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Original Article

Massive obstetric hemorrhage in maternal near miss in ICU: a retrospective analysis from a maternity center in Shanghai, China

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Abstract: *Objective:* Massive obstetric hemorrhage (MOH) is one of the major causes of maternal morbidity and mortality. The purpose of our study was to investigate the risk factors of MOH and further explore the effect of MOH on prognosis. *Study design:* Retrospective study of maternal near miss (MNM) with MOH was managed in a maternity center during a 10-year study period. Risk factors including maternal age, gestational age, weekend delivery, polyembryony, and comorbidities were analyzed. Maternal outcomes including disseminated intravascular coagulopathy (DIC), acute renal failure, abdominal hematoma, need for transfusion of blood products, shock, MODS, stroke, cardiac arrest, maternal mortality, neonatal mortality, hysterectomy, and abortion were also analyzed. Other clinical outcomes included ICU stay and hospital stay. *Results:* A total of 283 women with MNM were included in this study. MOH was present in 15.5%, shock was present in 7.07%, and DIC was present in 2.47%. The rate of transfusion of blood products was 30.03%. The rate of MOH declined significantly when gestational age increased (OR = 0.940, 95% CI = 0.908 - 0.974), and was higher in parous women than in nulliparous women (OR = 3.789, 95% CI = 1.769 - 8.116). Our results showed there was a remarkable connection between gestational age and childbearing history (P = 0.001). The rate of adverse maternal outcomes was higher in women with MOH than those without this history (P < .05). DIC was significantly correlated with MOH (P < .0001) and abdominal hematoma (P < .0001). AUROC of SOFA was significantly higher than that of other scores (P = 0.002) on reoperation. The AUROC of DIC was significantly higher than that of other scores (P = 0.001) on abdominal hematoma. *Conclusion:* Among women with MNM, gestational age and childbearing history were risk factors for MOH. SOFA scores had relatively good predictive abilities on reoperation, and the DIC scores had relatively good predictive abilities on abdominal hematoma.

Keywords: Massive obstetric hemorrhage, maternal near miss, adverse maternal outcome, risk factor

Introduction

Obstetric hemorrhage occurs in 5% of all deliveries and is usually defined as greater than 500 mL or greater than 1000 mL of estimated blood loss following a vaginal delivery and cesarean section, respectively [1]. Despite a global improvement in maternal mortality ratios, antepartum/intrapartum hemorrhage remains an important cause of maternal near miss (MNM). Obstetric hemorrhage is a leading cause of maternal death and morbidity worldwide. In Africa and Asia, obstetric hemorrhage accounts for more than 30% of all maternal deaths [1]. In China, obstetric hemorrhage accounts for 2-16% of all maternal deaths [23]. By comparison, obstetric hemorrhage is responsible for lower rates of maternal death in the developed world with 3.4% in United Kingdom between 2006 and 2008 [2] and 11.4% in the United States between 2006 and 2010 [3]. In the United Kingdom, the MOH rate is 6:10,000 deliveries, and the associated mortality rate is 1:1200 cases of MOH. The overall mortality rate due to obstetric hemorrhage is 0.39 per 100,000 maternities, and MOH is currently the third most frequent direct cause of maternal mortality [11].

Despite the relatively low rates of death from hemorrhage in well-resourced countries, concern has been raised about the rising incidence of obstetric hemorrhage, driven by increases in postpartum hemorrhage (PPH) due to uterine

Table 1. Clinical findings among 283 women with MNM

	Value
Age (y, mean ± SD)	29.2±5.73
Weight at delivery (kg, mean ± SD)	27.65±4.50
Shanghai (%)	25.8
Nulliparous (%)	42.8
Gestational age at diagnosis (wk, mean ± SD)	32.0±8.18
Polyembryony (%)	4.59
MBP (mmHg, mean ± SD)	103.0±24.64
Diabetes (%)	4.95
Sepsis (%)	4.59
Atrial fibrillation (%)	1.41
Chronic hypertension (%)	15.19
HELLP syndrome (%)	10.24
APACHE II score (mean ± SD)	9.29±3.95
SOFA score (mean ± SD)	1.25±2.05
DIC score (mean ± SD)	1.18±1.43
GCS score (mean ± SD)	14.8±1.40

