Serum CD5L predicts acute lung parenchymal injury and acute respiratory distress syndrome in trauma patients

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Abstract
Cluster of differentiation 5 antigen-like (CD5L), derived from alveolar epithelial cells partly, is a secreted protein. It is shown that CD5L is associated with lung inflammation and systemic inflammatory diseases, but the relationship between CD5L and trauma-related acute lung parenchymal injury (PLI), acute lung injury or acute respiratory distress syndrome (ARDS) is unclear. This study aims to explore the value of serum CD5L levels in predicting trauma-associated PLI/ARDS and its potential clinical significance.

This is a prospective observational study, and a total of 127 trauma patients were recruited from the emergency department (ED), and among them, 81 suffered from PLI/ARDS within 24 hours after trauma, and 46 suffered from trauma without PLI/ARDS. Fifty healthy subjects from the medical examination center were also recruited as controls for comparison. The serum CD5L level was measured within 24 hours of admission. The receiver operating characteristic analysis and logistic regression analysis were used to identify the correlation between high CD5L and trauma associated-PLI/ARDS within 24 hours following trauma.

The trauma associated-PLI/ARDS subjects showed a significantly higher level of serum CD5L on emergency department admission within 24 hours after trauma compared with its level in non-trauma associated-PLI/ARDS subjects and healthy subjects. The initial CD5L concentration higher than 150.3 ng/mL was identified as indicating a high risk of PLI/ARDS within 24 hours following trauma (95% confidence interval: 0.674–0.878; P < .001). Moreover, CD5L was an independent risk factor for trauma associated-PLI/ARDS within 24 hours following trauma.

CD5L could predict PLI/ARDS within 24 hours following trauma.

Abbreviations: ALI = acute lung injury, ALT = alanine aminotransferase, APACHE II = acute physiology and chronic health evaluation II, ARDS = acute respiratory distress syndrome, AST = aspartate aminotransferase, AUC = area under the curve, CD5L = cluster of differentiation 5 antigen-like, CI = confidence interval, CT = computed tomography, ED = emergency department, FiO2 = inspired oxygen fraction, ISS = injury severe score, OR = odds ratio, PaO2 = partial pressure of oxygen, PLI = lung parenchymal injury, PMN = neutrophils, ROC = receiver operating characteristic.

Keywords: CD5L, risk factor, trauma associated-PLI/ARDS

1. Introduction
More than 5 million deaths are caused by trauma each year worldwide. Trauma victims face a secondary cascade of prolonged systemic inflammation often leading to the occurrence of systemic inflammatory response syndrome, which may result in organ dysfunction and consequent death or long-term morbidity. Despite considerable progress in the strategies for an early management of trauma, an organ dysfunction syndrome such as acute respiratory distress syndrome (ARDS) often complicates the clinical outcome of these patients and represents a significant obstacle in health improvement after treatment.

The acute phase of ARDS is characterized by an uncontrollable inflammatory reaction in the lung tissue, and a large number of neutrophils (PMN), macrophages, and other inflammatory cells accumulate in the alveolus. Acute lung injury (ALI) and ARDS are characterized by a disruption of the epithelial barrier and endothelium followed by an imbalance of the coagulation and fibrinolysis systems.

Studies have shown that ARDS caused by trauma has a better clinical outcome than ALI caused by other risk factors. Therefore, some authors have proposed that the causes of ALI should be stratified. The probability of ARDS in trauma patients is 29% within 24 hours, and on the fifth day after trauma, more than 90% of patients have ARDS. The study divided trauma-associated ARDS into early-onset phenotypes and late-onset phenotypes. The
2 phenotypes are different in many factors. But in terms of mortality, there is no significant statistical difference between them. The current diagnosis of ARDS is based on the Berlin standard, mainly based on the patient’s arterial blood gas analysis, combined with the patient’s chest imaging. But the patient’s arterial blood is more difficult to obtain than venous blood.

