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ORIGINAL ARTICLE

Association between lung contusion volume and acute changes in fibrinogen levels: A single-center observational study

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Abstract

Aim: Organ tissue damage, including the lungs, may lead to acute coagulopathy. This study aimed to evaluate the association between lung contusion volume and serum fibrinogen level during the acute phase of trauma.

Methods: We conducted an observational study using electronic medical records at a tertiary-care center between January 2015 and December 2018. We included patients with lung contusions on hospital arrival. We used three-dimensional computed tomography to calculate lung contusion volumes. The primary outcome was the lowest fibrinogen level measured within 24 h of hospital arrival. We evaluated the association between lung contusion volume and outcome with multivariable linear regression analysis. Also, we calculated the sensitivity and specificity of lung contusion volume in patients with a serum fibrinogen level of ≤150 mg/dL.

Results: We identified 124 eligible patients. Their median age was 43.5 years, and 101 were male (81.5%). The median lung contusion volume was 10.9%. The median lowest fibrinogen level within 24 h from arrival was 188.0 mg/dL. After adjustment, lung contusion volume had a statistically significant association with the lowest fibrinogen level within 24 h from arrival (coefficient −1.6, 95% confidence interval −3.16 to −0.07). When a lung contusion volume of 20% was used as the cutoff, the sensitivity and specificity to identify fibrinogen depletion were 0.27 and 0.95, respectively.

Conclusion: Lung contusion volume was associated with the lowest fibrinogen level measured within 24 h from hospital arrival. Measuring lung contusion volume may help to identify patients with a progression of fibrinogen depletion.

KEYWORDS
blood transfusion, fibrinogen depletion, lung contusion, traumatic coagulopathy, volumetry

BACKGROUND

Lung contusion is common in chest trauma and previous reports showed that lung contusion was found in 30%–75% of chest trauma.[1] Depending on the severity of the injury, the mortality rate in patients with blunt lung injury is estimated to range from 25% to 60%.[1,2] Patients with severe blunt trauma have a high risk of presenting with severe coagulopathy.[3] Previous studies reported that organ tissue damage in specific body regions, including the lung, was associated with acute traumatic coagulopathy.[4,5] Coagulopathy is considered one part of the lethal triad in trauma,[6] and a previous article showed low serum fibrinogen level after hospital arrival to be an independent risk factor for death.[7] In the acute phase of trauma, decreasing serum fibrinogen occurs early and is followed by other coagulation factor deficits.[8]

Fibrinogen depletion after injury can be a marker of traumatic coagulopathy and is associated with poor outcomes.[9] European guideline refers to setting a target fibrinogen level of more than 150 mg/dL when treating trauma coagulopathy patients.[10] Administration of fresh frozen plasma (FFP) has been the main treatment for coagulopathy in trauma management.[11] Although cryoprecipitate or fibrinogen concentrate may be used for patients with fibrinogen depletion in trauma, commercially available cryoprecipitate and fibrinogen concentrates have limited indications in Japan.[12]

Computed tomography (CT) is one of the modalities used for evaluating lung contusion in patients with chest trauma,[13] and three-dimensional volume analysis software can be used to measure lung contusion volume in a relatively simple manner.[14] A previous report suggested that lung contusion volume calculated from CT images may be associated with poor clinical outcomes,[14] but studies examining the association between the extent of lung contusion and the progression of acute traumatic coagulopathy are limited.

We hypothesized that if lung contusion volume was associated with acute traumatic coagulopathy, it might contribute to predicting deteriorating coagulopathy in patients with lung contusion at the emergency department.

METHODS

Aim, study design and setting

This study aimed to examine the association between serum fibrinogen level during the acute phase of trauma and lung contusion volume calculated from CT images in the emergency department in blunt trauma patients with lung contusion.

A retrospective single-center observational study was conducted at the Trauma and Acute Critical Care Center, which is a tertiary-care center with 19 intensive care unit beds. This center receives approximately 250 cases of severe trauma annually and has emergency physicians, trauma surgeons, neurosurgeons, orthopedic surgeons, and interventional radiology physicians available at all times. Blood products transfusion is administered to patients with signs of hemodynamic instability or excessive bleeding in accordance with the Japanese trauma guideline, which recommends maintaining a hemoglobin level above 7 g/dL, serum fibrinogen level above 150 mg/dL, and platelet count above 50,000/μL.[8,15]

The institutional ethics committee approved this study and waived the requirement for informed consent (approval no. 20150).

