Indian Journal of Surgery (April 2021) 83(Suppl1):S113 –S119
https://doi.org/10.1007/s12262-020-02407-4

ORIGINAL ARTICLE

Predicting Outcomes After Blunt Chest Trauma—Utility of Thoracic Trauma Severity Score, Cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF-α), and Biomarkers (vWF and CC-16)

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Received: 30 November 2019 / Accepted: 22 May 2020 / Published online: 7 June 2020

Abstract

Thoracic trauma severity score (TTSS) has been used to assess severity and risk of pulmonary complications in patients with chest trauma. The role of cytokines and biomarkers in patients with chest trauma and its association with TTSS is not well elucidated. The aim of the study was to assess the cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF-α) and biomarkers (vWF, CC-16) in patients of thoracic trauma and correlate it with TTSS and patient's outcome. This was a prospective observational study. Serum and bronchoalveolar lavage fluid samples were collected from chest trauma patients. TTSS was calculated in all patients. Suitable controls for serum and bronchoalveolar lavage (BAL) sample were selected. The outcome parameters included patient discharge or death, duration of hospital, and intensive care unit (ICU) stay. Forty-three patients were included. There was no significant correlation between the measured cytokines and biomarkers and TTSS. The mean TTSS of patients who had a fatal outcome was significantly higher than the patients who recovered. Patients with a high TTSS score had a significant prolonged ICU stay. Patients with a prolonged hospital stay had lower values of CC-16. TTSS is a useful tool to predict severity of chest trauma and prolonged ICU stay. Lower levels of CC-16 in BAL fluid of chest trauma patients were associated with prolonged hospital stay suggestive of its protective role in the airway. Longer prospective studies are required to determine the role of cytokines and biomarkers in patients with thoracic trauma in predicting the patient's outcome.

Keywords Trauma · Mortality · Cytokines · Biomarkers · Injury · Infection

This paper was presented at the 78th annual meeting of American Association for the Surgery of Trauma (AAST) held from September 18 to 21 in 2019 at Dallas, Texas, USA.

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Introduction

Chest trauma has affected mankind since the Egyptian era. There has been a transition in etiology from natural disasters in the fifteenth century to country wars, to road traffic injuries today. Improved medical care and availability of prompt treatment have reduced the impact of thoracic trauma; however, it still continues to cause significant morbidity and mortality [1]. This is why a systematic risk assessment is needed to personalize intensive care support and surgical strategy, thus reducing the associated morbidity and mortality.

Patients with trauma to the chest present with a spectrum of manifestations, including pulmonary contusion, hemothorax, pneumothorax, and flail chest, the severity ranging from relatively trivial to life-threatening [1]. Various immunological mediators are involved in orchestrating the sequence of events. Acute inflammation secondary to the lung injury causes disruption of the lung endothelial and epithelial barriers, which in its most severe form can result in acute respiratory distress syndrome (ARDS) [2]. Assay of biomarkers associated with inflammation can help us understand the disease process better. The World Health Organization (WHO) defines biomarker as "any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease" [3]. Therefore, it is crucial to identify these biomarkers, not only to understand the mechanisms involved in lung injury and repair but also to predict prognosis and design future therapeutic targets.

Certain cytokines and biomarkers have been studied well for the role in inflammation. IL-1β, IL-6, IL-8, and TNF-α are pro-inflammatory cytokines that are responsible for the enhanced production of other cytokines and augmentation of damage. IL-10 is an anti-inflammatory cytokine, and it downregulates T cell proliferation and cytokine production. von Willebrand factor (vWF) has been well documented to be increased in plasma and bronchoalveolar lavage (BAL) fluid of patients with acute injury as well as being predictive of the outcome of these patients [4]. Club cell protein, formerly known as Clara cell secretory protein, also known as CC16, is produced primarily within the Clara cells of the distal respiratory and terminal bronchioles and observed to be elevated in ARDS [5]. These biomarkers have been found to be of diagnostic and prognostic importance in other conditions (Table 1). However, association of these biomarkers with traumatic chest injury is not well known. Therefore, identifying a single or a combination of sensitive and specific cytokines and biomarkers would be of mechanistic and clinical relevance [8].