MBP, Mean arterial blood pressure.

atony [4-9]. The incidence of massive obstetric hemorrhage due to other reasons needing management in ICU is also very high. Therefore, Intensive Care doctors are likely to be increasingly called upon to help manage the resuscitation of patients with massive obstetric hemorrhage, which includes overseeing transfusion decision-making and the treatment of hemorrhage-related coagulopathy. We therefore conducted this study to find whether certain clinical or laboratory parameters among women with MOH were connected with adverse maternal outcomes, such as maternal mortality rate or neonatal mortality. We would also like to contribute to the definition, management, and therapies for such a complex hemorrhage.

Patients and methods

The present retrospective study includes data from a referral center for high-risk pregnancies with around 13,000 births annually. The study was approved by the local ethics committee. Written informed consent was obtained from all patients or their legal guardians. Data of pregnant women with MOH in ICU throughout a 10 year-period (from 2007 to 2016) was extracted. Ethics approval was obtained from Shanghai General Hospital Instutional Review Board (reference number [2017] KY186).

Inclusion and exclusion criteria

Our hospital's electronic patient information management system was used to sort out the diagnoses reached as the diagnosis standards for MNM. Out of the files associated with these diagnoses, we considered inclusion criteria were 1) maternal near miss in ICU and 2) women with complete pre- and post-natal data. Exclusion criteria included women with no complete pre- and post-natal data.

Maternal near miss (MNM) is defined by the World Health Organization (WHO) as an event in which a woman almost died, but survived from the complication during pregnancy, childbirth or within 42 days of termination of pregnancy. The woman had to present at least one criterion of severity with regard to organ dysfunction or failure. For this purpose, standardized criteria were defined (clinical signs, laboratory-based or management-based) to identify near-miss cases. These criteria were previously validated in a Brazilian obstetric population [16]. The WHO also recommends that this approach should be used to evaluate the quality of obstetric care [17].

The study cohort was classified into two groups (MOH and no-MOH) according to the following massive obstetric hemorrhage defined as loss of over 2500 ml of blood, and is associated with significant morbidity, admission to intensive care, and obstetric hysterectomy. Other definitions include: a drop in hemoglobin concentration of ≥ 4 g/dl; the need for transfusion of ≥ 5 red cell concentrate units (RC); or the need to treat coagulopathy or perform invasive management procedures [12-14].

For every patient categoric data was collected including age, census register (Shanghai or not Shanghai), gestational age, gravidity, parity, gestational age at diagnosis, chronic hypertension, diabetes, hyperlipemia, prenatal checkup, APACHE II, SOFA, DIC, GCS scores, mean arterial blood pressure, and adverse maternal outcomes etc. Adverse maternal outcomes included disseminated intravascular coagulopathy (DIC), abdominal hematoma, shock, cardiac arrest, stroke, MODS, the need for transfusion, reoperation, maternal mortality, neonatal

Table 2. Risk factors for MOH among women with MNM

	MOH (n = 51)	No MOH (n = 232)	Univariate analysis		Multivariable analysis	
			OR	*p*	OR (95% CI)	*P*
Age (y, mean ± SD)	30.57±5.8	28.9±5.67	NA	.066		
Age > 30 y (%)	29 (56.9)	103 (44.4)	1.65	.144		
BMI > 25 (%)	20 (39.2)	95 (40.9)	0.93	.94		
Gestational age at diagnosis (wk, mean ± SD)	28.9±11.36	32.66±7.15	NA	.003	0.940 (0.908-0.974)	0.001
Shanghai (%)	17 (33.3)	56 (24.1)	1.57	.23		
Nulliparous (%)	12 (23.5)	109 (46.9)	0.35	< .01	3.789 (1.769-8.116)	0.001
Polyembryony (%)	2 (3.92)	11 (4.74)	0.82	1		
Chronic hypertension (%)	1 (1.96)	42 (18.1)	0.09	< .01		
Diabetes (%)	3 (5.88)	11 (4.74)	1.25	.72		
HELLP syndrome (%)	1 (1.96)	28 (12.1)	0.14	.03		
Vaginal delivery (%)	4 (7.8)	4 (1.7)	4.81	.03		
Abortion (%)	5 (9.8)	4 (1.7)	6.13	.01		
Weekend delivery	17 (33.3)	56 (24.1)	1.57	.23		

