

Original Article

Lactate and fibrinogen as good predictors of massive transfusion in postpartum hemorrhage

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Aim: This study aims to identify the clinical factors that can predict the requirement of massive transfusion among patients with postpartum hemorrhage (PPH).

Methods: Consecutive anonymized patients with PPH who were treated at the emergency department of our perinatal medical center were examined. Patients who had received transfusions before admission, those who had cardiac arrest on arrival, and those with history of blood gas analysis were excluded. Our primary outcome was the requirement of massive transfusion defined as packed red blood cells of ≥ 10 units/24 h. Univariable logistic analysis was carried out to identify the odds ratio and 95% confidence interval (CI) of the explanatory variables for the outcome.

Results: A total of 31 patients (massive transfusion, $n = 19$) were included in the main analysis. The crude odds ratio for fibrinogen per mg/dL and lactate per mmol/L were calculated as 0.98 (95% CI, 0.97–0.99) and 1.62 (95% CI, 1.08–3.02), respectively. The area under the curves for fibrinogen and lactate were 0.814 and 0.734, respectively, and optimal cut-off values for fibrinogen and lactate were 211 mg/dL and 4 mmol/L, respectively.

Conclusion: These findings suggest that lactate and fibrinogen can be predictors for the requirement of massive transfusion in patients with PPH.

Key words: emergency medicine, hemorrhagic shock, shock index

BACKGROUND

POSTPARTUM HEMORRHAGE (PPH) is the most common cause of maternal death in Japan,^{1,2} and delay in initiating blood transfusion was observed in approximately 20% of all maternal deaths due to PPH.¹ Rapid hemostatic resuscitation and massive transfusion (MT) are essential for saving maternal lives.

In Japan, the shock index (SI), which is defined as the ratio of heart rate to systolic blood pressure ($SI = \text{heart rate}$

$[\text{min}] / \text{systolic blood pressure} [\text{mm Hg}]$), has been conventionally used to determine the necessity for blood transfusion.^{3,4} However, some reports have argued that SI might be inappropriate for predicting a requirement for MT among PPH cases because of its low sensitivity (18–56%).^{5,6} Among patients in hemorrhagic shock due to trauma, levels of other indicators such as lactate, base excess, and fibrinogen, have been reported to be good predictors of MT requirement.⁷

Thus, the aim of this study was to identify more useful predictors of MT requirement in PPH cases.

METHODS

Study design, settings, and cohort

THIS STUDY WAS a retrospective cohort study and its setting was the emergency department of the Osaka City General Hospital, which has a tertiary critical care center and a perinatal medical center in the urban area of Osaka City, Japan. Inclusion criteria were patients with

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PPH who had been transferred to our emergency department from other local hospitals between April 2012 and March 2016. We excluded patients who had already received transfusions before being transferred to our facility, those who had collapsed due to cardiac arrest on admission, and patients who lacked data on lactate levels or blood gas analysis.

Outcome

The primary outcome was requirement of MT, which was defined as 10 units or more of packed red blood cells transfused within 24 h after admission. In Japan, 1 unit of packed red blood cells corresponds to 120 mL derived from 200 mL whole blood.

Measurement

We divided all eligible PPH patients into two groups, those who needed MT (MT group) and those who did not (non-MT group). Data on the following demographic characteristics and in-hospital details such as age, body mass index, basic information on pregnancy, vital signs on admission (heart rate, systolic blood pressure, and SI), cause of bleeding and hemoglobin, platelet, fibrinogen, lactate, and base excess levels on admission, and

hemostasis procedures were obtained by reviewing patient charts. Lactate was measured on an ABL 800 FLEX (Radiometer, Tokyo, Japan). As fibrinogen less than 50 mg/dL is unmeasurable and is displayed as “Low” in our hospital, its cut-off level was set at 40 mg/dL. Initiation and termination of transfusion were decided by the doctors in charge of the patients.

Statistical analysis

Patient characteristics and in-hospital information were compared between the two groups using the Wilcoxon rank sum test for numeric variables and Pearson's χ^2 -test for categorical variables. We applied univariate logistic regression analysis to calculate odds ratios and their 95% confidence intervals (CI) of the potential predictors for the primary outcome. We also used the receiver operating characteristic (ROC) curve to calculate the optimal cut-off value, and sensitivity and specificity of each predictor in identifying the requirement for MT. Two-sided P -value <0.05 was considered statistically significant. All statistical analyses were undertaken using JMP Pro 14 for Mac (SAS Institute, Tokyo, Japan).

