Investigation of surfactant protein-D and interleukin-6 levels in patients with blunt chest trauma with multiple rib fractures and pulmonary contusions: a cross-sectional study in Black Sea Region of Turkey

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ABSTRACT

Objective: Multiple rib fractures (RFs) and pulmonary contusions (PCs), with resulting systemic lung inflammation, are the most common injuries caused by blunt chest trauma (BCT) in motor vehicle accidents. This study examined levels of the inflammation marker interleukin (IL)-6 and those of the acute-phase reactant surfactant protein (SP)-D in patients with BCT.

Design: Prospective, cross-sectional, observational study.

Setting: Single-centre, tertiary care hospital in the Black Sea Region of Turkey.

Participants: The study included 60 patients with BCT who were hospitalised in our thoracic surgery department.

Parameters measures: The SP-D and IL-6 serum levels of patients with RFs (two or more RFs) (n=30) and patients with PCs (n=30) were measured after 6 hours, 24 hours and 7 days, and compared with those of age-matched and gender-matched healthy participants.

Results: The 6-hour serum SP-D levels of the RFs (p=0.017) and PCs (p<0.001) groups were significantly higher than those of the healthy controls. The 24-hour and 7-day SP-D levels of both groups were also higher than the control group. The serum IL-6 levels of both groups were significantly higher than those of the control group. We have found Injury Severity Score to be independently related to 6-hour IL-6 (β=1.414, p<0.001) and 24-hour IL-6 levels (β=1.067, p<0.001). The development of complications was independently related to 6-hour SP-D level (β=0.211, p=0.047).

Conclusions: RFs and PCs after BCT lead to local and systemic inflammation due to lung injury. The levels of the systemic inflammation marker IL-6 and those of the acute-phase reactant SP-D were elevated in the present study. The SP-D level may be used as a marker in the follow-up of BCT-related complications.

INTRODUCTION

Blunt chest trauma (BCT) accounts for 10–15% of all traumas and is responsible for 25% of traumatic deaths. BCT occurs mostly due to traffic accidents (ie, collisions with vehicles or pedestrians), work accidents and violence. Multiple rib fractures (RFs) are the most common injury due to BCT. These result in injury to the large vessels, head-neck, intrathoracic region and its vascular structures, and the spleen, liver and kidney. Even without these concomitant injuries, an isolated RF leads to pain, followed by atelectasis, which is an important cause of morbidity.

A pulmonary contusion (PC) refers to an injury of the lung interstitium and alveoli, without tissue lacerations. They are most often the result of BCT and have a mortality rate of 25–50%. PCs have been observed in 35% of cases, without deformities in the bone of the chest wall. PCs are the most...
commonly seen and life-threatening injuries due to BCT. With regard to its pathophysiology, PCs are thought to lead to the absorption of kinetic energy secondary to trauma of the rigid chest wall. The transmission of this energy to the surface of the lung results in stretching of alveoli due to positive pressure, collection of fluid in the lungs and haemorrhage within the interstitial space due to rupture of alveolar-capillary membranes and infiltration of polymorphonuclear leukocytes (PMNLs). The segmental lung injury, ventilation/perfusion mismatch, increased intrapulmonary shunting and high levels of lung tissue fluids lead to lung dysfunction. In severe injuries, increased mucus, decreased surfactant, increased capillary passage, filling of bronchi with blood and oedematous fluid lead to consolidation and atelectasis of neighbouring lung tissues. The severity of the trauma (ie, minimal consolidation, acute lung injury (ALI), or severe acute respiratory distress syndrome (ARDS)) determines local and systemic responses; depending on the severity, there is a wide spectrum of morbidity and mortality.

Surfactant that covers the surface of lung alveoli is released from type II pneumocytes. This surfactant provides favourable gas exchange by reducing the alveolar surface tension and preventing collapse of the alveoli. In the absence of surfactant or in the presence of a low level of surfactant, the permeability of the pulmonary capillary membrane of the alveoli increases, leading to ARDS. Surfactant is composed of A, B, C, and D protein subtypes. Surfactant protein (SP)-B and SP-C are known to have a protective effect in lung tissue. SP-A and SP-D are released from type II pneumocytes and Clara cells as acute-phase reactants, especially in response to infective agents to maintain host defence of the upper airways.

