory findings of 106 patients with acute fatty liver of pregnancy. Risk factors for maternal and fetal mortality were analyzed by univariate and multivariate logistic regression analysis. The new models based on the multivariate logistic regression analysis and model for end-stage liver disease were tested for all patients with acute fatty liver of pregnancy. The receiver operating characteristic curve was applied to compare the prediction efficiency, sensitivity, and specificity of the two models.

Results: Prenatal nausea ($p = 0.037$), prolonged prothrombin time ($p = 0.003$), and elevated serum creatinine ($p = 0.003$) were independent risk factors for maternal mortality in patients with acute fatty liver of pregnancy. The receiver operating characteristic curve showed that the area under the curve of the model for end-stage liver disease was 0.948, with a sensitivity of 100% and a specificity of 83.3%. The area under the curve of new model was 0.926, with a sensitivity of 90% and a specificity of 94.8%. Hepatic encephalopathy ($p = 0.016$) and thrombocytopenia ($p = 0.001$) were independent risk factors for fetal mortality. Using receiver operating characteristic curve, the area under the curve of the model for end-stage liver disease was 0.694, yielding a sensitivity of 68.8% and a specificity of 64.4%. The area under the curve of the new model was 0.893, yielding a sensitivity of 100% and a specificity of 73.3%.

Conclusion: Both the new predictive model for maternal mortality and the model for end-stage liver disease showed good predictive efficacy for maternal mortality in patients with acute fatty liver of pregnancy (the area under the curve = 0.948 and 0.926, respectively), and the new predictive model for fetal mortality was superior to the model for end-stage liver disease in predicting fetal mortality (the area under the curve = 0.893 and 0.694, respectively) with better sensitivity and specificity.

Background

Acute fatty liver of pregnancy (AFLP) is a rare but potentially life-threatening hepatic disorder that occurs during the third trimester or early postpartum period. It is defined as severe hepatic synthetic dysfunction due to microvascular steatosis. Although the reported incidence of AFLP was 1 in 7,000 to 1 in 15,000 pregnancies (1), it could progress rapidly to serious complications such as disseminated intravascular coagulation (DIC), postpartum hemorrhage, multiple organ dysfunction syndrome (MODS), acute hepatic failure (AHF), and maternal or fetal mortality. The pathogenesis of AFLP remains unclear, and most of the literature supports that it is secondary to mitochondrial defects in the fetal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase, as well as other enzymes potentially involved in fatty oxidation, leading to excessive accumulation of fatty acids in maternal hepatocytes, which, in turn, leads to lipotoxicity, oxidative damage, inflammation, and hepatocyte necrosis (2). Early recognition and diagnosis of AFLP

with prompt termination of pregnancy and intensive supportive care are essential for both maternal and fetal survival. With advances in multidisciplinary supportive management of patients with AFLP, maternal and fetal mortality rates have decreased significantly to 7–18% and 9–23%, respectively (3).

Early assessment of the prognosis of patients with AFLP may play an important role in improving maternal and fetal survival (4). Previous clinical studies on AFLP, largely based on a small number of patients owing to its low prevalence, have found significant differences in its epidemiology (1, 5), symptoms (6), complications (6), and outcomes (1, 7, 8). The model for end-stage liver disease (MELD) founded in 2000 by Malinchoc and Kamath of Mayo Clinic, the largest liver disease center in the United States, was a grading method for assessing the severity of end-stage liver disease. It was originally created to predict the survival of 231 patients with cirrhosis and portal hypertension after transjugular intrahepatic portosystemic shunt. The statistical model obtained by Cox proportional hazard regression identified four laboratory and clinical indicators that can be used to better assess the three-month survival of patients (9). Thereafter, Kamath *et al*. improved the scoring system to R = 3.8 ln (bilirubin) + 11.2 ln (INR) + 9.6 ln (creatinine) + 6.4 (10), which made the MELD one of the most widely used scoring systems for evaluating the prognosis of liver disease. Thus far, many studies have reported the ability of the MELD to predict the short-term prognosis of patients with acute liver failure and pregnancy-specific liver diseases (11, 12). However, large-sample studies have rarely investigated the efficacy of the MELD in predicting maternal and fetal outcome of AFLP, owing to the rarity of this condition. The existing literature predominantly consists of small hospital-based case series or historical cohorts identified retrospectively over a number of years. Therefore, there is an urgent need for clinical studies on AFLP, especially large-sample and multicenter prospective studies, to help clinicians make prognostic judgments.

Our study included 106 patients with AFLP who were admitted to our hospital during the past 10 years. We aimed to explore the independent risk factors for maternal and fetal mortality, and develop new models for predicting the poor prognosis of patients with AFLP.

Methods

Patients and clinical data

We retrospectively analyzed the data of 119 patients who were admitted to Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University and diagnosed with AFLP from September 2011 to November 2020. The diagnosis of all selected patients was reassessed using the Swansea criteria (wherein the diagnosis of AFLP requires the satisfaction of six or more criteria), as detailed in Table 1. Ten patients who also had a comorbid disease such as viral hepatitis, intrahepatic cholestasis during pregnancy; hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome; and drug-induced hepatitis, and three patients with incomplete prenatal data were excluded. A total of 106 patients with AFLP were finally enrolled in the study.

All patients were prenatally diagnosed with AFLP. Information regarding their laboratory findings, imaging data, and clinical symptoms was collected from the electronic medical records, and they were followed up within 1 month after discharge. The study was approved by the institutional review board of our hospital (approval no. SWYX: NO.2021-052). The ethics committee waived the need for obtaining informed consent from the patients, because the study was an observational, retrospective study using a database from which the patients' identification information had been removed. Data extracted from these medical records included demographic characteristics, clinical symptoms, laboratory findings, clinical course, and maternal and perinatal outcomes.