NA, Not applicable. *P* < 0.05 was considered significant. BMI, Body Mass Index.

mortality, hysterectomy, and abortion. Other clinical outcomes studied included ICU LOS and hospital LOS.

Patients with MOH routinely received uterotonic agents (oxytocin, methylergonovine, and prostaglandins) and hemostatics. Failure to achieve control of bleeding with the above measures prompts aggressive procedures such as abdominal hysterectomy. Special treatments included mechanical ventilation, hemopurification, continuous use of vasoactive drugs (DA/NE/E), and so on.

Statistical analysis

Although all participating women who met the inclusion and exclusion criteria were included during the study period, we could not recruit the population number that was calculated for statistical power. Therefore, our study population consisted of the MOH group and the no-MOH group in 1:4 ratio. Continuous variables are represented with mean and standard deviation. Multi-factor Regression Analysis was used to evaluate the clinical scores and laboratory parameters of women with MNM. For discrete variables, the Chi-square and Fisher's exact tests were used to evaluate the differences between groups. Logistic regression analysis was used to evaluate the outcomes according to risk factors selected by multiple logistic regression analysis. For multivariate analysis, multiple Poisson regression including all the predictive variables in the model was used. The receiver operating characteristic (ROC) curves for area under the curve (AUC) were performed. All statistical analyses were performed using the statistical package SPSS (version 20.0; SPSS Inc.). *P* values < .05 were considered statistically significant.

Results

Patient characteristics

A total of 283 patients reached the diagnose standards for MNM. Clinical characteristics and demographic data are showed in **Table 1**. The total incidence of adverse maternal outcome was 38%. Three patients admitted at > 32 weeks' gestation died (1%). Death was related to DIC in one case, lymphoma-associated hemophagocytic syndrome in one case and myocardial infarction in the other case.

Fifty-one women (18%) had MOH. Gestational age of these patients was significantly lower than that of patients without MOH (28.9±11.36 *vs.* 32.66±7.15 weeks' gestation; P < .05) (OR = 3.789, 95% CI = 1.769-8.116). The risk factors studied is presented in **Table 2**. The rate of MOH was significantly increased among multipara compared to the rate among nulliparous (24.1% *vs.* 9.9%; P < .05) (OR = 0.940, 95% CI = 0.908-0.974). PT and DIC score were statistically increased in women with MOH (peak PT levels, 12.34±1.91 vs. 11.55±2.40 s, respec-

Table 3. Clinical scores and laboratory parameters of women with MNM

	MOH (n = 51)	No MOH (n = 232)	*p*
APACHE II score	11.49±4.47	8.86±3.62	0.049
SOFA score	2.37±2.75	1.00±1.77	0.031
DIC score	1.76±1.53	1.05±1.38	0.234
GCS score	14.39±2.52	14.96±.59	0.519
AST U/L	56.71±126.68	68.12±119.68	0.544
ALT U/L	38.32±90.93	53.35±111.24	0.948
TB ummol/L	15.63±19.59	17.19±24.45	0.178
Cr ummol/L	75.48±80.56	72.11±87.53	0.573
GLU mmol/L	6.10±2.97	5.20±2.17	0.042
TG mmol/L	2.22±1.27	3.83±6.04	0.015
CHO mmol/L	4.26±1.37	5.74±2.91	0.293
HGB g/L	85.85±19.89	109.48±21.56	0.777
HCT	0.26±.06	0.57±2.61	0.303
PLT 10^9/L	142.06±70.17	181.27±82.62	0.623
WBC 10^9/L	15.09±8.09	12.87±6.29	0.086
TT s	18.34±3.67	18.59±3.89	0.035
PT s	12.34±1.91	11.55±2.40	0.723
APTT s	31.76±12.28	27.36±8.57	0.485
INR	1.04±.15	1.01±.56	0.279
Fib g/L	2.30±1.13	3.58±1.02	< 0.001
D-Dimer mg/L	7.70±13.15	4.20±5.72	0.002