Besides the lungs, SP-D is released from many other tissues including stomach, intestinal mucosa, pancreas, heart, most of the exocrine glands and epithelial cells of the body.

The production of interleukin (IL)-6—a potent proinflammatory cytokine—increases after thoracic trauma leading to migration of inflammatory cells such as PMNLs to damaged lung tissues secondary to increased systemic inflammatory response. PMNLs increase the production of reactive oxygen species, IL-6 and other cytokines leading to further lung tissue damage and may delay the healing of damaged lung tissue. An experimental study has shown the level of IL-6 to be significantly elevated in lung homogenates and plasma after 2 hours of lung trauma. IL-6 has been reported to play an active role in the development of PC by increasing the inflammation.

The aim of this study was to investigate whether IL-6, a systemic inflammatory marker, and SP-D, an acute-phase reactant, were useful parameters in the follow-up of patients with BCT by measuring their levels at different times after BCT in patients with RFs and PCs.

**MATERIALS AND METHODS**

This study was carried out at the Department of Chest Surgery of the Faculty of Medicine, and it was conducted between October 2012 and October 2013. It comprised 60 patients with RFs and PCs who were hospitalised due to BCT. The exclusion criteria included tracheobronchial injuries, those who underwent thoracotomy due to BCT or had video-assisted thoracoscopic surgery (VATS), those who were mechanically ventilated in the emergency department on arrival or later and those who were admitted to the hospital for >1 hour after the trauma. Ethical approval was obtained (Recep Tayyip Erdogan University, approval no: 2012/129) and written informed consent was obtained from the patients for publication of this report and any accompanying images.

The patients were divided into two groups according to the form of lung injury: group 1 included the patients with two or more RF who had no PC (n=30) and group 2 included the patients with PC who had no RF (n=30). An age-matched and sex-matched control group was selected from healthy participants (n=30). Blood samples were taken from the patients 6 hours, 24 hours and 7 days after the trauma, and the levels of SP-D and IL-6 were measured. The blood samples obtained after 6 hours were drawn without fasting, whereas the 24-hour and 7-day samples were obtained after an overnight fast, centrifuged within 1 hour at 2500×g for 10 min to isolate the serum, followed by storage at −80°C. All the samples were tested in a biochemical laboratory on the same day.

The patients’ data were analysed according to age, gender, trauma type, aetiology of the trauma, thoracic and extrathoracic injuries and morbidity but not mortality as none of the patients died.

**The diagnosis of PC and Injury Severity Score**

Injury Severity Score (ISS) of the patients was calculated using a well-known method. CT scan of the chest may show nodular or ground-glass opacities that do not respect the peripheral lung boundaries, diffuse areas of ground-glass opacities in the upper lobes with subpleural sparing and multiple areas of consolidations with air bronchograms. The production of interleukin (IL)-6—a potent proinflammatory cytokine—increases after thoracic trauma leading to migration of inflammatory cells such as PMNLs to damaged lung tissues secondary to increased systemic inflammatory response. PMNLs increase the production of reactive oxygen species, IL-6 and other cytokines leading to further lung tissue damage and may delay the healing of damaged lung tissue. An experimental study has shown the level of IL-6 to be significantly elevated in lung homogenates and plasma after 2 hours of lung trauma. IL-6 has been reported to play an active role in the development of PC by increasing the inflammation.

The aim of this study was to investigate whether IL-6, a systemic inflammatory marker, and SP-D, an acute-phase reactant, were useful parameters in the follow-up of patients with BCT by measuring their levels at different times after BCT in patients with RFs and PCs.
intra-assay and interassay CV were 4.9% and 7.3%, respectively. The sensitivity was calculated as 0.008 ng/mL.

Statistical analysis
All statistical analyses were performed using the SPSS programme, V.18.0 (IBM, Chicago, Illinois, USA). The results are given as the mean±SD. The homogeneity of the groups’ data was analysed using the Kolmogorov-Smirnov test. All the groups were homogeneous. A two-by-two comparison of the RFs, PCs and control groups was performed by the Student’s t-test. A paired t-test was used for the RFs and PCs within-group comparisons of the 6-hour, 24-hour and 7-day serum IL-6 and SP-D levels. Correlation analysis was performed using Pearson’s correlation test. By using stepwise multivariate regression analysis; parameters that were independently associated with dependent variables of hospitalisation duration, ISS and complications development were analysed. A p value of <0.05 was considered significant.