Demographic characteristics included age, gestational weeks, parity, mode of delivery, single or twin fetus, fetal sex, admission to ICU or not, and days from the first symptom to delivery. Clinical symptoms included abdominal pain, anorexia, nausea, vomiting, polyuria, jaundice, encephalopathy, and high blood pressure. Laboratory findings included prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen, white blood cell count, hemoglobin, percentage of neutrophils, neutrophils (N), platelet count (PLT), procalcitonin, blood urea nitrogen (BUN), blood creatinine (Cr), blood glucose, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), direct bilirubin (DBIL), and albumin (Alb). Primary prognostic outcomes included maternal and fetal mortality.

Swansea criteria for diagnosis of AFLP

The international diagnostic criteria for AFLP were based on the Swansea diagnostic standards, as shown in Table 1 (8, 13). Six or more criteria are required to diagnose AFLP. The exclusion criteria were as follows: viral hepatitis, intrahepatic cholestasis of pregnancy, HELLP syndrome, drug-induced hepatitis, autoimmune hepatitis, and other diseases.

Table 1
Swansea criteria for diagnosis of AFLP

Variable	Finding
Vomiting	Positive
Abdominal pain	Positive
Polydipsia or polyuria	Positive
Hepatic encephalopathy	Positive
Bilirubin	> 14 μmol/L
Hypoglycemia	< 4 mmol/L
Uric acid	> 340 μmol/L
Leukocytosis	> 11×10^9/L
Ascites or ultrasound shows bright liver	Positive
ALT	> 42 U/L
Serum ammonia	> 47 μmol/L
Serum creatinine	> 150 μmol/L
Coagulopathy	
PT	> 14 s
APTT	34 s
Liver biopsy	Diffuse micro vesicular steatosis in hepatocytes
ALT: alanine aminotransferase; PT: prothrombin time; APTT: activated partial thromboplastin time	

Statistical analysis

Continuous variables were expressed as mean and standard deviation, and categorical variables were expressed as count and percentages. Continuous variables were tested using Student's *t* test, *t* test with Welch correction, or Mann–Whitey *U* test, depending on normal distribution and homogeneity in variance. The counting data were tested using the chi-square test. Multiple logistic regression analysis was used to determine the independent risk factors for different outcomes and build prognostic prediction models. The new models and the MELD were used to assess all patients with AFLP. The receiver operating characteristic (ROC) curve was applied to compare the predictive efficiency, sensitivity, and specificity of the two models in evaluating the prognosis of patients with AFLP.

Results

Clinical characteristics of AFLP patients

A total of 106 patients with AFLP were enrolled in this study. Their demographic characteristics and clinical symptoms are shown in Table 2. Laboratory findings and prognostic outcomes are shown in Tables 3 and 4, respectively. The average maternal age was 29.8 ± 4.8 years, and the average gestational age was 35.8 ± 2.9 weeks. The median duration from the first symptom to delivery was 7.9 ± 7.9 days. In total, 43 (40.6%) patients were primigravida and 63 (59.4%) were multigravida; 98 (92.5%) patients delivered by cesarean section and 8 (7.5%) patients delivered vaginally. A total of 91 (76.5%) male and 28 (23.5%) female infants were born. Among all patients with AFLP, 96 (90.6%) were admitted to the intensive care unit (ICU) after delivery. The common clinical symptoms included abdominal pain (30.2%), anorexia (56.6%), nausea (46.2%), vomiting (48.1%), polydipsia and polyuria (9.4%), jaundice (23.6%), hepatic encephalopathy (7.5%), and hypertension (15.1%).

Table 2
Demographic characteristics and clinical symptoms of patients with AFLP (n = 106)

Variable	Mean ± SD/No. (%)
Demographic characteristics	
Maternal age (year)	29.8 ± 4.8
Gravidity	
1	31 (29.2)
2	29 (27.4)
≥ 3	46 (43.4)
Parity	
1	43 (40.6)
2	54 (50.9)
3	9 (8.5)
Delivery	
Cesarean section	98 (92.5)
Vaginal	8 (7.5)
Number of fetuses	
Single	93 (87.7)
Twins	13 (12.3)
Gender of baby	
Female	24 (22.6)
Male	69 (65.1)
Female/male	2 (1.9)
Female/female	1 (0.9)
Male/male	10 (9.4)
Admitted to ICU	96 (90.6)
Days from the first symptom to delivery	7.9 ± 7.9
Days of pregnancy when the first symptom occurred	250.5 ± 20.2
Symptoms	

Variable	Mean ± SD/No. (%)
Abdominal pain	32 (30.2)
Anorexia	60 (56.6)
Nausea	49 (46.2)
Vomiting	51 (48.1)
Polydipsia/polyuria	10 (9.4)
Jaundice	25 (23.6)
Hepatic encephalopathy	8 (7.5)
Hypertension	16 (15.1)

Coagulation tests yielded obviously abnormal results, including prolonged PT (22.5 ± 15.9 s), APTT (53.8 ± 27.4 s), and INR (2.1 ± 2.1), and decreased fibrinogen levels (1.6 ± 1.3 g/L). The results of blood routine tests showed increased leukocyte (15.1 ± 5.6 × 10^9/L) and neutrophil (11.5 ± 4.8 × 10^9/L) counts, decreased hemoglobin (111.2 ± 24.4 g/L), and normal PLT count (150.3 ± 7.4 × 10^9/L). PCT was significantly increased (4.6 ± 11.3 ng/mL). Liver function tests revealed increased levels of ALT (292.2 ± 281.6 U/L), AST (289.2 ± 270.8 U/L), GGT (97.2 ± 63.9 U/L), ALP (414.0 ± 220.4 U/L), TBIL (134.1 ± 102.8 μmol/L), and DBIL (82.5 ± 60.9 μmol/L). Renal function was impaired, as evident from increased BUN (8.0 ± 5.5 mmol/L) and Cr (169.9 ± 95.7 μmol/L) levels. Abdominal ultrasound was performed for 71 patients, out of which 42 (59.2%) patients showed positive results. However, 35 patients did not undergo prenatal abdominal ultrasound. The maternal mortality rate was 9.4% (10/106) and the fetal mortality rate was 15.1% (16/106). The common severe complications included acute kidney injury (AKI; 67.0%), DIC (28.3%), postpartum hemorrhage/wound seroma (27.4%), sepsis (26.4%), MODS (28.3%), and AHF (22.6%).