T, Temperature; P, pulse; R, respiratory rate; SpO_2, Pulse oxygen saturation; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MAP, Mean arterial pressure; AST, aspartate amino transferase; ALT, alanine aminotransferase; TB, total bilirubin; Cr, creatinine; GLU, blood glucose; TG, triglyceride; CHO, cholesterol; HDL-C, high-density lipoproteincholesterol; LDL-C, low-density lipoprotein cholesterol; HGB, hemoglobin; HCT, hematocrit; PLT, Platelets; WBC, White blood cell; BNP, Brain natriuretic peptide; TT, thrombin time; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, International Normalized Ratio; Fib, fibrinogen; FDP, Fibrinogen Degradation Product; ATIII%, Antithrombin III; D-DII, D-dimer. P < 0.05 was considered significant.

tively; peak DIC score, 1.76±1.53 *vs.* 1.05±1.38, respectively). However, the rate of peak serum levels of PT > 13.2 s and DIC score > 5 was not statistically different between patients with MOH and those without MOH. Logistic regression analysis showed an independent and significant association between incidence of gestational age at diagnosis and multipara only (P < 0.001). The rates of vaginal delivery (7.8% *vs.* 1.7%, P < 0.01) and previous abortion (9.8% *vs.* 1.7%; P < 0.01) were significantly higher among women with MOH. But the multivariate analysis showed no independent association of vaginal delivery and previous abortion.

Clinical scores of patients

Multi-factor regression analysis showed statistical differences between patients with and without MOH in APACHE II scores (11.49±4.47 *vs.* 8.86±3.62, P = 0.049) and SOFA scores (2.37±2.75 *vs.* 1.00±1.77, P = 0.031).

Laboratory parameters of patients

GLU (6.10±2.97 *vs.* 5.20±2.17, P = 0.042), D-Dimer (7.70±13.15 *vs.* 4.20±5.72, P = 0.013) were statistically higher among women with MOH. TT (18.34±3.67 *vs.* 18.59±3.89, P = 0.035), Fib (2.30±1.13 *vs.* 3.58±1.02; P < 0.001) and TG (2.22±1.27 *vs.* 3.83±6.04; P = 0.015) were statistically lower among women with MOH by multi-factor regression analysis. Other laboratory parameters were not statistically different between patients with and without MOH as shown in **Table 3**.

Clinical outcomes of patients

Clinical outcomes were also analyzed. Incidences of MNM Mortality (3.9%), perinatal mortality (43%), hysterectomy (9.8%), DIC (13.7%), abdominal hematoma (13.7%), shock (31.4%), cardiac arrest (7.8%), stroke (7.8%), MODS (11.8%) and reoperation (11.8%) were statistically increased in women with MOH. 85 women (30%) needing transfusion of blood products. The rates of transfusion were statistically increased in women with MOH (96% vs. 16%; *P* < 0.01). The need for transfusion of RBC ≥ 5 U was also statistically increased among women with MOH (78% vs. 6%; P < 0.01). Logistic regression analysis showed an increased risk of transfusion of blood products among women with MOH only (*P* < 0.01, **Table 4**).

In this study, the reasons of MOH in ICU were placental factors (74.5%), coagulation disorders (13.7%), trauma (1.96%) and uterine atony (9.80%).