A number of methods are present to assess the severity of injury in a trauma patient. The injury severity score (ISS) developed by Baker et al. in 1974 takes into account the individual organ system scores are calculated using the abbreviated injury score (AIS) [9].There is an anatomic-physiological standardized scoring system for initial clinical decision-making in blunt chest trauma [10]. The severity of chest trauma is assessed in the emergency department based on thoracic trauma severity score (TTSS), but its association with cytokines and biomarkers and patient prognosis is not well elucidated [1, 10]. In this prospective observational study, we have measured the concentration of local and systemic cytokines, TNF-α, IL-1β, IL-6, IL-8, and IL-10, and biomarkers like vWF and CC16 in patients with blunt chest trauma who were on ventilators. We then studied the correlation between the levels of these proteins with TTSS and patient outcome. We have also studied the correlation between TTSS and patient outcome.

Materials and Methods

This was a prospective observational study conducted between May 2015 and May 2017. All patients with blunt chest trauma, aged between 18 and 65 years, who were intubated were included in the study. Patients with malignancies, history of steroid use, or other known immunodeficiency state, chemical or burn injuries, receiving hormone therapy, chronic disease of the liver, kidney, or lung, and with isolated traumatic brain injury or post-splenectomy were excluded. The blood and BAL samples were collected from the included chest trauma patients. Healthy healthcare workers were selected as controls for the blood samples. Patients of carcinoma esophagus with no evidence of tracheal involvement, who undergo routine preoperative bronchoscopy, were selected as controls for BAL sample. The cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF-α) and biomarkers (vWF, CC16) were assayed both in serum and BAL fluid, and the estimation was done by sandwich enzyme-linked immunosorbent assay (ELISA). ELISA MAX™ Deluxe Set Human kits (BioLegends, San Diego, CA, USA) were used for the assay of cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF-α), REAADS® vWF:Ag ELISA kit (Corgenix Medical Corporation, Broomsfield, CO, USA) was used to assay vWF, and CC16 ELISA kit (Sincere Biotech, Beijing, China) was used to assay CC-16. The levels of cytokines were measured in pg/ml; level of vWF was expressed as percentage of normal and that of CC16 in ng/ml.

Assessment of severity of chest injury was done by thoracic trauma severity score [10]. The severity of trauma was graded into four groups based on an established scale. Diagnosis of ARDS was done using the Berlin definition [11]. The primary endpoint of the study was to assay cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF-α) and biomarkers (vWF, CC16) in serum and BAL in patients of traumatic chest injury on ventilatory support and its comparison with controls. The secondary objectives were to correlate TTSS with two parameters, namely, cytokines and biomarkers levels and patient outcome. Outcome measures included duration of intensive care unit

Table 1 Diagnostic utility of cytokines and biomarkers in various conditions

Variable	Disease
IL-1β	Alzheimer's disease, ventilator-associated pneumonia, neonatal sepsis, surgical site infection, endometriosis [6]
IL-6	Alzheimer's disease, neonatal sepsis, surgical site infection, endometriosis, tuberculosis, left ventricular dysfunction, gastric cancer, lupus nephritis, endometriosis, gastric cancer, ectopic pregnancy [6]
IL-8	Neonatal sepsis, neurological outcome after cardiac arrest, ovarian cancer, ectopic pregnancy [6]
IL-10	Neonatal sepsis [6]
TNF	Neonatal sepsis, surgical site infection, endometriosis, tuberculosis, ectopic pregnancy [6]
vWF	von Willebrand disease [6, 7], ARDS [6]
CC16	Chronic obstructive lung disease [6], sarcoidosis [6], ARDS

IL-1β interleukin-1β (pg/ml), *IL-6* interleukin-6 (pg/ml), *IL-8* interleukin-8 (pg/ml), *IL-10* interleukin-10 (pg/ml), *TNF-α* tumor necrosis factor alpha (pg/ml), *vWF* von Willebrand factor (%), *CC16* Clara cell factor 16 (ng/ml)

(ICU) stay, duration of hospital stay, and discharge from hospital or death. Patients were managed according to the standard management protocol and no study-specific intervention was performed. Clinical follow-up was done daily until discharge or death.

Statistical Analysis

Data was analyzed by using statistical software Stata 14. 0. Qualitative data was expressed as frequency and percentage. Quantitative data was expressed as mean and standard deviation (SD) and median (min-max) for normal and skewed data respectively. For statistical purposes, we considered a TTSS of less than or equal to 5 as a low score and a TTSS of more than 5 as a high score. Chi-square/Fisher exact test was used to find the association between categorical variables. Continuous variables were compared using *t* test and the rank-sum tests. $p < 0.05$ was considered as statistically significant.