Table 3
Laboratory findings of patients with AFLP (n = 106)

Variable	Mean ± SD	Reference range
Prothrombin time (s)	22.5 ± 15.9	10.7–14
Activated partial thromboplastin time (s)	53.8 ± 27.4	28–45
International normalized ratio (INR)	2.1 ± 2.1	0.8–1.2
Fibrinogen (g/L)	1.6 ± 1.3	1.75–4.35
Leukocyte (× 10^9/L)	15.1 ± 5.6	3.5–9.5
Hemoglobin (g/L)	111.2 ± 24.4	130–175
Neutrophil% (%)	75.3 ± 8.5	40–75
Neutrophil (× 10^9/L)	11.5 ± 4.8	1.8–6.3
Platelets (× 10^9/L)	150.3 ± 7.4	125–350
Procalcitonin (ng/mL)	4.6 ± 11.3	0–0.05
Blood urea nitrogen (mmol/L)	8.0 ± 5.5	2.8–7.14
Creatinine (μmol/L)	169.9 ± 95.7	40–135
Glucose (mmol/L)	4.4 ± 2.0	3.9–6.3
Uric acid (μmol/L)	495.3 ± 157.5	208–428
Aspartate aminotransferase (U/L)	289.2 ± 270.8	15–40
Alanine aminotransferase (U/L)	292.2 ± 281.6	9–50
Glutamyl transpeptidase (U/L)	97.2 ± 63.9	10–60
Alkaline phosphatase (U/L)	414.0 ± 220.4	45–125
Total bilirubin (μmol/L)	134.1 ± 102.8	3.5–23.5
Direct bilirubin (μmol/L)	82.5 ± 60.9	0.5–6.5
Albumin (g/L)	28.2 ± 5.7	40–55

Table 4

Complications and outcomes of patients with AFLP (n = 106)

Variable	No. (%)
Maternal complications	
Acute kidney injury	71 (67.0)
Disseminated intravascular coagulation	30 (28.3)
Postpartum hemorrhage/wound seroma	29 (27.4)
Sepsis	28 (26.4)
Multiple organ dysfunction syndrome	30 (28.3)
Acute hepatic failure	24 (22.6)
Maternal outcome	
Death	10 (9.4)
Fetal outcome	
Death	16 (15.1)

Risk factors for maternal mortality, and the new predictive model

The distinction in demographic and clinical characteristics and laboratory findings between survivors and non-survivors is summarized in Table 5. Univariate analyses showed that maternal mortality was significantly related to nausea ($p = 0.042$), hepatic encephalopathy ($p = 0.027$), prolonged PT ($p < 0.0001$), prolonged APTT ($p = 0.0009$), increased INR ($p < 0.0001$), decreased fibrinogen ($p = 0.004$), increased leukocytes ($p = 0.018$), increased neutrophils ($p = 0.012$), thrombocytopenia ($p = 0.0003$), increased Cr ($p = 0.002$), increased TBIL ($p = 0.006$), increased DBIL ($p = 0.024$) and decreased Alb ($p = 0.017$).

Table 5
Comparison of demographic, clinical, and laboratory characteristics between maternal survivors and non-survivors

Variable	No. (%)		
	Alive (n = 96)	Dead (n = 10)	P-value
Demographic characteristics			
Maternal age (year)	29.7 ± 4.8	31.5 ± 4.7	0.245
Gravidity			0.307
1	29 (30.2)	2 (20.0)	
2	27(28.1%)	2 (20.0)	
≥ 3	40 (41.7)	6 (60.0)	
Parity			0.239
1	40 (41.7)	3 (30.0)	
2	49 (51.0)	5 (50.0)	
3	7 (7.3)	2 (20.0)	
Delivery			0.560
Cesarean section	89 (92.7)	9 (90.0)	
Vaginal	7 (7.3)	1 (10.0)	
Number of fetuses			0.608
Single	83 (86.5)	10 (100.0)	
Twins	13 (13.5)	0	
Gender of baby			0.531
Female	20 (20.8)	4 (40.0)	
Male	63 (65.6)	6 (60.0)	
Female/male	2 (2.1)	0	
Female/female	1 (1.0)	0	
Male/male	10 (10.4)	0	
Delivery in other hospital			0.219
Yes	19 (19.8)	4 (40.0)	
No	77 (80.2)	6 (60.0)	

Variable	No. (%)		
	Alive (n = 96)	Dead (n = 10)	P-value
Admitted to ICU	86 (89.6)	10 (100.0)	0.593
Symptoms			
Abdominal pain	29 (30.2)	3 (30.0)	> 0.9999
Anorexia	54 (56.3)	6 (60.0)	> 0.9999
Nausea	41 (42.7)	8 (80.0)	0.042*
Vomiting	44 (45.8)	7 (70.0)	0.191
Polydipsia/polyuria	9 (9.4)	1 (10.0)	> 0.9999
Jaundice	24 (25.0)	1 (10.0)	0.446
Encephalopathy	5 (5.2)	3 (30.0)	0.027*
Hypertension	14 (14.6)	2 (20.0)	0.645
Days from the first symptom to delivery	7.7 ± 7.9	9.1 ± 8.3	0.375
Days of pregnancy when the first symptom occurred	250.8 ± 20.9	247.4 ± 8.8	0.273
Laboratory findings			
PT (s)	20.7 ± 14.8	39.4 ± 16.8	< 0.0001****
APTT (s)	50.8 ± 23.5	82.8 ± 43.3	0.0009***
INR	1.9 ± 2.0	4.1 ± 2.1	< 0.0001****
Fibrinogen (g/L)	1.6 ± 1.3	0.8 ± 0.5	0.004**
Leukocyte (× 10^9/L)	14.6 ± 5.1	19.6 ± 7.6	0.018*
Hemoglobin (g/L)	111.1 ± 24.7	111.7 ± 22.0	0.776
N%	75.1 ± 8.7	77.0 ± 5.5	0.500
N (× 10^9/L)	11.2 ± 4.5	15.3 ± 5.9	0.012*
Platelets (× 10^9/L)	157.7 ± 72.6	79.2 ± 32.0	0.0003***
PCT (ng/mL)	4.8 ± 12.0	3.6 ± 3.5	0.985
BUN (mmol/L)	7.7 ± 5.3	10.8 ± 6.1	0.077
Cr (mg/dL)	156.6 ± 76.1	297.1 ± 160.6	0.002**
GLU (mmol/L)	4.3 ± 1.4	5.2 ± 5.0	0.182