Computed tomography (CT) is the standard for diagnosing lung parenchymal injury (PLI) and chest trauma, and assessing the risk of complications. Although CT can diagnose PLI immediately, the degree of damage of PLI is still progressing, and the area of injury may continue to expand. Initially, mechanical damage to the lung parenchyma can cause diffuse intra-alveolar hemorrhage and alveolar rupture. In the next 1 to 2 hours, blood and exudate penetrate into the interstitium, and finally accumulate in the alveoli and interstitial spaces together with tissue fragments and inflammatory cells. The accumulation of exudate and inflammatory cells in the alveoli reached a peak in 24 to 48 hours after trauma. In addition, as the disease progresses, alveolar walls may become thicker due to edema and continuous bleeding of blood vessels. Therefore, lung tissue morphology is constantly changing and progressing. CT scans may not actually reflect clinical severity in a short time after trauma, and chest CT can more accurately diagnose PLI after 24 to 48 hours of trauma. However, some critically ill patients after multiple injuries may temporarily be unable to perform chest CT scans. In addition, CT exposes patients to potentially harmful ionizing radiation. Thus, identifying trauma patients at high risk for PLI/ARDS on emergency department (ED) admission within 24 hours following trauma could enhance decision making on choosing an appropriate therapy early.

Cluster of differentiation 5 antigen-like (CD5L), also known as apoptosis inhibitor of macrophage, is a member of the scavenger receptor cysteine-rich domain superfamily. It is a secreted protein, mainly expressed by macrophages in the organism, and alveolar epithelium cells are also identified as an additional cellular source of CD5L expression. This protein is involved in the development of a variety of inflammatory diseases, also playing a role in ALI, since its level in the serum rapidly increases during the first few days in the ALI animal model induced by lipopolysaccharides. Therefore, our speculation was that CD5L could predict PLI/ARDS within 24 hours following trauma.

2. Materials and methods

2.1. Participants

In this prospective study, a total of 127 trauma patients with damage of tissues and organs caused by various mechanical factors (car accidents, stab wounds, cuts, contusions) were enrolled at the ED between August 2019 and August 2020 (Fig. 1). In addition, the gender and age were matched with the trauma group, and 50 volunteers from the medical examination center were randomly included as a control group during the same period. The inclusion criterion was patients whose serum samples could be obtained within 24 hours following trauma, and the subjects of both genders should be in a range age of 18 to 80 years. Patients were excluded if they had any of the following conditions: patients who were re-hospitalized, patients who had a medical history of chronic lung disease, the blood sample was not collected within 24 hours following trauma (participants with missing data for each variable of interest were excluded); patients had a medical history of cancer, pneumonitis, sepsis, liver fibrosis, atopic dermatitis autoimmune disease (including systemic lupus erythematosus and rheumatoid arthritis). The Berlin definition of ARDS events was used based on acute onset within 24 hours, bilateral pulmonary infiltrates.

![Figure 1. Details of subject enrollment and reason for exclusion from the present study. Participants with missing data for each variable of interest were excluded (n=24). ARDS = acute respiratory distress syndrome, ED = emergency department, PLI = lung parenchymal injury.](image-url)
consistent with pulmonary edema, impaired oxygenation (partial pressure of oxygen [PaO2]/inspired oxygen fraction [FiO2] ratio <300mmHg), and impaired oxygenation not fully explained by cardiac failure.[34] The diagnosis of PLI is mainly based on the imaging (CT) manifestations of the patient at the time of admission. The imaging that showed lung contusion, pneumothorax, increased exudation of single or multiple lung lobes, fluid chest, fluid pneumothorax are all diagnosed as PLI. Eighty-one traumatic subjects suffering from trauma associated-PLI/ARDS group, while 46 traumatic subjects suffered from trauma without PLI/ARDS. Forty-eight patients suffered from mild trauma (injury severe score [ISS] ≤16), and 79 patients suffered from moderate or severe trauma (ISS >16) based on the ISS.

2.2. Ethics

Our study was approved by the scientific and ethics committee of the First Affiliated Hospital of Chongqing Medical University (No. 2020-348). Informed consent was obtained from all the enrolled subjects or their relatives.

2.3. Sample collection

The peripheral blood sample was collected from 127 traumatic subjects within 24 hours on the day of admission to the ED and 50 healthy subjects used as controls from the medical examination center. The blood sample was placed in glassware and the particle part was separated by centrifugation at 1000g for 20 minutes at room temperature to obtain the serum, which was frozen at −70°C until analysis.