Participants

Patients with blunt trauma were transported directly to our center or transferred from another hospital within 3 h of the injury from January 2015 to December 2018, who had lung contusion as their discharge diagnosis were included. Diagnosis of lung contusion was performed by more than two board-certified attending physicians specializing in emergency trauma care who were unrelated to this study by considering the mechanism of chest trauma, the presence of chest injuries, and X-ray and CT findings on admission.[16] Those women who were pregnant at the time of admission and patients with out-of-hospital cardiac arrest were excluded.

Variables

We extracted the following patient data from electronic health records; age, sex, mechanism of injury, vital signs on arrival (systolic blood pressure, heart rate, respiratory rate, body temperature), Glasgow Coma Scale score on arrival, Injury Severity Score (ISS), concomitant rib fractures, concomitant pneumothorax, concomitant hemothorax, concomitant injury to other body regions (head/neck, abdomen, pelvis/lower extremities), and in-hospital mortality. We defined shock as a systolic blood pressure of 90 mmHg or less on arrival, and severe trauma as an ISS greater than 15, which are both potential confounders reported in the previous literature.[17,18]

A dual-source 64-slice CT system (SOMATOM Definition Flash, Siemens Medical Solutions, Forchheim, Germany) is always available in our center. All eligible patients underwent a whole-body CT scan in the emergency department. Lung contusion volume was identified by CT with a slice thickness of 5 mm in the lung window setting (window width, 1200 Hounsfield units; window level, -600 Hounsfield units) and the presence of consolidation or ground-glass areas as described in other articles.[19,20] Volumetric measurements of lung contusion were traced by using Volume Analyzer SYNAPSE VINCENT (FUJIFILM Holdings Corporation, Tokyo, Japan), a three-dimensional volume analysis software. The traced areas were manually adjusted if they contained intact lung areas or if lung contusion was not contained. Lung contusion volume was expressed as a percentage of injured lung volume to the total thoracic cavity volume. An example case was showed in Figure S1.

The primary outcome was the lowest serum fibrinogen level measured within 24 h of hospital arrival. Secondary outcomes were the initial fibrinogen level on hospital arrival, and the total blood transfusion among patients who underwent transfusion within 24 h of hospital arrival.[21]

Statistical analysis

Patient characteristics are described as medians and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. We assessed the association of the lowest serum fibrinogen level within 24 h of hospital arrival with lung contusion volume using univariable and multivariable linear regression analyses. Crude and adjusted regression coefficients and 95% confidence interval (CI) were estimated. We performed the same analyses with the initial fibrinogen level on hospital arrival. Multivariate analyses were adjusted for age, sex, concomitant injury to other body regions (head/neck, abdomen, pelvis/lower extremities), severe trauma, presence of shock, and transfusion of FFP, which are known to be potential confounders according to previous studies.[13,22–24]

We set a serum fibrinogen level of 150 mg/dL as the cut-off value for the development of coagulopathy and analyzed its relationship with lung contusion volume.[21] We calculated sensitivity and specificity at different cutoffs (10%, 20%, and 30%) of lung contusion volume to detect a serum fibrinogen level of 150 mg/dL or lower.

A p value < 0.05 was considered statistically significant. All analyses were performed using R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 1069 trauma patients were admitted to our center. Among them, 303 patients had blunt chest trauma, and 128 patients were diagnosed as having lung contusion. Four patients were excluded due to cardiac arrest on arrival, and no patients were pregnant. In total, 124 patients were eligible in this study (Figure 1).

The median age of the patients was 43.5 years (Q1–Q3; 22.75–58), and males accounted for 101 (81.5%) of them. The most common mechanism of injury was motorcycle crash in 50 cases (40.3%), followed by falls from height in 21 cases (16.9%). Shock was recognized in the emergency department in 14 patients (11.2%). The median ISS was 29 (Q1–Q3; 19–38). Complications of chest trauma included rib fractures in 61 patients (49.2%), hemothorax in 47 (37.9%), and pneumothorax in 33 (26.6%). Other concomitant injuries were head/neck in 76 patients (61.3%), abdomen in 33 (26.6%), and pelvis/lower extremities in 49 (39.5%). The median lung contusion volume was 10.9% (Q1–Q3, 7.6–14.95). In-hospital mortality was 9.7% of the total cohort (Table 1). The median lowest serum fibrinogen level within 24 h of hospital arrival (188.0 mg/dL) was lower than the median level in the initial blood test on arrival (209.0 mg/dL). Blood transfusions were administered within 24 h of hospital arrival in 43 patients (34.7%). The median FFP administration volume within 24 h of hospital arrival was 10 units. (Table 2).