Variable	No. (%)		
	Alive (n = 96)	Dead (n = 10)	P-value
Uric acid (μmol/L)	490.6 ± 151.6	540 ± 210.8	0.611
AST (U/L)	295.5 ± 275.2	229.2 ± 227.5	0.308
ALT (U/L)	301.5 ± 287.9	203.2 ± 201.3	0.237
GGT (U/L)	97.51 ± 62.7	93.8 ± 78.1	0.545
ALP (U/L)	416.6 ± 223.2	388.5 ± 199.6	0.979
TBIL (μmol/L)	124.7 ± 92.7	224.1 ± 150.5	0.006**
DBIL (μmol/L)	78.1 ± 58.3	124.5 ± 72.3	0.024*
Alb (g/L)	28.6 ± 5.7	24.2 ± 5.1	0.017*

The above significant variables and BUN (p = 0.077) were included in the logistic regression analysis performed using the forward selection approach, in order to avoid missing important risk factors. The results of logistic regression analysis showed that nausea (p = 0.037), prolonged PT (p = 0.003), and increased Cr (p = 0.003) were independent risk factors for maternal mortality, as shown in Table 6. Based on these three variables, a new predictive model for maternal mortality was established using the following formula: 2.911 × Nausea + 0.07 × Prothrombin time + 0.011 × Creatinine − 8.86.

Table 6
Analysis of independent risk factors for maternal death

Variable	B	S.E.	OR	95%CI	P-value
Nausea	2.911	1.398	18.376	1.186–284.707	0.037*
Prothrombin time	0.07	0.024	1.073	1.024–1.124	0.003**
Creatinine	0.011	0.004	1.012	1.004–1.019	0.003**
Constant	−8.86	2.218			

The ROC curve was used to evaluate the predictive efficiency of the new model and the MELD with regard to the prognosis of maternal death (Fig. 1, Table 7). The threshold of the MELD was 29.835 and the area under the curve(AUC) was 0.948, with a sensitivity of 100% and a specificity of 83.3%. The threshold of the new model was 0.186 and the AUC was 0.926, with a sensitivity of 90% and a specificity of 94.8%. Both the new model and the MELD showed good predictive efficacy for maternal mortality in patients with acute fatty liver of pregnancy and the new model was superior to the MELD in terms of specificity.

Table 7
Comparison of the two models for predicting maternal mortality

Model	Threshold	Sensitivity (%)	Specificity (%)	AUC	95%CI
MELD	29.835	100	83.3	0.948	0.904–0.992
New model	0.186	90	94.8	0.926	0.825–1

Risk factors for fetal mortality, and the new predictive model

As shown in Table 8, univariate analysis showed that fetal mortality was significantly related to encephalopathy ($p = 0.017$), prolonged PT ($p = 0.0005$), prolonged APTT ($p < 0.0001$), increased INR ($p = 0.0008$), decreased fibrinogen ($p = 0.016$), elevated leukocyte ($p = 0.043$), thrombocytopenia ($p < 0.0001$), decreased GGT ($p = 0.019$), increased TBIL ($p = 0.007$), increased DBIL ($p = 0.018$), and decreased Alb ($p = 0.006$).

Table 8
Comparison of demographic, clinical, and laboratory characteristics between fetal survivors and non-survivors

Variable	No. (%)		
	Alive (n = 90)	Dead (n = 16)	P-value
Demographic characteristics			
Maternal age (year)	29.6 ± 4.7	31.1 ± 5.6	0.275
Gravidity			0.258
1	28 (31.1)	3 (18.7)	
2	22 (24.4)	7 (43.8)	
≥ 3	40 (44.5)	6 (37.5)	
Parity			0.299
1	39 (43.3)	4 (25.0)	
2	43 (47.8)	11 (68.8)	
3	8 (8.9)	1 (6.2)	
Delivery			0.099
Cesarean section	85 (94.4)	13 (81.3)	
Vaginal	5 (5.6)	3 (18.7)	
Number of fetuses			0.411
Single	80 (88.9)	13 (81.3)	
Twins	10 (11.1)	3 (18.7)	
Gender of baby			0.531
Female	22 (24.4)	11 (68.8)	
Male	58 (64.4)	2 (12.5)	
Female/male	2 (2.2)	0	
Female/female	7 (7.8)	3 (18.7)	
Male/male	1 (1.1)	0	
Admitted to ICU	81 (90.0)	15 (93.8)	> 0.999
Symptoms			
Abdominal pain	28 (31.1)	4 (25.0)	0.772