This study was approved by the Clinical Research Ethics Committee of Osaka City General Hospital (No. 1812105).

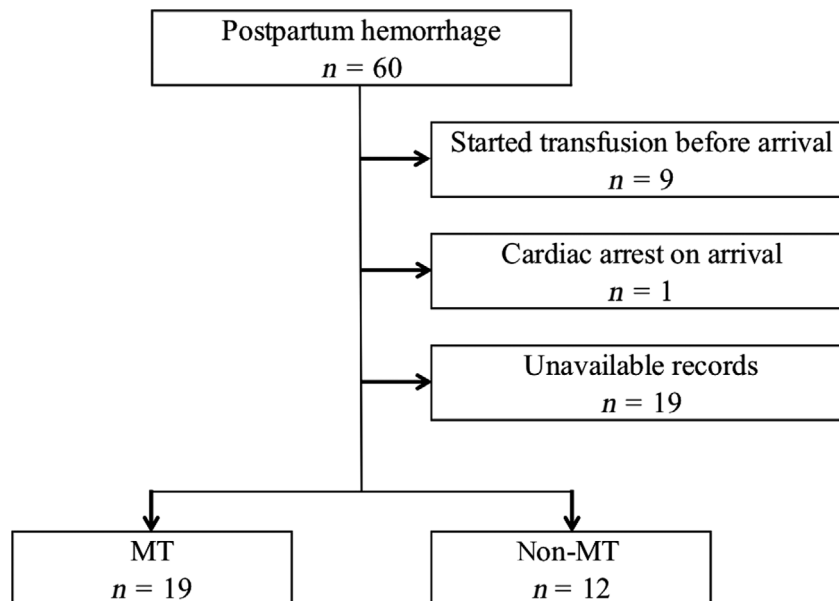


Fig. 1. Study flowchart. Sixty patients were referred to our hospital for the management of postpartum hemorrhage. Twenty-nine patients were excluded for several reasons: already started transfusion before arrival ($n = 9$), cardiac arrest on arrival ($n = 1$), and no record of blood gas assessment ($n = 19$). Finally, 31 patients were included in this study and they were divided into two groups: those who required massive transfusion (MT group, $n = 19$) and those who did not (non-MT group, $n = 12$).

RESULTS

AMONG THE 60 patients with PPH, we excluded nine patients who had already received a transfusion before being transferred to our hospital, one patient who was in cardiac arrest, and 19 patients without data on lactate or blood gas levels. Therefore, 31 patients were included in the analysis cohort (Fig. 1). The demographic characteristics and in-

hospital details are listed in Table 1. Compared to the non-MT group, the MT group had significantly lower fibrinogen (median [med], 139 [interquartile range (IQR), 91.0–201.0] mg/dL versus med, 245.5 [IQR, 176.3–186.8] mg/dL, $P = 0.04$) but higher lactate (med, 4.0 [IQR, 3.0–6.0] mmol/L versus med, 3.0 [IQR, 2.0–4.0] mmol/L, $P = 0.03$) values (Table 1). Univariate logistic regression analysis yielded odds ratios of 0.98 (95% CI, 0.97–0.99) for fibrinogen (per

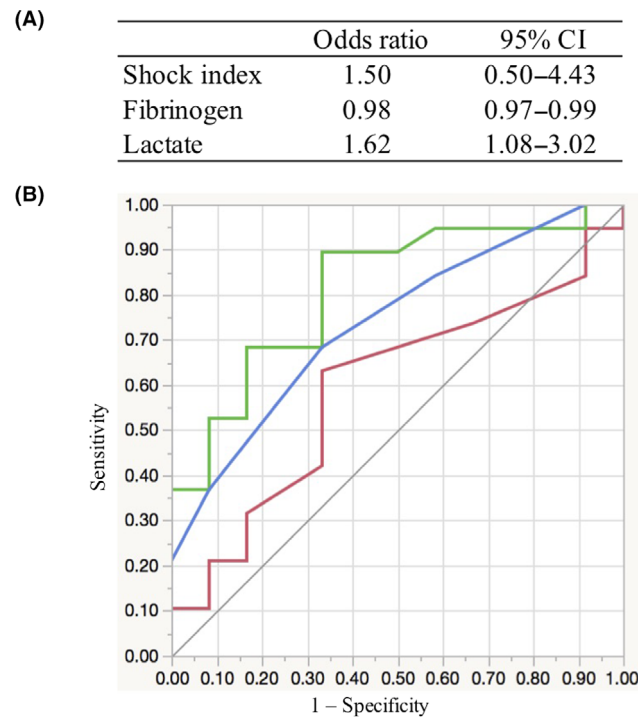
Table 1. Comparison of results between patients with postpartum hemorrhage who underwent massive transfusion (MT) or not