Univariable linear regression analysis showed a statistically significant association between the lowest serum

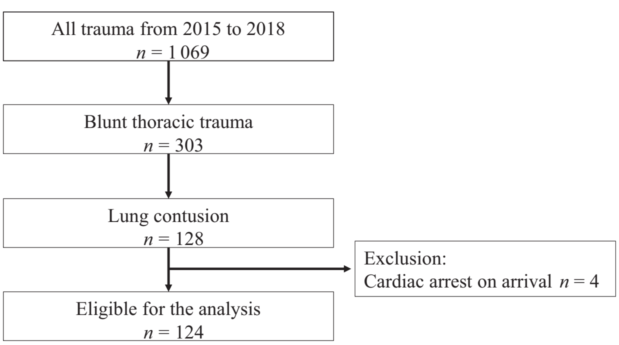

FIGURE 1 Patients flow diagram.

TABLE 1 Characteristics of trauma patients with lung contusion.

Characteristics	Total $n = 124$
Age, years, median, (Q1–Q3)	43.5 (22.75–58)
Age group, n (%)	
<18 years	18 (13.7)
18–64 years	86 (69.4)
≥65 years	21 (16.9)
Male sex, n (%)	101 (81.5)
Mechanism, n (%)	
Car crash	16 (12.9)
Motorcycle crash	50 (40.3)
Bicycle crash	10 (8.1)
Pedestrian crash	9 (7.3)
Fall from height	21 (16.9)
Fall down stairs	13 (10.5)
Fall on the ground	1 (0.8)
Others	4 (3.2)
Vital signs on arrival, median, (Q1–Q3)	
Systolic blood pressure, mmHg	127 (111.8–146.5)
Heart rate, /min	89 (78.0–107.2)
Respiratory rate, /min	22 (20.0–27.0)
Temperature, °C	36.5 (36.0–36.8)
Glasgow Coma Scale	14 (12.75–15)
Shock on hospital arrival, n (%)	14 (11.2)
ISS, median, Q1–Q3	29 (19.0–38.0)
ISS >15, n (%)	105 (84.7)
Other thoracic injuries, n (%)	
Rib fracture	61 (49.2)
Pneumothorax	36 (29.0)
Hemothorax	47 (37.9)
Concomitant injury, n (%)	
Head/neck	76 (61.3)
Abdomen	33 (26.6)
Pelvis/lower extremities	49 (39.5)
Bilateral lung contusion, n (%)	104 (83.9)
Lung contusion volume, mL, median, (Q1–Q3)	294.5 (227.8–430.5)
Lung contusion volume, %, median, (Q1–Q3)	10.9 (7.6–15.0)
In-hospital mortality, n (%)	12 (9.7)

Note: Shock was defined as systolic blood pressure <90 mmHg.
Abbreviation: ISS, Injury Severity Score.

fibrinogen level within 24h of hospital arrival and lung contusion volume (coefficient –2.5, 95% CI –4.24 to –0.82, $p=0.004$). Multivariable linear regression analysis adjusted for potential confounders showed a statistically significant difference between the lowest serum fibrinogen level within 24h of hospital arrival and lung contusion volume (coefficient –1.6, 95% CI –3.16 to –0.07, $p=0.043$). Scatter plots were showed in Figure S2. There was no statistically significant association between the initial fibrinogen level on arrival and lung contusion volume in the univariable and multivariable linear regression analyses (coefficient –1.3, 95% CI –2.78 to 0.25, $p=0.104$; coefficient –0.5, 95% CI –2.04 to 0.96, $p=0.483$, respectively) (Table 3).

Sensitivity and specificity of lung contusion volume at a cutoff of 10% for fibrinogen depletion defined as a serum fibrinogen level of 150mg/dL within 24h of hospital arrival were 0.76 (95% CI, 0.60–0.88) and 0.55 (95% CI, 0.44–0.66), respectively. When the cutoff of 20% for the lung contusion volume was used, the sensitivity was 0.27 (95% CI, 0.14–0.43), and the specificity was 0.95 (95% CI, 0.88–0.99). When the cutoff value of 30% was used, the sensitivity was 0.12 (95% CI, 0.04–0.26) and the specificity was 1.0 (95% CI, 0.96–1.0) (Table 4).