RESULTS
The mean age of the RFs group and PCs group was 53.6±15.8 and 54.6±17.2 years, respectively. The mean age of the control group was 55.1±8.8 years. The gender, smoking habits and presence of chronic disease were similar in the three groups. The types of trauma in the PCs and RFs groups were similar. Tube thoracostomy treatment was applied in most of the PCs group, whereas conservative treatment was applied in the RFs group. However, they were not statistically significant. There were no complications in the vast majority of patients with RFs and PCs. The sociodemographic characteristics of the three groups and the treatment and complication characteristics of the RFs and PCs groups are shown in table 1. ISS of RFs and PCs groups were similar (p=0.105). The regions of extrathoracic trauma and ISS of RFs and PCs groups are shown in table 2 (all p>0.05).

The 6-hour serum levels of SP-D in the RFs and PCs groups were significantly higher than those of the healthy control group. The 24-hour and 7-day SP-D levels of both groups were higher than the basal SP-D levels of the control group. The comparison of the 6-hour, 24-hour and 7-day SP-D levels of the PCs and RFs groups showed that they were higher in the PCs group, but the difference was not statistically significant (all p>0.05). The comparison of the SP-D levels of the RFs

| Table 1 | Sociodemographic characteristics of the patients with BCT and the control group and symptoms associated with the trauma of group BCT |
|---------|---------------------------------------------------------------------------------|
| **Background** | **Control n=30** | **RF (n=30)** | **PC (n=30)** | **p Value** |
| Age | 55.1±8.8 | 53.6±15.8 | 54.6±17.2 | 0.923 |
| Gender (M/F) | 22/8 | 23/7 | 25/5 | 1.000 |
| Comorbidities | | | | |
| Diabetes mellitus | 1 | 3 | 1 | 0.262 |
| Hypertension | 5 | 7 | 7 | 0.529 |
| Tuberculosis | 0 | 0 | 1 | 1.000 |
| Smoking (n) | 10 | 15 | 11 | 0.190 |
| Smoking (pack/day) | 15.3±18.3 | 13.1±20.1 | 17.3±20.0 | 0.425 |
| Hospital length of stay | 8.5±2.9 | 9.2±2.2 | 3.266 |
| Type of trauma | | | | |
| Falls | 17 | 19 | 0.867 |
| Motor vehicle interior | 9 | 4 | 0.216 |
| Motor vehicle exterior | 3 | 6 | 0.318 |
| Assault | 1 | 1 | 1.000 |
| Other types of chest trauma | | | | |
| No | 21 | 17 | 0.715 |
| Pneumothorax | 4 | 5 | 0.966 |
| Haemothorax | 2 | 5 | 0.810 |
| Haemopneumothorax | 3 | 3 | 1.000 |
| Localisation (right/left) | 11/19 | 15/15 | 0.311 |
| Thoracic trauma treatment modality | | | | |
| Conservative | 26 | 21 | 0.777 |
| Tube thoracostomy | 3 | 9 | 0.126 |
| Pleurocan drainage | 1 | 0 | 0.553 |
| Complications | | | | |
| No | 26 | 25 | 0.997 |
| Atelectasis | 2 | 3 | 0.668 |
| Pneumonia | 2 | 1 | 0.903 |
| Pleural effusion | 0 | 1 | 0.589 |

BCT, blunt chest trauma; PC, pulmonary contusions; RF, multiple rib fractures.
and PCs groups with the basal level revealed that these were lower after 6 hours, 24 hours and 7 days, but the difference was not significant (all \( p > 0.05 \)). The SP-D levels of the RFs and PCs groups are shown in Table 3. The 6-hour SP-D levels of all the groups are shown in Figure 1.

The serum level of IL-6 was significantly higher in the RFs and PCs groups than in the control group. The 6-hour IL-6 level of the PCs group was higher than that of the RFs group. The 24-hour and 7-day IL-6 levels of the PCs group were higher than those of the RFs group, and the difference was statistically insignificant. In both groups, the 6-hour IL-6 level was significantly higher than the 24-hour and 7-day levels. The details on the IL-6 levels are presented in Table 3, and the 6-hour IL-6 levels of the groups are shown in Figure 2.