Variable	No. (%)		
	Alive (n = 90)	Dead (n = 16)	P-value
Anorexia	50 (55.6)	10 (62.5)	0.785
Nausea	41 (45.6)	8 (50.0)	0.790
Vomiting	43 (47.8)	8 (50.0)	> 0.999
Polydipsia/polyuria	10 (11.1)	0	0.353
Jaundice	21 (23.3)	4 (25.0)	> 0.999
Encephalopathy	4 (4.4)	4 (25.0)	0.017*
Hypertension	14 (15.2)	2 (12.5)	> 0.999
Days from the first symptom to delivery	7.4 ± 7.2	10.8 ± 10.7	0.394
Days of pregnancy when the first symptom occurred	251.0 ± 19.5	242.6 ± 19.2	0.051
Laboratory findings			
PT (s)	20.8 ± 13.0	31.9 ± 25.3	0.0005***
APTT (s)	48.9 ± 19.7	81.4 ± 44.6	< 0.0001****
INR	1.9 ± 1.5	3.3 ± 4.1	0.0008***
Fibrinogen (g/L)	1.7 ± 1.3	1.1 ± 1.0	0.016*
Leukocyte (× 10^9/L)	14.8 ± 5.7	17.0 ± 4.2	0.043*
Hemoglobin (g/L)	112.6 ± 24.1	102.9 ± 25.0	0.141
N%	75.0 ± 8.6	76.9 ± 7.5	0.419
N (× 10^9/L)	11.3 ± 4.9	13.0 ± 3.9	0.087
Platelets (× 10^9/L)	164.2 ± 70.3	72.2 ± 28.1	< 0.0001****
PCT (ng/mL)	3.2 ± 2.9	10.8 ± 24.9	0.074
BUN (mmol/L)	7.7 ± 4.5	10.0 ± 9.1	0.422
Cr (mg/dL)	163.3 ± 83.9	206.4 ± 143.7	0.259
GLU (mmol/L)	4.4 ± 2.0	4.3 ± 1.8	0.778
Uric acid (μmol/L)	496.4 ± 141.6	488.7 ± 233.5	0.463
AST (U/L)	254.9 ± 183.2	309.5 ± 232.1	0.468
ALT (U/L)	299.1 ± 289.8	253.7 ± 234.5	0.485

Variable	No. (%)		
	Alive (n = 90)	Dead (n = 16)	P-value
GGT (U/L)	101.4 ± 63.0	73.1 ± 65.6	0.019*
ALP (U/L)	428.3 ± 226.6	333.1 ± 164.8	0.131
TBIL (μmol/L)	122.2 ± 91.5	201.3 ± 136.4	0.007**
DBIL (μmol/L)	76.1 ± 56.2	118.1 ± 75.0	0.018*
Alb (g/L)	28.9 ± 5.5	24.6 ± 5.5	0.006**

Multivariate logistic regression analysis showed that encephalopathy (p = 0.016) and thrombocytopenia (p = 0.001) were independent risk factors for fetal mortality (Table 9). Thereafter, a new predictive model for fetal mortality was established using the following formula: 2.411 × encephalopathy − 0.44 × platelets + 2.506

Table 9
Analysis of independent risk factors for fetal mortality

Variable	B	S.E.	OR	95%CI	P-value
Encephalopathy	2.411	0.999	11.141	1.574–78.87	0.016*
Platelets	−0.44	0.013	0.957	0.933–0.981	0.001**
Constant	2.506	1.087			
SE: standard error; CI: confidence interval					

In predicting fetal mortality, the threshold of the MELD was 25.124 and the AUC was 0.694, with a sensitivity of 68.8% and a specificity of 64.4%. The threshold of the new model was − 45.234 and the AUC was 0.893, with a sensitivity of 100% and a specificity of 73.3%. Thus, compared with the MELD, the new model could more accurately predict fetal death, with a higher sensitivity and specificity (Fig. 2, Table 10).

Table 10
Comparison of the two models for predicting fetal mortality

Model	Threshold	Sensitivity (%)	Specificity (%)	AUC	95%CI
MELD	25.124	68.8	64.4	0.694	0.543–0.846
New model	−45.234	100	73.3	0.893	0.832–0.955
MELD: model for end-stage liver disease; AUC: area under the curve; CI: confidence interval					

Discussion

AFLP is a rare and fatal obstetric emergency that occurs in the second and third trimester of pregnancy or in the early postpartum period. It can lead to acute liver failure, AKI, multiple organ failure, and even maternal and fetal mortality. Many studies have analyzed the high-risk factors for the morbidity associated with AFLP, fatal complications, and perinatal death. Recent studies have shown that being a primigravida, multiple pregnancies, carrying a male fetus, other liver diseases during pregnancy, previous history of AFLP, and preeclampsia are the potential risk factors for AFLP(1, 14–16). The recognition of high-risk factors is helpful for the prevention and treatment of AFLP, and can consequently improve the prognosis of the mother and the child. Early diagnosis; prompt delivery; and multidisciplinary supportive care from the departments of obstetrics, blood transfusion, and the ICU have resulted in improved maternal mortality (3). Although liver biopsy is the gold standard for the diagnosis of AFLP, it is rarely performed owing to its invasive nature and owing to the fact that it can cause complications in the presence of coagulopathy. In addition, liver biopsy is just a diagnostic method and does not contribute significantly to the treatment of AFLP. Therefore, none of the patients with AFLP in this study underwent liver biopsy.

The 106 patients with AFLP who were enrolled in this study delivered 119 fetuses, including 13 twin pregnancies and 93 single pregnancies. The incidence of twin pregnancy was 12.3% (13/106), which occurred only in the surviving group; however, there was no statistically significant difference in the incidence of twin pregnancy between the survivor and non-survivor groups (13.5% vs. 0, p = 0.608). This finding is similar to the results of another retrospective study conducted in China by Cheng *et al*. (17) that showed that the incidence of twin pregnancy among patients with AFLP was 28.1%; however, there was a statistically significant difference between the survivor and non-survivor groups (44.4% vs. 7.1%, p = 0.02). This indicated that twin pregnancy may be a potential protective factor for patients with AFLP; however, this is contrary to the results of the prospective study conducted by Knight *et al*. (1). Although our study enrolled the largest number of patients among the three studies (n = 106), it was still not a sufficiently large sample. Because of the rarity of AFLP, our study does not have the power to determine whether this is a statistically significant relationship or just a chance finding. A previous study by Gao *et al*. showed that male fetus, intrauterine death, postpartum diagnosis of AFLP, DIC, and prolonged PT and APTT were potential risk factors for maternal mortality in AFLP, whereas a history of legal termination of pregnancy, and increased TBIL and serum Cr were independent risk factors (18). In this study, male fetuses (p = 0.580) and a history of legal termination of pregnancy (p = 0.239) showed no statistically significant difference between the two groups and were not included in the potential risk factors for maternal mortality in AFLP.