Characteristic		MT ($n = 19$)	Non-MT ($n = 12$)	P -value
Age, years	Median (IQR)	36.0 (32.0–38.0)	32.5 (30.5–36.0)	0.23
BMI		23.1 (20.3–25.2)	22.9 (20.9–23.5)	0.63
Gravida		2.0 (1–3)	2.5 (2–3)	0.30
Para		1.0 (0–1)	1.0 (0–2)	0.37
Gestational weeks at delivery		39.0 (38.0–40.0)	39.5 (38.0–40.0)	0.63
Infertility treatment	n (%)	2 (10.5)	2 (16.7)	0.62
Cesarean section		7 (36.8)	2 (16.7)	0.14
HDP		1 (5.3)	1 (8.3)	0.30
Cause of bleeding				
Atonic bleeding	n (%)	9 (47.3)	8 (66.7)	0.29
Uterine inversion		3 (15.8)	2 (16.7)	0.55
Uterine rupture		2 (10.5)	0 (0.0)	0.25
Placenta previa		0 (0.0)	0 (0.0)	NA
Amniotic fluid embolism		2 (10.5)	0 (0.0)	0.25
Hematoma		1 (5.3)	1 (8.3)	0.74
Retained placenta		1 (5.3)	1 (8.3)	0.74
Placental abruption		1 (5.3)	0 (0.0)	0.42
Transfusion				
RBC, units	Median (IQR)	14.0 (12.0–26.0)	6.0 (2.5–6.0)	<0.01
FFP, units		14.0 (6.0–28.0)	6.0 (0.5–10.0)	0.01
Vital signs				
HR, b.p.m.	Median (IQR)	119.0 (95.0–133.0)	109.5 (92.3–119.8)	0.30
sBP, mmHg		116.0 (91.0–128.0)	110.5 (91.3–123.8)	0.56
Shock index		1.1 (0.8–1.4)	1.0 (0.8–1.2)	0.40
Laboratory data/blood gas analysis				
Hb, g/dL	Median (IQR)	5.6 (4.1–6.2)	7.4 (6.1–9.3)	0.05
Plt, $\times 10^4/\mu\text{L}$		12.9 (9.7–17.0)	19.9 (12.0–24.0)	0.07
Fibrinogen, mg/dL		139 (91.0–201.0)	245.5 (176.3–186.8)	0.04
Lactate, mmol/L		4.0 (3.0–6.0)	3.0 (2.0–4.0)	0.03
BE, mEq/L		5.9 (3.4–10.3)	4.0 (2.8–6.7)	0.17
Hemostasis				
Surgical intervention	n (%)	8 (42.1)	1 (8.3)	0.08
UAE		1 (5.3)	0 (0.0)	
Other [†]		10 (52.6)	11 (91.7)	

Comparison between the two groups was evaluated with the Wilcoxon rank sum test for numeric variables and Pearson's χ^2 -test for categorical variables.

[†]Uterotonic agents, uterine massage, uterine balloon tamponade, and reduction of uterine inversion.

BE, base excess; BMI, body mass index; FFP, fresh frozen plasma; Hb, hemoglobin; HDP, hypertensive disorder of pregnancy; HR, heart rate; IQR, interquartile range; NA, not applicable; Plt, platelets; RBC, red blood cells; sBP, systolic blood pressure; UAE, uterine arterial embolization.



	AUC	Cut-off	Sensitivity	Specificity
— SI	0.592	1.1	0.63	0.33
— Fib	0.814	221.0 mg/dL	0.89	0.53
— Lac	0.734	4.0 mmol/L	0.68	0.65

	The Difference between AUC	95% CI	P-value
SI vs. Fib	-0.221	-0.480 to 0.037	0.093
Fib vs. Lac	0.077	-0.158 to 0.311	0.521
SI vs. Lac	-0.145	0.284 to -0.006	0.041

Fig. 2. Univariate analysis of shock index (SI), fibrinogen (Fib), and lactate (Lac) among patients with postpartum hemorrhage who underwent massive transfusion (MT). A, Univariate analysis showed that Fib and Lac were associated with the requirement for MT. The odds ratio for Fib was 0.98 (95% confidence interval [CI], 0.97–0.99) and that of Lac was 1.62 (1.08–3.02). SI was not associated with a need for MT. B, Area under the curves (AUC) of Lac and SI were significantly different.