ISS had positive correlation with 6-hour SP-D (\( r=0.333, \ p=0.001 \)), 24-hour SP-D (\( r=0.297, \ p=0.005 \)), 7-day SP-D (\( r=0.349, \ p=0.001 \)), 6-hour IL-6 (\( r=0.461, \ p<0.001 \)), 24-hour IL-6 (\( r=0.322, \ p=0.002 \)) and 7-day IL-6 levels (\( r=0.208, \ p=0.050 \)). The 6-hour SP-D level showed a strong positive correlation with the 6-hour IL-6 (\( r=0.705, \ p<0.001 \)) and 24-hour IL-6 levels (\( r=0.462, \ p<0.001 \)) and 24-hour IL-6 levels (\( r=0.474, \ p<0.001 \)). The SP-D level on day 7 was also strongly correlated with the 6-hour IL-6 (\( r=0.282, \ p=0.029 \)) and 24-hour IL-6 levels (\( r=0.305, \ p=0.018 \)).

Stepwise multivariate regression analyses have shown that the complications development (\( \beta=0.392, p=0.016 \)) and the age of the patient (\( \beta=0.245, p=0.049 \)) to be independently related to hospitalisation duration. We have found also ISS to be independently related to 6-hour IL-6 (\( \beta=1.414, p<0.001 \)) and 24-hour IL-6 levels (\( \beta=1.067, p<0.001 \)). The development of complications was independently related to ISS (\( \beta=0.263, p=0.014 \) and 6-hour SP-D level (\( \beta=0.211, p=0.047 \)). Smoking/non-smoking, gender, the presence of comorbidities such as diabetes mellitus, hypertension and tuberculosis had not any relation with hospitalisation duration, ISS and the development of complications (all \( p>0.05 \)). The results of regression analysis are shown in Table 4.

The comparison of 6 and 24-hour levels of SP-D and IL-6 levels of PCs and RFs groups were similar among those with concomitant chronic disease and smokers and those without complications and non-smokers. However, 24-hour SP-D levels of those with chronic diseases were only significantly higher than 24-hour SP-D levels of those without chronic diseases (\( p=0.040 \)). The levels of 6-hour and 24-hour SP-D and IL-6 levels of the patients with and without chronic diseases and those of smokers are given in Table 5.

**DISCUSSION**

In this study, the SP-D and IL-6 levels of patients with RFs and PCs after BCT were compared with those of healthy controls. The results showed that the 6-hour levels of the RFs and PCs groups were significantly higher than those of the healthy controls and that they remained higher after 24 hours and 7 days compared with those of the controls. ISS had a significant positive correlation with SP-D and IL-6 levels. Multivariate stepwise regression analysis has shown the presence of comorbidities such as hypertension, diabetes mellitus and tuberculosis to have no effects on the hospitalisation duration, ISS and the development of complications.
The hospitalisation duration was observed to have a significant relation with the patient’s age and the presence of complications. We have found ISS to have significantly an independent relation with 6-hour IL-6 and 24-hour IL-6 levels. Additionally, we have found that the development of complications to have an independent relation with 6-hour SP-D level and ISS.

A few studies reported that the SP-D level was decreased in cases of BCT. In an experimental study, 6-hour and 48-hour SP-D levels were reported to be low, whereas 24-hour levels were mildly increased. However, the increases/decreases in the SP-D levels were not statistically significant. The findings of that study were based on measurements of SP-D levels in samples of bronchoalveolar lavage (BAL) and in the lungs of rats. In contrast, the present study measured SP-D levels in human serum. Another study found that SP-D levels were low in a rat model of BCT but that they were similar to those of an N-acetyl cysteine administered group and a non-trauma group. The cause of the low level of SP-D in that study was not identified. Furthermore, the findings were based on BCT only in rats, with no systemic trauma. In contrast, the present study consisted of humans with polytrauma and systemic inflammatory responses.