Predictive value of DIC, APACHEII and SOFA scores on reoperation and abdominal hematoma

The AUROC values were used to compare the predictive abilities of the three scores (**Figures**

Table 4. Clinical outcomes of women with MNM

Outcome	N%		*P* value
	MOH (n = 51)	No MOH (n = 232)	
MNM Mortality (%)	2 (3.9)	1 (0.43)	0.55
Perinatal mortality (%)	22 (43.1)	23 (9.91)	< 0.01
Apgar			
1 min	4.31±4.38	7.65±3.42	< 0.01
5 min	5.20±4.70	8.48±2.97	< 0.01
10 min	5.43±4.85	8.79±2.84	< 0.01
Hysterectomy (%)	5 (9.8)	0	< 0.01
DIC (%)	7 (13.7)	0	< 0.01
Abdominal hematoma (%)	7 (13.7)	0	< 0.01
Shock (%)	16 (31.4)	4 (1.72)	< 0.01
Cardiac arrest (%)	4 (7.84)	2 (0.86)	0.01
Stroke (%)	4 (7.84)	3 (13.0)	0.02
MODS (%)	6 (11.8)	1 (0.43)	< 0.01
Reoperation (%)	6 (11.8)	7 (3.02)	0.02
ICU LOS (days)	11.58±10.8	15.02±14	0.055
HLOS (days)	15±14	11.6±10.1	0.055
Mechanical ventilation (%)	10 (19.6)	24 (10.3)	0.1
Hemopurification (%)	1 (1.96)	6 (2.59)	1.0
Transfusion of blood products (%)	49 (96.1)	36 (15.5)	< 0.01
Transfusion of RBC ≥ 5 U	40 (78.4)	15 (6.46)	< 0.01
Anticoagulation (%)	8 (15.7)	31 (13.4)	0.83
Hemostasis (%)	18 (35.3)	31 (13.4)	< 0.01
Vasoacti veagent DA/NE/E (%)	7 (13.7)	6 (2.59)	0.02

MODS, multiple organ dysfunction syndrome; SIRS, Systemic inflammatory response syndrome; CRRT, Continuous renal replacement therapy; APACHE, Acute Physiology And Chronic Health Evaluation; ICULOS, Intensive care unit length of stay; HLOS, Hospital length of stay; DA/NE/E, dopamine/noradrenergic/noradrenergic. P < 0.05 was considered significant.

1 and **2**) on reoperation and abdominal hematoma. The AUROC of Reoperation for DIC, APACHEII, and SOFA were 0.680 (95% CI = 0.489-0.871), 0.729 (95% CI = 0.0.558-0.900), and 0.751 (95% CI = 0.609-0.892), respectively. The AUROC of abdominal hematoma for DIC, APACHEII, and SOFA were 0.866 (95% CI = 0.674-1.000), 0.634 (95% CI = 0.372-0.895), and 0.826 (95% CI = 0.642-1.000), respectively. By comparing AUROCs, the AUROC of SOFA was significantly higher than that of other scores (p = 0.002) on reoperation. The AUROC of DIC was significantly higher than that of other scores (p = 0.001) on abdominal hematoma. These results suggested that SOFA scores had relatively good predictive abilities on reoperation, and the DIC scores had relatively good predictive abilities on abdominal hematoma.

Discussion

Although different criteria have been used for the diagnosis [4, 7], MOH due to uterine atony was still correlated with a high risk of adverse maternal outcome compared with MNM [3, 8] or the obstetric population in a lot of research on obstetrics and gynecology [9, 10]. In this study, the main reason for MOH in ICU were placental factors (74%) and coagulation disorders (14%). Women with MOH had many adverse maternal outcomes, such as MNM Mortality (3.9%), perinatal mortality (43%), hysterectomy (9.8%), DIC (13.7%), abdominal hematoma (13.7%), shock (31.4%), cardiac arrest (7.8%), stroke (7.8%), MODS (11.8%), and reoperation (11.8%). These changes may be a reflection of recent trends in treatment in MOH, which contain increased application of coagulation factors [11] and improvement in the threshold for transfusion [2, 7].