mg/dL) and 1.62 (95% CI, 1.08–3.02) for lactate (per mmol/L) (Fig. 2A). The area under the curves (AUC) of the ROC for fibrinogen, lactate, and SI were 0.814 (95% CI, 0.609–0.924), 0.734 (95% CI, 0.532–0.874), and 0.592 (95% CI, 0.379–0.776), respectively. The AUC of ROC for lactate was significantly higher than that of SI ($P = 0.041$) (Fig. 2B). A fibrinogen cut-off value of 211 mg/dL had a sensitivity and specificity of 0.89 and 0.53, respectively. Similarly, a lactate cut-off value of 4 mmol/L had sensitivity and specificity of 0.68 and 0.65, respectively (Fig. 2).

DISCUSSION

OUR RETROSPECTIVE STUDY found that fibrinogen and lactate levels on admission were associated with a requirement for MT and that lactate could better predict the requirement for MT than SI. To the best of our knowledge, this study is the first to describe the association between lactate levels and a requirement for MT among PPH patients.

Fibrinogen plays a role in platelet aggregation during secondary hemostasis. If blood coagulation factors and

fibrinogen levels are depleted due to massive bleeding, secondary hemostatic mechanisms do not work, resulting in coagulopathy. Therefore, maintaining adequate fibrinogen levels is important for hemostasis in patients with massive bleeding. Even though a previous study has reported that fibrinogen was associated with the need for MT in PPH,⁵ we do not consider fibrinogen to be an appropriate marker for initiating MT in emergent settings as it takes time to get the results of fibrinogen levels. In contrast, lactate levels can be measured easily and quickly in most emergency departments; therefore, under emergent conditions, lactate levels might be better predictors of MT than fibrinogen.

Generally, lactate is produced by anaerobic metabolism due to reduced tissue perfusion in hemodynamically unstable patients. In trauma, lactate levels of more than 4.7 mmol/L on admission have been associated with mortality;⁸ levels of more than 4.0 mmol/L predicted the need for MT.⁹ Therefore, it is reasonable to assume that lactate levels could be useful for predicting the need for MT in PPH, and thereby, the severity of PPH.

The advantages of using SI are simplicity and speed and it can be used in primary care or maternity hospital settings. Similar to SI, lactate levels can be measurable in these settings using a small hand-held device. Moreover, we believe that lactate levels could be more reliable predictors than SI because there was a significant difference in AUC between lactate and SI. Thus, it follows that if lactate levels are greater than 4 mmol/L, PPH patients should be referred to a critical care center if they are in a primary care setting. In tertiary care settings, lactate measurement could be useful for activating the MT protocol and for promoting the initiation of definitive hemostasis procedures.

We did not observe an association between SI and a requirement for MT because SI might not accurately represent the hemodynamic status of patients with hypertensive disorders of pregnancy. Furthermore, no clear cut-off value for the initiation of the MT protocol is currently accepted.^{3,4} Era *et al.*⁵ reported that $SI \geq 1.12$ is a cut-off for initiating MT, however, the sensitivity was too low (approximately 50%) for use in clinical settings. Thus, we believe that SI is not appropriate as a predictor of the requirement of MT in PPH cases.

This was an exploratory study to identify potential hypotheses for future studies and has several limitations. First, the exact time elapsed from delivery of the baby to hospital arrival and/or quantity of blood loss was unknown. Second, the decision to start or terminate transfusion and the amount of transfusion units administered were decided by the physicians in charge and were not standardized. Third, as some cases without adequate records were excluded, there might be selection bias. Fourth, multivariate analysis was not used

because of the small sample size. Although lactate levels might have been influenced by duration of labor¹⁰ or the intensity of labor pain,¹¹ such information was unavailable. Finally, this study was based on data from a single institution with small sample size; therefore, we cannot definitively state the clinical significance of lactate, SI, or fibrinogen. Further studies with larger sample sizes are needed to more accurately define the clinical significance of these factors.

CONCLUSION

WE SHOW THAT fibrinogen and lactate are associated with the requirement of MT in PPH patients. However, due to its simplicity and rapidity of evaluation, lactate levels might be more useful for predicting the requirement for MT.

DISCLOSURE

Approval of the research protocol: This study was approved by the Clinical Research Ethics Committee of Osaka City General Hospital (No. 1812105).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None declared.

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