Results

During the study period, 865 patients of thoracic trauma were admitted and managed in our department. Majority of them (96%) were manged non-operatively. Non-operative interventions in the form of intercostal tube drainage was required approximately in 71% patients. Forty-three patients with blunt trauma chest required ventilatory support and were included in the study. The male-female ratio was 35:8. Mean age was comparable between cases and controls (37.1 ± 12.7 years vs. 40.7 ± 11.3 years, $p = 0.17$). Mean age was comparable between patients who died and who recovered (36.7 ± 11.9 years vs. 38.8 ± 16.5 years, $p = 0.6$). The mean hospital stay of chest trauma patients was 25.4 ± 21.6 days with a median of 22 days. The mean ICU stay was 13.6 ± 10.9 days with a median of 11 days. The range of hospital stay was between 2 and 110 days and that of ICU stay was between 1 and 48 days.

Tube thoracostomy was required in 64.7% of the patients, indications being hemothorax and/or pneumothorax. Extended focused assessment with sonography for trauma (eFAST) was performed in all patients and 18 patients had a positive study. Thirty-five patients were eventually discharged from the hospital. They are on regular follow-up and are doing well. However, eight patients who had sustained chest injury with or without polytrauma succumbed. Two patients with isolated lung injury and six patients with polytrauma died. The most common organ system leading to death was the pulmonary system, in the form of ARDS.

The mean TTSS was 6.5 ± 2.1 with the median score being 6. The minimum score observed was 3 and the maximum scored observed was 12. A majority of patients had a grade 2 TTSS score i.e., twenty-three, followed by grade 1 injury and grade 3 injury, seventeen, and three respectively. None of our patients had a grade 4 injury. Of the three patients who had a score of more than 10, two patients died. A paired *t* test was run on the sample of 43 thoracic trauma patients to determine whether there was a statistically significant mean difference between the TTSS score of patients who were discharged compared with those who died. Patients who died had a significantly higher TTSS as compared with those who were discharged ($p = 0.048$).

The mean hospital stays in patients with grade 2 and grade 3 injuries were longer than that of patients with grade 1 injury (29.5 days vs. 20.4 days) but the difference did not achieve statistical significance. However, the mean ICU stay in patients with TTSS more than five was 70% longer than that of patients with score less than or equal to 5 and the difference was statistically significant (17 days vs. 10.2 days, $p = 0.04$).

The median values of cytokines and biomarkers were compared between the controls and baseline values of the patients

(Tables 2 and 3 and Figs. 1 and 2). Serum IL-1β and IL-10 were significantly raised in thoracic trauma patients (p = 0.00 and p = 0.00 respectively), whereas IL-6, vWF, and CC16 failed to reach a statistically significant increase as compared with that of controls. IL-8 level in serum was found to be significantly higher in controls (p = 0.01) and TNF-α in serum was comparable in both groups. BAL IL-1β, IL-6, and IL-10 were significantly raised in thoracic trauma patients (p = 0.00, p = 0.00, and p = 0.00 respectively), whereas IL-8 and TNF-α failed to reach a statistically significant increase as compared with that of controls. vWF in BAL was found to be marginally higher in controls (27.9% vs. 25.7%). CC16 in BAL was found to be significantly higher in controls compared with that of cases (0.62 ng/ml vs. 0.40 ng/ml, p = 0.01).

The cytokines and biomarkers measured in both serum and BAL samples of patients were comparable between patients with high (> 5) and low (≤ 5) TTSS. The levels of all the cytokines and biomarkers in both serum and BAL were comparable in patients who were discharged vs. patients who had a fatal outcome. IL-1β, IL-6, IL-8, IL-10, TNF-α, and vWF in serum and BAL samples failed to achieve significant correlation with the hospital or ICU stay. It could not be clearly determined whether increase or decrease in these biomarkers would affect the hospital or ICU stay. However, it was seen that the lower levels of CC16 in BAL were associated with significantly longer hospital stay (r = −0.45, p = 0.005).