Study of confounding variables for the risk of MOH determined by univariate analysis showed that gestational age, multiparity, vaginal delivery and previous abortion were correlated with a high risk of MOH and the influence was significant of gestational age at diagnosis. Then multivariable analysis showed that gestational age and childbearing history were risk factors for massive obstetric hemorrhage. These conclusions seemed to be in line with previous studies [5, 26]. The smaller the gestational age, the pregnant women turned to MOH easier. In our study nulliparous was showed a lower rate of MOH, which meant pluripara was discovered to be correlated with a high risk of MOH in MNM. Maternal age, BMI, polyembryony, and chronic hypertension were found to not be independently correlated with MOH.

In the past, maternal laboratory parameters and clinical characteristics described in MOH definition were the focus. However, in our study we found no differences between MOH and no-MOH in most laboratory parameters. Except for Fib and D-dimer, most other laboratory

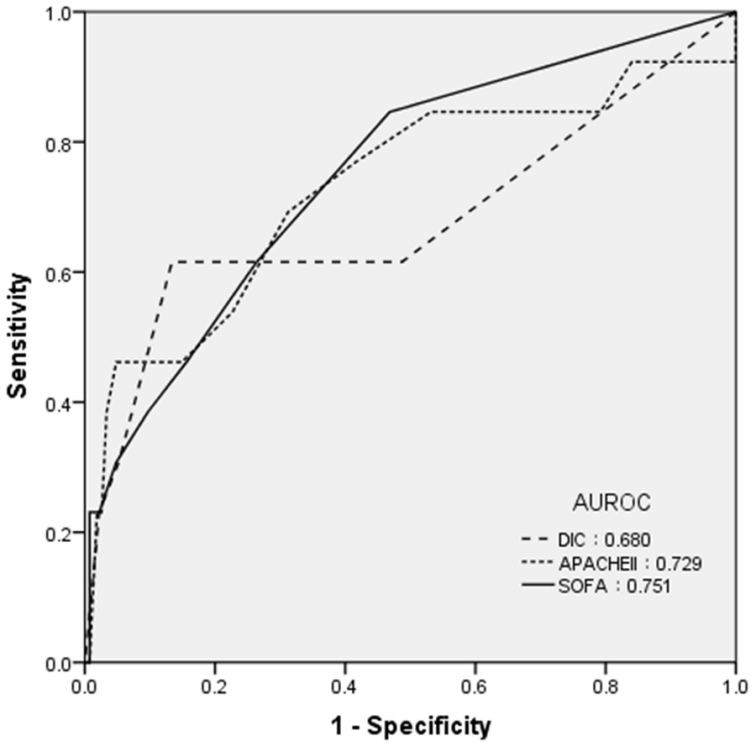

Figure 1. ROC curves of scores for the prediction of reoperation: DIC scores vs. APACHEII scores vs. SOFA scores.