Previous studies have rarely included a prediction model for fetal mortality. In this study, a new model for predicting fetal mortality was established and the predictive value of the MELD for fetal mortality was also verified. The results of multivariate logistic regression analysis indicated that hepatic encephalopathy (p = 0.016) and thrombocytopenia (p = 0.001) were independent risk factors for fetal mortality in patients with AFLP. Hepatic encephalopathy is a comprehensive disorder of central nervous

system dysfunction caused by severe liver disease. As the most direct complication of liver damage in patients with acute liver failure, it is one of the causes of death in patients with liver disease. Its occurrence suggests that patients with AFLP have had acute liver failure before delivery and the fetus has a high incidence of intrauterine distress and stillbirth. In patients with preeclampsia and HELLP syndrome, thrombocytopenia is an independent risk factor for postpartum complications such as infection, thromboembolism, and DIC, and these complications are also common in patients with AFLP (19). The retrospective study by Cheng *et al*. showed that carrying a male fetus and vaginal delivery were risk factors for fetal mortality; however, these two variables did not show significant positive predictive value in our study (17). Gao *et al*. found that fetal distress and prolonged APTT were risk factors for fetal mortality (18). The univariate analysis in our study showed that prolonged APTT was a risk factor for fetal mortality ($p < 0.0001$), but multivariate analysis showed no positive predictive value. The new model based on hepatic encephalopathy and thrombocytopenia was compared with the MELD with regard to the prediction of fetal mortality. The threshold of the MELD was 25.124 and the AUC was 0.694, with a sensitivity of 68.8% and a specificity of 64.4%. The threshold of the new model was 45.234 and the AUC was 0.893, with a sensitivity of 100% and a specificity of 73.3%. Thus, compared with the MELD, the new model could more accurately predict fetal mortality, with a higher sensitivity and specificity.

In this study, the common clinical symptoms of patients with AFLP were anorexia (56.6%), vomiting (48.1%), nausea (46.2%), abdominal pain (30.2%), jaundice (23.6%), hypertension (15.1%), polydipsia and polyuria (9.4%), and cerebral encephalopathy (7.5%), which was similar to the results of a national prospective study on AFLP conducted in the UK. This study, conducted between February 2005 and August 2006, reported that 60% of the patients with AFLP experienced vomiting, 56% experienced abdominal pain, 12% experienced polydipsia, and 9% had encephalopathy (1). In the present study, the common severe complications besides death were AKI (67.0%), DIC(30%), MODS(30%), postpartum hemorrhage(29%), sepsis(28%) and AHF(22.6%), which is consistent with the results of the study by Chen *et al*. (20). In their study, the most common maternal complication was acute renal dysfunction (79.5%), followed by DIC (47.7%) and MODS (38.6%).

Maternal and fetal mortality rates attributable to AFLP vary greatly among studies, with the maternal mortality rate ranging from 12–18% and the fetal mortality rate ranging from 7–58% (21). Our previous clinical study showed that the maternal and fetal mortality rates of 52 patients with AFLP admitted to our hospital from January 2001 to December 2011 were 8% and 23%, respectively (22). In this study, a total of 106 patients with AFLP were admitted to our hospital from September 2011 to November 2020, and 119 fetuses were delivered. The maternal and fetal mortality rates were 9.4% (10/106) and 15.1% (18/119) respectively, both of which were lower than those reported in other studies. Compared with the last decade, the maternal mortality rate has declined slightly and the fetal mortality rate has decreased significantly in our hospital. This may be related to the loosening of the two-child policy, leading to an increasing number of older mothers and, consequently, more complications during pregnancy, causing a slight increase in maternal mortality. However, with the development of multidisciplinary supportive management in our hospital, especially pediatric intensive care, the level of comprehensive treatment of the fetus has been greatly improved, leading to a significant decline in the fetal mortality rate.

In this study, prenatal nausea ($p = 0.037$), prolonged PT ($p = 0.003$), and elevated serum Cr ($p = 0.003$) were independent risk factors for maternal mortality in patients with AFLP. Another study reported that ascites, thrombocytopenia, and serum Cr were independent risk factors for postpartum complications in pre-eclampsia and HELLP syndrome (23). The clinical symptoms of AFLP are similar to those of HELLP syndrome, and both are pregnancy-specific liver diseases. The predictive model for AFLP also included one clinical symptom and two laboratory findings, and elevated serum Cr was an independent risk factor for both AFLP and HELLP syndrome. However, the difference between the PLT count in AFLP was statistically significant in univariate analysis ($p = 0.0003$) and was eliminated in multivariate logistic regression analysis. This suggests that thrombocytopenia is a potential risk factor for maternal mortality in AFLP, which needs to be verified by a larger-sample study. Transaminase levels have not been shown to be important across most disease models in liver disease, including our model for AFLP ($p > 0.05$). A single-center retrospective study with 130 cases (AFLP = 32; HELLP = 81; pre-eclampsia and liver disease = 17) showed that both the MELD and the new model with two objective variables, namely serum TBIL and INR, were reliable for predicting the short-term mortality in patients with pregnancy-specific liver disease (followed up until 3 months after delivery or until death) (12). In the present study, TBIL and INR were statistically significant in univariate analysis ($p = 0.006$ and $p < 0.0001$, respectively), but they were eliminated in multivariate logistic regression analysis, which also suggested that increased TBIL and prolonged INR are potential risk factors for maternal mortality in AFLP; further prospective studies with larger sample sizes are warranted to explore the risk factors for maternal mortality in patients with AFLP.