2.4. Data collection

Clinical and demographic characteristics, including age, gender, vital signs on ED arrival were recorded. Ventilation and vasopressors were used during the follow-up, and Glasgow Coma Scale score 3 to 15, ISS, and acute physiology and chronic health evaluation II (APACHE II) were assessed within 24 hours following trauma. ARDS is based on clinical data, and it was diagnosed based on the Berlin criteria.[34] ARDS was diagnosed on the basis of arterial blood gas analysis and CT scan performed at admission.

2.5. Quantification of CD5L levels and clinical data

Serum CD5L concentration was measured in duplicate using the commercial enzyme linked immunosorbent assay kit following the manufacturer’s instructions. Arterial blood gas analysis, blood routine analysis, and coagulation were measured in all subjects upon the ED admission. The serum levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine were detected by a Roche Modular DDP automatic biochemical analyzer and Roche Diagnostics reagents (Roche, GER). Lactate was measured by a blood-gas analyzer (GEM3000, Beckman, USA). Coagulation was detected by Stago. Routine blood test and blood gas analysis were performed in the clinical laboratory of the hospital.

2.6. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (Version 25, IBM Corp., Armonk, NY, USA). The categorical variables are presented as percentages, and the continuous variables are expressed as mean ± standard deviation if normally distributed, otherwise, parameters are presented as median and interquartile range. The Chi-Square test was used for the comparison of the categorical data. Mann–Whitney U test and the Kruskal Wallis test were used for the comparisons of 2 or multiple groups, respectively. The Spearman correlation coefficient was computed to evaluate the correlations. The receiver operating characteristic (ROC) curve and area under the curve (AUC) were drawn to evaluate the predictive value of CD5L in the diagnosis of trauma associated-PLI/ARDS. The cutoff values were based on the point of the maximum sum of sensitivity and specificity. The multivariate logistic regression model was carried out to demonstrate that the high CD5L level was a risk factor in the development of trauma associated-PLI/ARDS within 24 hours of trauma. P values less than .05 were considered statistically significant.

3. Results

3.1. Characteristics of trauma patients and healthy subjects

There were 127 trauma victims enrolled in this study. Demographic characteristics and clinical data of trauma group and healthy group were described in Table 1. No significant
difference in age ($P = .098$) and gender ($P = .498$) was observed between the trauma and healthy group. However, the concentration of hemoglobin, platelets count, hematocrit, and the level of creatinine were significantly lower in patients who suffered trauma. Moreover, in trauma patients, white blood cell count, bilirubin, ALT, and AST were higher than our healthy group ($P < .001$).

### 3.2. CD5L were higher in subjects who suffered severe trauma

In Figure 2, a comparison of serum CD5L concentrations between uninjured and injured patients stratified by clinical severity is shown. CD5L levels were significantly higher in severe traumatic subjects ($P < .001$). Significant differences of serum CD5L levels on admission were found between the 3 groups ($P < .001$). ROC curve identified the concentration of CD5L as a biomarker to discriminate between mild trauma victims and moderate/severe trauma victims with an AUC of 0.644 (95% confidence interval [CI]: 0.542–0.747; $P < .05$). The ROC curve is presented in Figure 3.

### 3.3. CD5L was higher in subjects who developed PLI/ARDS on ED admission

A total of 81 trauma patients suffered from PLI/ARDS on ED admission. The serum CD5L level in the trauma associated-PLI/ARDS group, non-trauma associated-PLI/ARDS group, and healthy group is shown in Figure 4, which shows the statistically significant difference among the 3 groups ($P < .001$). To further demonstrated the predictive value of CD5L for trauma associated-PLI/ARDS, the ROC was created, which allowed to discriminate between trauma associated-PLI/ARDS on ED admission and non-trauma associated-PLI/ARDS patients with an AUC of 0.798 (95% CI: 0.674–0.878; $P < .001$). A cutoff value of 150.3 ng/mL CD5L resulted in a sensitivity of 0.642 and a specificity of 0.761 (Fig. 5).