TABLE 2 Coagulation test results and transfusion volume after arrival.

Characteristics	Total $n=124$
Coagulation test results, median, (Q1–Q3)	
Lowest fibrinogen level within 24h of hospital arrival, mg/dL	188.0 (131.5–232.5)
Initial fibrinogen level on hospital arrival, mg/dL	209.0 (174.5–241.0)
FDP on arrival, μg/mL	58.1 (19.1–114.0)
D-dimer on arrival, μg/mL	17.4 (5.7–34.8)
PT-INR on arrival	1.1 (1.0–1.2)
Transfusion administered within 24h, units, median, (Q1–Q3), ($n=43$)	
Red blood cell	10 (4–22)
Fresh frozen plasma	10 (6–27)
Platelet concentrate	0 (0–20)

Abbreviations: FDP, fibrinogen degradation products; PT-INR, prothrombin time international normalized ratio.

DISCUSSION

In this study, we examined patients with lung contusion volume assessed with CT scans performed in the emergency department and its association with coagulopathy. Lung contusion is a common injury in chest trauma, which increases mortality and accounts for approximately 25%–60% of mortality from blunt trauma.[2] Of the 124 patients diagnosed as having lung contusion in this study, 12 patients (9.7%) died. The rate of mortality in our study was lower than that in previous reports.[2] This may be because our study included patients regardless of ISS, therefore, included lower severity of the contusion and associated injuries than previous studies.

This study showed the association between lung contusion volume and serum fibrinogen levels, although the initial fibrinogen level in patients with lung contusion on hospital arrival had no statistically significant association with lung contusion volume. Increased lung contusion volume was independently associated with a lower serum fibrinogen level, and the fibrinogen level decreased after hospital arrival.

Lung injury refers to tissue damage in the lung, which causes histone release and neutrophil migration, resulting in inflammation of lung tissue.[25,26] In addition, previous literature suggested that in response to inflammatory stimuli triggered by trauma, tissue factors from alveolar epithelial cells may activate an extrinsic coagulation cascade that can cause fibrin deposition and fibrinogen depletion.[27] Similarly, as lung tissue factor is localized in alveolar epithelial cells, macrophages, and hyaline membrane, a past study showed that acute traumatic coagulopathy can be caused by the release of tissue factors from

TABLE 4 Sensitivity and specificity of lung contusion associated with serum fibrinogen level cutoff value of 150mg/dL.

Lung contusion volume, %	Sensitivity (95% CI)	Specificity (95% CI)
10	0.76 (0.60–0.88)	0.55 (0.44–0.66)
20	0.27 (0.14–0.43)	0.95 (0.88–0.99)
30	0.12 (0.04–0.26)	1.00 (0.96–1.00)

Abbreviation: CI, confidence interval.

TABLE 3 Associations of lung contusion percentage with outcomes by univariable and multivariable linear regression analyses.

	Unadjusted estimates			Adjusted estimates		
Outcomes	Coef.	95% CI	*p* Value	Coef.	95% CI	*p* Value
Lowest fibrinogen level within 24h of hospital arrival, mg/dL	–2.5	–4.24 to –0.82	0.004	–1.6	–3.16 to –0.07	0.043
Initial fibrinogen level on hospital arrival, mg/dL	–1.3	–2.78 to 0.25	0.104	–0.5	–2.04 to 0.96	0.483

Note: The model was adjusted for age, sex, head/neck injury, abdominal injury and pelvis/lower extremities injury, shock on hospital arrival (systolic blood pressure <90mmHg), severe trauma (injury severity score >15), and transfusion of fresh frozen plasma.

Abbreviations: Coef., coefficient; CI, confidence interval.

the injured lung parenchyma when a lung contusion occurs.[27] A difference in the delay in the decrease in serum fibrinogen levels measured on hospital arrival and those measured within 24h of hospital arrival was seen in our study and might be attributable to a gradual progression of coagulation and inflammatory response. A previous report indicated that intravenous contrast extravasation in severe lung contusions was associated with higher mortality.[28] Contrast extravasation in lung contusion suggests ongoing hemorrhage and the potential formation of a large hematoma, contributing to acute traumatic coagulopathy and a poorer outcome. Nevertheless, we included all patients with lung contusion, irrespective of contusion volume, and not all cases underwent contrast-enhanced CT scanning. Consequently, information on contrast extravasation in lung contusion was not collected in our study. Lung contusion volume, however, could serve as a valuable indicator, as it can be measured using CT images regardless of contrast enhancement.