Previous clinical studies have shown that the MELD based on TBIL, Cr, and INR shows good predictive efficacy for acute liver failure and pregnancy-specific liver disease (11, 12). A study conducted in China showed that the MELD was a good predictor of all complications of AFLP, including ascites, hepatic encephalopathy, sepsis, and renal insufficiency (all AUCs > 0.8), and the optimal cut-off values were close to 30 (24). Our study also verified that both the MELD and the new model show good predictive efficacy in predicting maternal mortality in AFLP (AUC = 0.948 and 0.926, respectively).

Overall, compared with previous models based on only laboratory findings, the new predictive model for maternal mortality included one clinical symptom and two laboratory findings, which was more readily available, less expensive and easier to implement clinically. To the best of our knowledge, the symptom of nausea that we identified as an independent risk factor for AFLP has not been previously described.

This study had a long duration of almost 10 years, and is the largest single-center clinical study on AFLP so far. The number of patients with AFLP enrolled in this study is only second to that in the multicenter study by Gao *et al*., in which our hospital has participated in the past (18). As all patients with AFLP came from one single center, they received similar obstetric and multidisciplinary treatments after hospitalization, and some limitations of different medical levels were counter-balanced.

There are some limitations to our research. Firstly, we did not evaluate the morbidity of AFLP owing to the deficiency of data on total pregnant women during the study period. Secondly, this was a single-center and small-sample study because of the rarity of AFLP, which might reduce the general applicability of our

findings, although we had extended the study period to one decade and our study was a retrospective study. Thirdly, as Shandong Provincial Hospital is a tertiary referral center for critical patients in China, some patients with AFLP were referred to our hospital after severe postpartum complications, and their condition was relatively critical. The manner and timing of medical intervention during their prenatal treatment differed, which directly affected the prognosis of the patients.

Conclusions

We identified a group of risk factors for maternal and fetal mortality among patients with AFLP and developed two new prognostic models. Both the new predictive model for maternal mortality and the MELD showed good predictive efficacy for maternal mortality in patients with acute fatty liver of pregnancy (the area under the curve = 0.948 and 0.926, respectively), while the new predictive model for fetal mortality was superior to the model for end-stage liver disease in predicting fetal mortality (the area under the curve = 0.893 and 0.694, respectively) with better sensitivity and specificity.

Abbreviations

AFLP: acute fatty liver of pregnancy; MELD: model for end-stage liver disease; ALT: alanine aminotransferase; PT: prothrombin time; APTT: activated partial thromboplastin time; ROC: receiver operating characteristic; ICU: intensive care unit; INR: International normalized ratio; N: neutrophils; PLT: platelet count; BUN: blood urea nitrogen; Cr: blood creatinine; GLU: Glucose; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; ALK: Alkaline phosphatase; TBIL: total bilirubin; DBIL: direct bilirubin; Alb: albumin; DIC: disseminated intravascular coagulation.

Declarations

Ethics approval and consent to participate

The study has been performed in accordance with the Declaration of Helsinki and has been approved by Biomedical Research Committee of Shandong Provincial Hospital (approval no. SWYX: NO.2021-052), which waived the need for obtaining informed consent from the patients, because the study was an observational, retrospective study using a database from which the patients' identification information had been removed.

Consent for publication

Not applicable.

Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CW, MC and ZM contributed to conception and design of the study. CW and WF organized the database. MC performed the statistical analysis. ZM wrote the first draft of the manuscript. MM, JZ, QW and GQ revised sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Figures