### 3.4. Correlation between CD5L and clinical data

The serum CD5L value of all the enrolled subjects has a weak correlation with the ISS ($r = 0.286, P = .001$, Fig. 6A). However, a weak but significant correlation ($r = 0.395, P < .001$, Fig. 6B) was observed between the level of serum CD5L and APACHE II score. The serum CD5L level showed a weak and negative correlation with the PaO2/FiO2 ($r = -0.300, P = .001$, Fig. 6C). Moreover, a correlation ($r = 0.609, P < .001$, Fig. 6D) was observed between CD5L and the value of the percentage of PMN.

### 3.5. Serum CD5L level was independently related to trauma associated-PLI/ARDS development on ED admission

Demographic and clinical data of trauma patients who did or did not suffer from PLI/ARDS on ED admission are presented in...
Table 2. The univariate analysis revealed that the risk factors for PLI/ARDS that were statistically significant (P < 0.05) were the following: ISS, pulse, mechanical ventilation, pondus hydrogeni, blood base excess, percentage of PMN, hematocrit, ALT, AST, prothrombin time, international normalized ratio, D dimer, fibrin degradation products, APACHE II, and CD5L. The multivariate logistic regression analysis revealed that the risk factors related with the trauma associated-PLI/ARDS on ED admission were ISS score (odds ratio [OR] 1.098 per 1-unit score increase; 95% CI: 1.022–1.180), serum CD5L level (OR 1.008; 95% CI: 1.002–1.013), D-dimer level (OR 1.072; 95% CI: 1.015–1.133) (Table 3). In particular, these results demonstrated that the ISS score, the serum CD5L level, and the D-dimer level were also independent risk factors of trauma associated-PLI/ARDS.

4. Discussion

This study revealed that the serum CD5L level within 24 hours following trauma was increased among trauma victims, especially in trauma associated-PLI/ARDS group on ED admission. Previous studies demonstrated that trauma victims diagnosed with ARDS have a higher overall injury severity score.[35,36] Although the CD5L level in moderate/severe trauma...
patients was significantly higher than that in the mild trauma ones, the CD5L level was not correlated with the ISS score. Importantly, the level of CD5L in trauma patients who suffered from PLI/ARDS on ED admission was higher than that in non-trauma associated-PLI/ARDS group, and the level of CD5L showed a weak and negative correlation with PaO2/FiO2. Thus, our results demonstrated the association between trauma associated-PLI/ARDS and serum CD5L. One study reported that the disturbance in the coagulation and fibrinolytic system is also one of the pathogenesis of ARDS in its acute phase.\textsuperscript{114}

Most studies have also confirmed that trauma severity is a risk factor for trauma-associated ARDS. We also found that ISS score is an independent risk factor for trauma-associated PLI/ARDS. Studies have shown that patients with ARDS within 24 hours of trauma have a higher overall trauma severity.\textsuperscript{33,36} This study shows that among trauma patients, there are significant differences between severe trauma and mild trauma in lung injury, ARDS, mechanical ventilation, whether to perform tracheal intubation, and other related respiratory complications. Studies have found that the serum free form of CD5L increased in the mouse model of ALL, and the lung tissue CD5L gene expression increased.\textsuperscript{133} Our study showed that compared with healthy volunteers, the serum CD5L level of trauma patients increased within 24 hours after trauma ($P$$<$.001), and the serum CD5L level of severe trauma patients was higher than that of mild

| Variable                  | OR (95%CI) | $P$ value |
|---------------------------|------------|-----------|
| ISS                       | 0.110      | 1.117 (1.043–1.196) | .002 |
| D-dimer                   | 0.064      | 1.066 (1.016–1.119) | .01 |
| CD5L                      | 0.008      | 1.008 (1.003–1.014) | .003 |

### Table 3

Multivariable model of risk factors related with trauma associated-PLI/ARDS.

| Variable                  | B         | OR (95%CI) | $P$ value |
|---------------------------|-----------|------------|-----------|
| ISS                       | 0.110     | 1.117 (1.043–1.196) | .002 |
| D-dimer                   | 0.064     | 1.066 (1.016–1.119) | .01 |
| CD5L                      | 0.008     | 1.008 (1.003–1.014) | .003 |