A number of studies reported that the SP-D level reflected systemic inflammation and that it was elevated in BCT and other lung diseases such as chronic obstructive pulmonary disease, radiation pneumonitis and pneumonia. Increased serum SP-D levels were also reported to be related to cardiovascular diseases. The role of SP-D in cardiovascular disease risk is attributed to its function as an acute-phase reactant, which reflects local and systemic inflammation. A previous study of the BAL of patients with ARDS reported low SP-A, SP-B and SP-C levels but high SP-D levels in these patients. SP-D levels were found to be high in ALI during endotoxaemia and to provide a balance between systemic and pulmonary inflammation and limit lung injury. An elevation in SP-D levels was reported to be associated with mortality in patients receiving mechanical ventilation. Elevated SP-D levels lead to hyperplasia of alveolar type II cells and damage endothelial and epithelial cells. A high serum SP-D level among patients receiving mechanical ventilation was found to be an independent predictive marker of organ failure and mortality. In the present study, the SP-D levels of the patients with BCT, especially those of the PCs group, were markedly higher than those of the healthy control group. During the follow-up, the 6-hour post-trauma SP-D level showed a slightly decreasing trend. However, it was much higher than that of the basal level of the controls. The results support the hypothesis that the SP-D level increases in patients with BCT and that it reflects the severity of local and systemic inflammation and the course of BCT.

Figure 1  Serum SP-D values after 6 hours in all the groups. PC, pulmonary contusion; RFs, rib fractures; SP-D, surfactant protein-D.

Figure 2  Serum IL-6 values after 6 hours in all the groups. IL-6, interleukin-6; PC, pulmonary contusion, RFs, rib fractures.

Table 4  Stepwise multiple regression analysis shows the independent variable effects on hospitalisation duration, ISS and the development of complications

| Dependent variable | Independent variables | Beta regression coefficient | p Value |
|--------------------|-----------------------|---------------------------|--------|
| Hospitalisation duration | Age | 0.245 | 0.049 |
| ISS | Presence of complications | 0.302 | 0.016 |
| Development of complications | 6-hour IL-6 levels | 1.414 | 0.001 |
| 24-hour IL-6 levels | 1.067 | 0.001 |
| ISS | 0.263 | 0.014 |
| 6-hour SP-D level | 0.211 | 0.047 |

IL-6, interleukin-6; ISS, Injury Severity Score; SP-D, surfactant protein-D.
A previous study reported that the systemic inflammatory response was markedly increased in patients with polytrauma, especially those with lung trauma. Extensive PMNL migration to the region of trauma occurs after BCT, and this is accompanied by an increase in systemic inflammation. The subsequent elevation in the release of cytokines and enzymes, such as myeloperoxidase, leads to lung tissue injury. PMNLs can rapidly phagocytose harmful materials to reduce lung injury; however, PMNLs may cause abundant release of proinflammatory cytokines, and they may lead to increase in lung injury. SP-A and SP-D regulate the production and secretion of tumour necrosis factor α (TNF-α). They facilitate opsonisation by neutrophils, thereby encouraging phagocytosis.

The release of cytokines and chemokines, such as TNF-α and IL-6, after BCT have been reported to increase lung injury. A previous study reported that the IL-6 level of BAL samples was increased after BCT, with the increase in the level thought to be parallel to systemic inflammation. Increases in local and systemic IL-6 levels were also reported to be associated with ALI. In a BCT rat model, the 24-hour IL-6 levels were significantly higher than those of controls, and all the inflammatory parameters tested returned to normal 7 days after the trauma. In a similar rat model of BCT, IL-6 and TNF-α levels were high 6 hours and 24 hours after the trauma. Intensive inflammation of alveolar epithelial and endothelial cells of the lung, especially in cases of PC, can lead to degeneration, necrosis and impairment of alveolar gas exchange. IL-6 is a major proinflammatory cytokine and a major regulator of the response to inflammation and infection. In the present study, the increase in the IL-6 level may have indirectly led to an increase in the levels of other proinflammatory cytokines, which reflects inflammation and the extent of lung damage. There was a strong positive relation between the SP-D and IL-6 levels in the present study.