In this study, an increase of lung contusion volume was associated with a decrease in the lowest serum fibrinogen level measured within 24h of hospital arrival, which may result in worsening of bleeding, the requirement for blood transfusion, and increased mortality in patients with severe trauma.[29] When treating blunt trauma patients with lung contusions, measuring the volume of the lung contusion may be beneficial, as fibrinogen depletion may develop into progression of coagulopathy.

To identify fibrinogen depletion of 150mg/dL or lower, we calculated the sensitivity and specificity of lung contusion volume. To detect a serum fibrinogen level of 150mg/dL or lower, the cutoff value of 20% or greater in lung contusion volume showed a specificity of more than 95%. Wang et al. mentioned it was feasible to calculate lung contusion volume by CT in the emergency department, and they showed that a lung contusion volume of >20% was significantly more likely to result in acute respiratory distress syndrome.[30] Our findings indicated that it may also be clinically useful to assess the volume of pulmonary contusions. Mitra et al. presented the COAST (COAgulopathy in Severe Trauma) score for the assessment of coagulopathy in trauma patients in prehospital situations, which included chest decompression as one of the parameters, although its specificity was low.[13] The present study showed more than 95% specificity when using a cutoff value of 20% lung contusion volume, which may be useful in identifying coagulopathy.

Our findings suggest that when treating blunt trauma patients with lung contusions, measuring lung contusion volume from the initial CT scan may help identify patients with the potential for progression of fibrinogen depletion and trigger early treatment for acute traumatic coagulopathy. We expect that this approach may contribute not only to predicting transfusion requirements but also to preventing deteriorating coagulopathy and improving it at an early stage of trauma care through prompt administration of FFP.

This study has several limitations. First, it is a single-center, retrospective study, and the small number of cases did not allow generalization of our results and limited explorative subgroup analysis; thus, a multicenter study would be desirable. Second, patients with lung contusion may have a complication of pneumonia, which may result in misclassification of the lung contusion. However, since we used measurement with three-dimensional volume analysis software with manual adjustments by more than two board-certified attending physicians and considering the patient's history such as fever and dyspnea before the injury happened, and the degree of elevation of inflammatory values, we believe that the misclassification was minimized. Third, fibrinogen values were assessed at the lowest level within 24h of hospital arrival, and trauma management, including the administration of FFP, could have affected the lowest value of fibrinogen. However, we considered such an overestimation of the lowest serum fibrinogen level would bias our results toward the null. Moreover, we did not include potential confounding factors in our study, such as hemodilution, hypothermia, and acidemia, as highlighted in a previous review.[24] Although the review described that hemodilution and hypothermia may act as intermediary factors following resuscitation in the causal pathway of trauma-induced coagulopathy, and acidemia and hypothermia may act as intermediary factors following shock, rather than potential confounders, this issue could affect our results. In addition, we could not collect sufficient information on relevant past medical history, such as liver diseases and medication, such as anticoagulants, because of the retrospective nature of our study. This could affect our results.

CONCLUSIONS

In this study, among blunt trauma patients with lung contusion, lung contusion volume was significantly associated with the lowest serum fibrinogen level measured within 24h of hospital arrival. When treating blunt trauma patients with lung contusions, measurement of lung contusion volume from the initial CT scan may help to identify patients with the potential for progression of fibrinogen depletion and trigger early treatment for acute traumatic coagulopathy. More extensive prospective studies are required to clarify the relationship between lung contusion and coagulopathy and how it would affect patient outcomes.

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CONFLICT OF INTEREST STATEMENT

Dr. Hiroshi Ogura and Dr. Takeshi Shimazu are the Editorial Board members of AMS Journal and the co-authors of this article. Also, Dr. Jun Oda is the Editor-in-Chief of the journal. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. Peer-review was handled independently by AMS Journal editorial office and Dr. Kuwagata as the Editor to minimize bias.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol: This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The institutional ethics committee at Osaka University approved this study and waived the requirement for informed consent (approval no. 20150).

CONSENT FOR PUBLICATION

This study got consent for publication from patients or patients' families when they were admitted to our center.

NOTATION OF PRIOR ABSTRACT PUBLICATION/PRESENTATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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