ARDS = acute respiratory distress syndrome; CD5L = cluster of differentiation 5 antigen-like; CI = confidence interval; ISS = injury severity score; OR = odds ratio; PLI = lung parenchymal injury.
Kornblith et al[35] pointed out that CD5L can involve in the pathogenesis of ARDS.[17] Although our study shows that the concentration of D-dimer and fibrin degradation products in trauma-associated PLI/ARDS patients is higher than that in non-traumatic-associated PLI/ARDS patients, there is no clear relationship between CD5L levels and D-dimer or FDP. Kornblith et al[35] pointed out that CD5L can involve in the inflammatory response during ALI by activating a lipid mediator.

Our research shows that CD5L is related to the percentage of PMN. PMN participate in trauma associated-ARDS and can activate the coagulation system. Trauma can activate the nicotinamide adenine dinucleotide phosphate oxidase complex of PMN to enhance oxygen bursts. Traumatic shock and traumatic coagulopathy induce the production of reactive oxygen species in a C5a-dependent manner, resulting in the loss of the endothelial barrier and organ damage.[17] Therefore, we speculated that CD5L might be an inflammatory mediator participating in the development of PLI/ARDS within 24 hours following trauma on ED admission. The pathogenesis of CD5L and PMN in coagulation abnormalities and ARDS caused by trauma is still unclear, and the correlation between them needs to be further studied.

It is demonstrated that the second, smaller peak of death following trauma in the first 24 hours normally due to hypoxia, hypovolemia, or severe head trauma. After the first 24 hours, there is a high risk of the development of immunological dysfunction or systemic inflammatory response syndrome and subsequently sepsis.[2] So we speculate that trauma patients are less likely to develop sepsis in the first 24 hours after trauma. Therefore, in order to exclude the influence of sepsis as a confounding factor, we only set up a single time point of trauma within 24 hours.

Furthermore, the initial CD5L concentration higher than 150.3 ng/mL indicated a high risk of PLI/ARDS on ED admission following trauma, suggesting that the higher concentration of initial CD5L was correlated with a higher risk of PLI/ARDS after trauma. In addition, the correlation was not reduced in the multivariate logistic regression analysis. Collectively, our results suggested that the serum CD5L level could represent a predictive value for trauma associated-PLI/ARDS.

Although previous studies only showed that the serum CD5L level was increased among patients with sepsis,[3,8,9] and with pneumonia[40] they did not consider the changes in the serum CD5L level in the PLI/ARDS caused by these diseases. Our study takes into account the confounding factor of the ARDS caused by these infection diseases, so patients with pneumonia and sepsis are excluded.

This work has some limitations. Our study considered only trauma associated-PLI/ARDS, but not other risk factors of ARDS including sepsis, pneumonia, and shock.[41] Moreover, the subsequent changes in serum CD5L level in trauma patients were not clear in the following days. Further research should be done to determine the dynamic changes of serum CD5L levels in trauma patients at multiple time points during hospitalization. Thus, a prospective analysis with a longer follow-up should be performed to elucidate the significance of CD5L as an independent risk factor for predicting PLI/ARDS following trauma in a long term. In addition, from a clinical point of view, CD5L, as a biomarker for diagnosing trauma-related PLI/ARDS, does not seem to have high specificity and sensitivity, and is not sufficient as a main method for diagnosing trauma-associated PLI/ARDS. Our study is a single-center study. Trauma patients are in serious condition, so there is a certain degree of bias. In addition, in the past few decades, we have not succeeded in reducing the mortality of ARDS patients. The study did not focus on the treatment of the cause of ARDS, and provided effective information for the pathogenesis of ARDS and possible therapeutic targets. Moreover, due to the small number of cases in this study, it was not possible to study patients who died from trauma-related PLI/ARDS. Therefore, to fully understand the role of CD5L in trauma-related PLI/ARDS patients, further animal and clinical studies are needed to evaluate its underlying mechanism.

In conclusion, our findings demonstrated that CD5L could predict trauma associated-PLI/ARDS on the day of ED admission within 24 hours following trauma. High serum CD5L level was related with high risk of PLI/ARDS following trauma on ED admission.

Author contributions

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