Discussion

Significant morbidity and mortality have plague chest trauma since its first description in the Egyptian era. Today, one out of four patients following trauma requires admission for thoracic injury. Operative intervention is required in 10% patients with blunt injury thorax and 15–20% patients with penetrating injury

Table 2 Comparison of cytokines and biomarkers in serum samples of cases vs. control

Variables	Cases	Controls	p value
IL-1β	245.5 (0–579.3)	8.1 (3.9–12. 4)	0.0000
IL-6	20.2 (2.3–216.9)	5.8 (4.3–1137.2)	0.1108
IL-8	51.2 (21.8–13,283)	349.9 (11.6–612.3)	0.0154
IL-10	92.7 (12.8–5046)	12.07 (7.8–16.5)	0.0000
TNF	19.9 (0–244.8)	20.65 (15.2–1304)	0.9411
vWF	101.5 (15.3–136.7)	100.1 (24.1–157.4)	0.4603
CC16	0.67 (0.34–7.91)	0.55 (0.38–9.0)	0.2843

IL-1β interleukin-1β (pg/ml), *IL-6* interleukin-6 (pg/ml), *IL-8* interleukin-8 (pg/ml), *IL-10* interleukin-10 (pg/ml), *TNF-α* tumor necrosis factor alpha (pg/ml), *vWF* von Willebrand factor (%), *CC16* Clara cell factor 16 (ng/ml)

Table 3 Comparison of cytokines and biomarkers in BAL samples of cases vs. control

Variables	Cases	Controls	p value
IL-1β	44.3 (8.4–398.6)	20.5 (4.9–113.9)	0.0037
IL-6	51.5 (3.6–4835.6)	5.2 (4.1–12.1)	0.0000
IL-8	921.1 (0–32,663.3)	524.8 (174.9–524.8)	0.2750
IL-10	19.6 (0.3–18,354)	13.3 (10.8–1307)	0.0002
TNF	86.1 (0–1598.1)	71.0 (29.7–431.9)	0.9571
vWF	25.7 (0.3–230.4)	27.9 (12.7–103.1)	0.8237
CC16	0.40 (0.17–4.00)	0.62 (0.25–2.06)	0.0152

IL-1β interleukin-1β (pg/ml), *IL-6* interleukin-6 (pg/ml), *IL-8* interleukin-8 (pg/ml), *IL-10* interleukin-10 (pg/ml), *TNF-α* tumor necrosis factor alpha (pg/ml), *vWF* von Willebrand factor (%), *CC16* Clara cell factor 16 (ng/ml)

[12]. During the study period majority of our patients with blunt chest trauma (96%) were managed non-operatively. On the other hand, in our study population (n = 43), 12% patients required operative intervention for thoracic injuries and tube thoracostomy was performed in 64.7% patients.

Thoracic trauma severity score (TTSS) has been previously studied in association with patient mortality [13]. We studied the relationship of TTSS with a patient's inflammatory parameters, hospital stay, ICU stay, and final outcome. The distribution of patients among the various grades on injury in our study was similar to that found in other studies [10, 13, 14]. The total duration of hospital stay of patients with a high score was one and half times the duration of stay of patients with a low score (29.5 days vs. 20.4 days) but it was not statistically significant. Patients with a high score had a significantly longer ICU stay (17 days vs. 10.2 days). Persistent requirement of ventilatory support was the reason for prolonged ICU stay in most patients. Subglottic stenosis is known to occur with prolonged endotracheal intubation [15]. The above observation indicates that high TTSS predicts prolonged ventilatory support requirement in patients of thoracic trauma. With further validation, we suggest high TTSS can help implement early tracheostomy strategy in thoracic trauma patients to prevent complications of prolonged endotracheal intubation. ICU stay of patients who had a fatal outcome was longer compared with patients who recovered.

We observed six of the eight patients who died had a high TTSS score. Our results were comparable with most other studies, where ARDS was the most common cause of death in thoracic trauma patients [16, 17]. In our study, the mean TTSS of patients who had a fatal outcome was significantly more than that of patients who recovered (7.9 days vs. 6.2 days). It has been observed that TTSS was significantly higher in patients who died of thorax-related complications than in patients who died because of non-thorax-related complications and survivors [18]. Researchers have evaluated