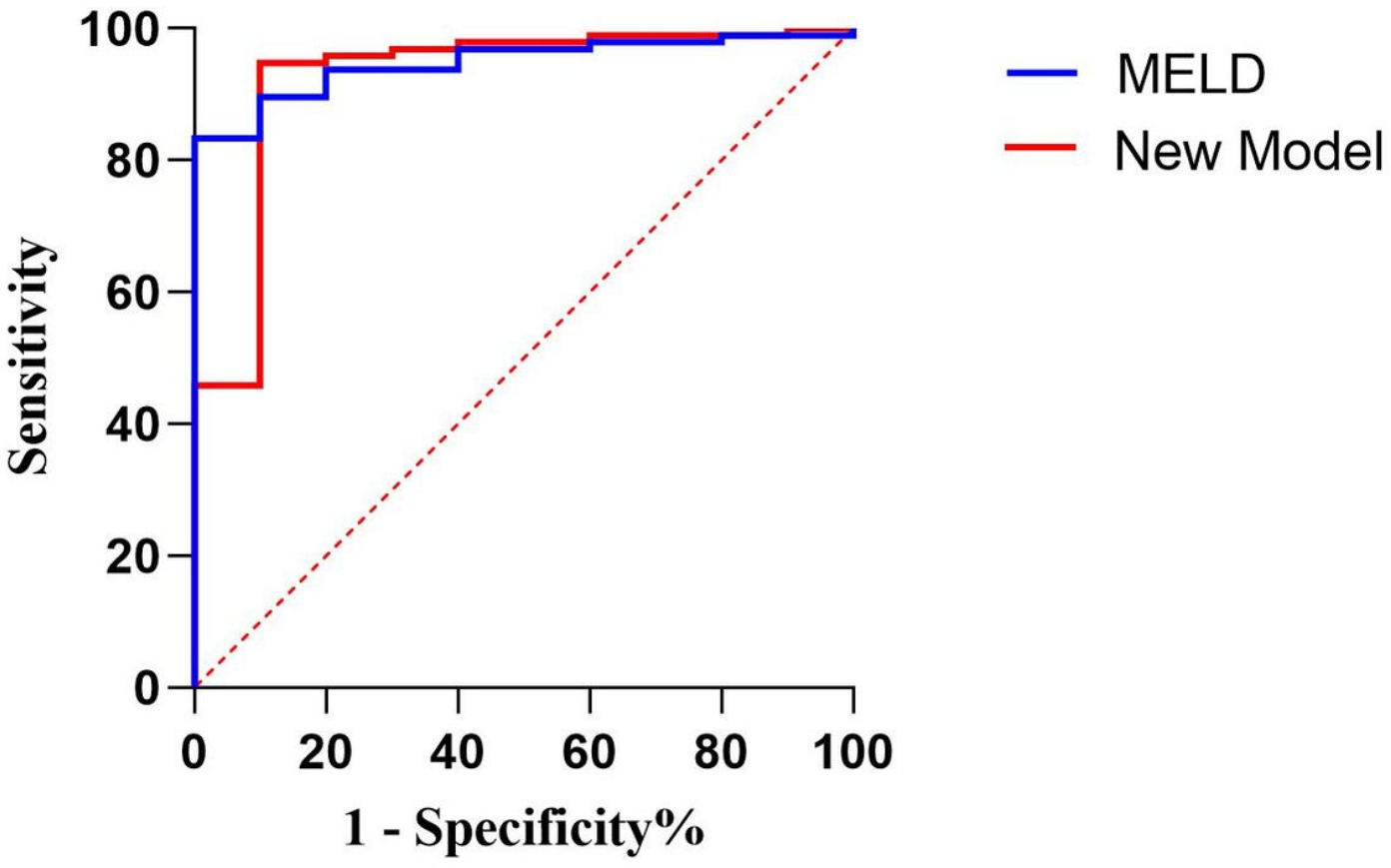

Figure 1

Receiver operating characteristic curve of the model for end-stage liver disease scoring system and the new model in predicting maternal death

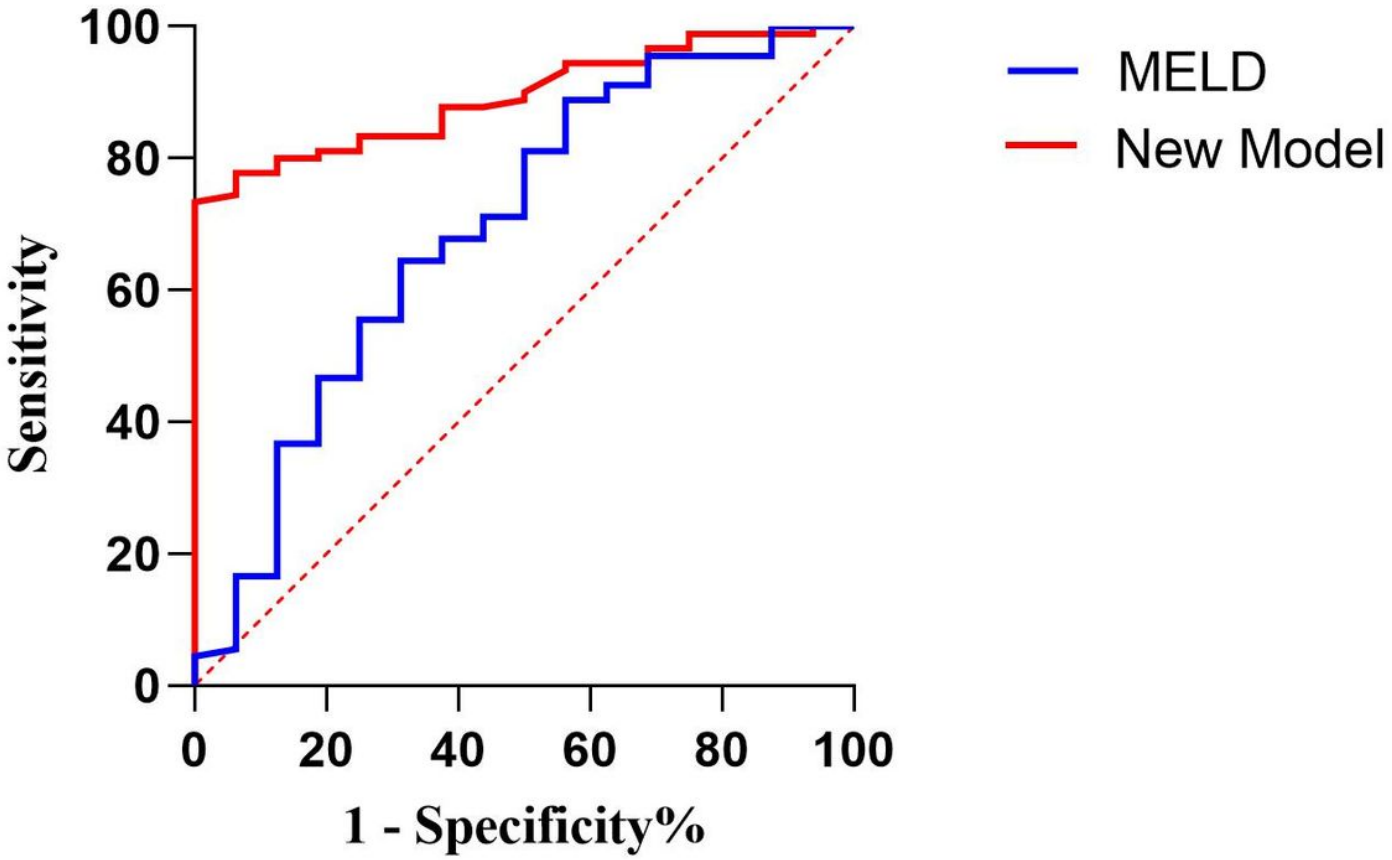

Figure 2

Receiver operating characteristic curve of the model for end-stage liver disease scoring system and the new model in predicting fetal death.