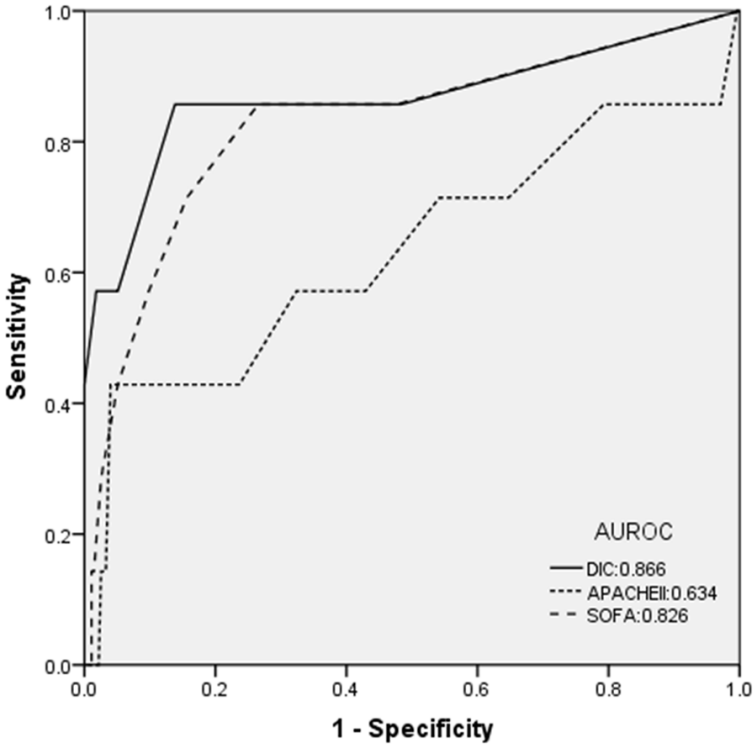

Figure 2. ROC curves of scores for the prediction of abdominal hematoma: DIC scores vs. APACHEII scores vs. SOFA scores.

parameters were not statistically different between the 2 groups. This made clinicians unable to accurately assess the severity of critical pregnant women. However, APACHE II scores and SOFA scores were significant high in MOH group than no-MOH group. APACHE II score was thought to predict the risk of death, and it was closely related to the prognosis. It is used to guide the treatment and improve the medical quality and reasonable utilization of medical resources in ICU. The higher the score, the worse the prognosis, and the worse the prognosis, the higher the observed fatality rate. Therefore, our study showed that the MOH group was more serious than no-MOH, which predicting a poor clinical outcome. Except for ICU LOS and hospital LOS, most other adverse maternal outcomes were statistically different between the 2 groups. Currently, the SOFA score is a widely used scoring system for assessing the severity of organ damage in critically ill patients, from single organs to multiple organs, from organ damage to organ failure. In our study the SOFA score of MOH group was higher than no-MOH group. MNM with MOH shared a high risk of multiple organs failure. DIC scores were used to make an assessment of coagulation disorders in patients. As coagulation is enhanced and fibrinolysis is inhibited in late pregnancy [6, 7], simultaneous hypovolemia and depletion of coagulation factors develop when MOH occurs [8]. When coagulation factors are not supplemented, hemostasis is difficult to achieve. When coagulation factors become depleted, production of fibrin de-

gradation products increases due to enhanced fibrinolysis, and uterine contractions are secondarily inhibited, resulting in uterine atony [9, 10]. In our study, Fib was lower and D-Dimer was statistically higher among women with MOH by Multi-factor Regression Analysis. As a result, bleeding increased even further, which may have caused DIC, abdominal hematoma, reoperation, and other adverse maternal outcomes [15].

By further analysis we found that SOFA scores had relatively good predictive abilities on reoperation, and DIC scores had relatively good predictive abilities on abdominal hematoma. These findings show the significance of clinical scores instead of laboratory results alone for the assessment of the effect of hemostasis, and transfusion of blood products, or other treatment to improve clinical outcomes of MOH.

The limitations of our study mostly result from its retrospective design. The present study was performed in a single center with a small sample size. Additionally, patient's long-term survival has not been well assessed. Therefore, a research study with a larger sample size is needed. Our study is not a perfect regimen, further refinement and further trials on this subject are needed.

The strength of the study is that few previous studies have investigated the association between APACHE II, SOFA, DIC scores and clinical outcomes of MOH. Therefore, to our knowledge, this study is the first to show that recognition of these patients by using clinical scores instead of laboratory parameters may be beneficial for treatment. Furthermore, this is likely the first study that fully investigated the effect of weekend delivery on maternal outcomes in MOH.

In our research, among women with maternal near miss; gestational age, and childbearing history are risk factors for massive obstetric hemorrhage. SOFA scores had relatively good predictive abilities on reoperation, and the DIC scores had relatively good predictive abilities on abdominal hematoma. Therefore, treatment in cases of MOH should concern clinical features, laboratory results, and clinical scores together.

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Disclosure of conflict of interest

None.

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