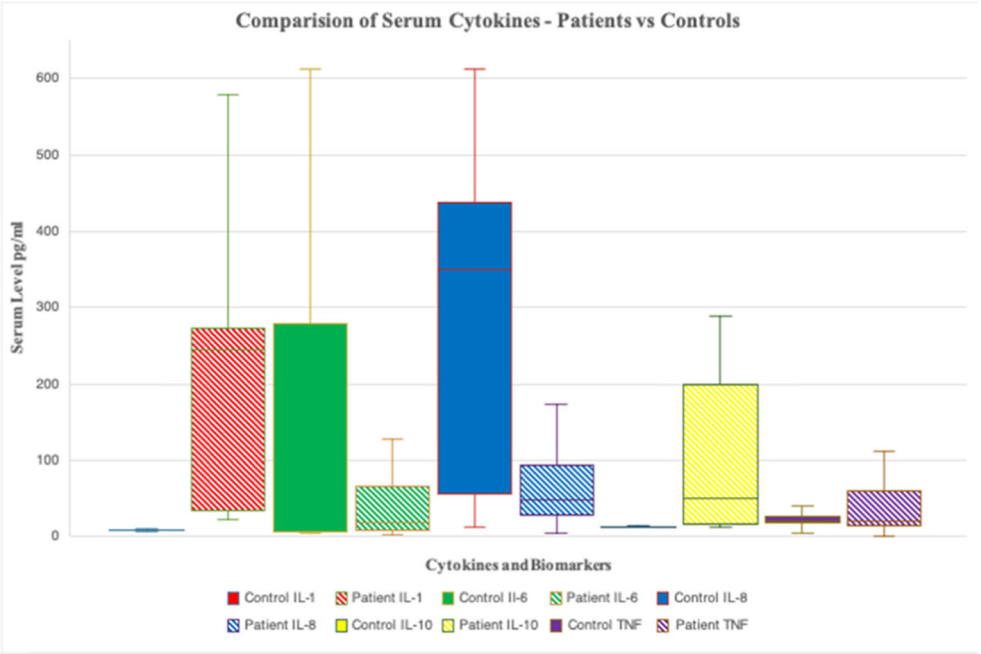

Fig. 1 Box plot comparing serum cytokines between cases and controls

TTSS in predicting the outcome of isolated blunt trauma chest and concluded that patients with a score of more than seven had an increased risk of mortality [16, 17].

Pathophysiological basis of thoracic trauma induced lung injury is not well established. The mechanism of acute lung injury (ALI) has been extensively studied in non-trauma patients [19–21]. Poor prognosis observed in patients with ARDS has led to extensive research to study the pathophysiology of the disease, to find potential new biomarkers for diagnosis and develop new therapeutic targets to improve patient outcome [22, 23]. A group of researchers studied the utility of a panel of biomarkers for diagnosis and pathogenesis of lung injury in trauma patients [22, 23]. They found that baseline and persistently elevated plasma levels of IL-6, IL-8, and TNF-α in chest trauma patients were a predictor of mortality [23]. They also suggested if validated prospectively, use of this biomarker panel could facilitate the clinical diagnosis of ALI/ARDS.

To the best of our knowledge, the pathophysiological basis of chest trauma induced acute lung injury on a patient's