In a study of SP-D and IL-6 levels of traumatic and non-traumatic ALI groups, the SP-D levels of the traumatic ALI group were lower, whereas the IL-6 levels of the same group were high. However, in that study, there was no comparison with a control group, and the number of patients in the traumatic group was about one-tenth of the number in the non-traumatic group. Another dissimilarity between that study and the current one is that the patients received mechanical ventilation, which might have affected the SP-D level. None of the patients in the present study were connected to a mechanical ventilator. Another study reported decreased IL-6 levels in patients with ARDS who received recombinant SP-C. The study did not contain any information on SP-D levels. The positive relation between SP-D and IL-6 may be due to SP-D acting as an acute-phase reactant, the release of SP-D from tissues other than the lung and the positive relation of SP-D with other proinflammatory cytokines. In this study, we have found the presence of comorbidity and smoking to have no significant effect on ISS, hospitalisation duration and the development of complications. The SP-D and IL-6 levels of smokers and the patients with comorbidities were also similar with SP-D and IL-6 levels of non-smokers and the patients without comorbidities. The 24-hour SP-D level of the patients with comorbidities was only significantly higher than that of those without comorbidities. ISS had an independent significant relation with 6-hour and 24-hour IL-6 levels. However, hospitalisation duration and the development of complications had no relation with IL-6 levels. Based on the results of this study the levels of IL-6 may be helpful in the determination of the severity of the patients with trauma only within the first 24 hours. Okeny et al have shown the measurement of IL-6 in the first hours of the trauma to be helpful in determining the severity of the trauma. However, the measurement performed after these hours to be clinically insignificant.

### Table 5

|                               | SP-D at 6th hour (mean±SD) ng/mL | SP-D at 24th hour (mean±SD) ng/mL | IL-6 at 6th hour (mean±SD) pg/mL | IL-6 at 24th hour (mean±SD) pg/mL |
|-------------------------------|---------------------------------|-----------------------------------|---------------------------------|-----------------------------------|
| The presence of chronic diseases (n=15) | 167.6±87.1                      | 168.2±91.1*                       | 20.3±13.0                       | 14.4±11.9                        |
| The absence of chronic disease (n=45) | 147.9±70.6                      | 126.1±59.5                        | 18.0±7.4                        | 13.2±7.3                         |
| The presence of complications (n=9) | 214.8±119.2                     | 207.5±110.9                       | 22.7±18.2                       | 17.7±18.2                        |
| The absence of complications (n=51) | 153.5±72.9                      | 148.9±78.7                        | 19.2±10.5                       | 13.4±9.2                         |
| Smoking (n=36)                | 171.2±89.8                      | 167.2±96.3                        | 20.9±13.4                       | 14.8±12.1                        |
| No smoking (n=24)            | 150.0±72.1                      | 143.4±66.5                        | 18.0±9.1                        | 13.0±9.1                         |

Other all p values are not significant (p>0.05). *p=0.040 versus the presence of chronic diseases.

IL-6, interleukin-6; SP-D, surfactant protein-D.
marker for early prediction of the development of complications in patients with trauma. However, except for 6-hour SP-D level, the measurement of SP-D levels may be of no clinical importance. High SP-D levels in the first hours of the trauma may cause higher lung tissue injury than IL-6 leading to the development of complications.

**Limitations of the study**

The number of participants in the RFs and PC groups was small. BAL sampling was not performed. In addition, there was no long-term follow-up. It would have been useful to compare BAL levels of SP-D and IL-6 with the serum levels of SP-D and IL-6.

**CONCLUSION**

The level of systemic inflammation reflects local inflammation after BCT. In this study, the levels of IL-6, a marker of systemic inflammation, and SP-D, an acute-phase reactant, were high in patients with BCT and polytrauma. Serum 6-hour SP-D levels may be good markers for determining the development of complications in follow-ups of patients with BCT. There is a need for detailed studies on SP-D levels in BCT. The IL-6 level may be helpful in determining the severity of the trauma in the first 24 hours.

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**Contributors**

AK1, MCC and HT were involved in the study design. AK1, AA and HT were involved in the data collection. MCC and AK2 were involved in the biochemical analysis. EC and SY were involved in the statistical analysis. AK1 and EC were involved in the writing. AK2, SY and MCC participated in the critical revision of the manuscript. HT, AA and EC were involved in the study supervision. (AK1, Aysel Kurt; AK2, Aynur Kirbas).

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**Competing interests**

None declared.

**Provenance and peer review**

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**Data sharing statement**

No additional data are available.

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