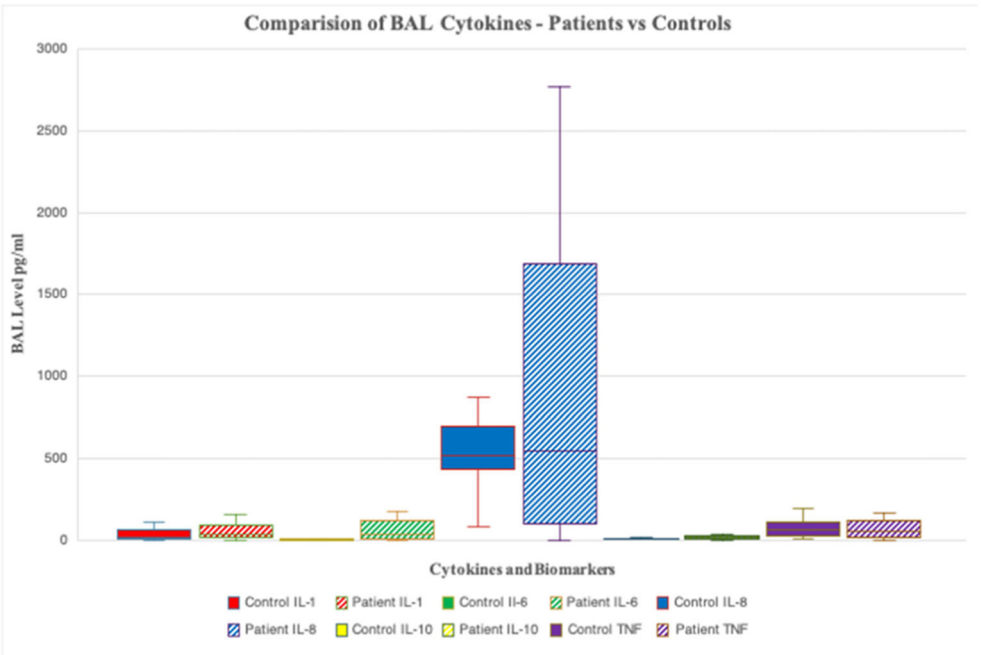

Fig. 2 Box plot comparing BAL cytokines between cases and controls. Box chart represents data as quartiles. The box represents the middle two quartiles, the lines above the box represent the top 25% values, and the lines below the box represent the bottom 25% values. The horizontal line in the box is representative of the median value. Outliers have been omitted to improve visualization of the graph; however, it has not been omitted from the calculation and calibration of the graft

outcome has not been studied before. Compared with our controls, the serum and BAL fluid of patients had increased levels of IL-1β and IL-10, whereas levels of IL-6 and IL-8 were increased only in BAL fluid. We extensively studied the relation of the panel of cytokines and biomarkers between patients with a high and low TTSS, but no significant difference could be established. Several studies have been published which discuss the role of these cytokines and biomarkers independently in predicting the mortality of patients with ARDS, but these are limited to patients with non-trauma-related lung injury [24, 25]. A group of researchers have demonstrated a strong association of increased IL-8 levels with mortality [22–25]. We observed IL-1β and IL-10 were elevated in both serum and BAL fluid as compared with controls and IL-6 and IL-8 were increased in only BAL fluid as compared with controls. These immunological markers were increased in patients, who had a fatal outcome compared with those who recovered, but no consistent pattern was observed and the difference was not significant. This indicates that an elevation in these biological parameters is only indicative of the underlying disease process; however, it cannot predict the patient outcome.

We also studied the impact of these cytokines and biomarkers on the hospital and ICU stay of the patients. In our study, no definite pattern of correlation was observed between IL-1β, IL-6, IL-8, IL-10, TNF-α, vWF, and duration of hospital stay and ICU stay. It was seen that lower values of CC16 in BAL fluid were associated with a significant prolonged hospital stay. This observation suggests the important protective role of CC16 in the airway in combating inflammation. A study from the Medical University of Vienna on patients with polytrauma showed raised CC16 levels in serum can predict occurrence of pneumonia [26]. Researchers have demonstrated the diagnostic utility of raised serum CC16 in patients with ARDS and also its correlation with severity of ARDS and duration of ICU stay [27]. Anti-inflammatory and protective roles of CC16 have been observed in patients of COPD and this has incited interest in the development of recombinant CC16 for therapy [28, 29]. Animal experiments on rats exposed to cigarette smoke demonstrated amelioration of pathological damage and reduced production of TNF-α, IL-6, and IL-8 after administration of intra nasal recombinant CC16 [30]. Thus, CC16 can be used to predict prolonged hospital stay, if prospectively validated.

The major strength of our study is that it is the first prospective study on chest trauma patients in which we correlated clinico-radiological severity scoring system with biological parameters of inflammation and with the patient's outcome. Presence of a control group to validate the increase in serum and BAL fluid cytokines and biomarkers of thoracic trauma patients greatly strengthens the study. The drawback was the short duration follow-up and patients with limited range of TTSS were included in the study.

Conclusion

Thoracic trauma severity score is an excellent tool to assess the degree of anatomical and physiological insult incurred by a patient of chest injury. Patients with a high TTSS (> 5) have a significantly longer ICU stay. The serum and BAL fluid of patients had increased levels of IL-1β and IL-10, whereas levels of IL-6 and IL-8 were increased only in BAL fluid. There was no significant correlation between the measured cytokines and biomarkers and TTSS. Lower levels of CC-16 in BAL fluid patients were associated with prolonged hospital stay, suggestive of its protective role in the airway. However, longer prospective studies are required to determine the role of cytokines and biomarkers in patients with thoracic trauma in predicting the patient's outcome.

Funding Information Intramural funding was received for this study from All India Institute of Medical Sciences, New Delhi.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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