Predictive value of C-reactive protein in critically ill patients who develop acute lung injury

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KEYWORDS
Acute lung injury; CRP

Abstract Background: Acute lung injury (ALI) is associated with significant mortality and morbidity. C-reactive protein (CRP) level a marker of systematic inflammation is widely-used in numerous clinical conditions, however little is known about the characteristics of CRP levels in patients with ARDS and acute lung injury (ALI).

The aim of this work was to examine the plasma level of C-reactive protein (CRP) in patients with acute lung injury (ALI) and its relationship with prognosis, outcome, and severity of illness.

Patients and methods: The study was carried out on 100 consecutive patients, who were admitted to the Critical Care Medicine Departments in Alexandria Main University Hospital. Inclusion criteria were patients were aged > 18 years who had one or more of the acute lung injury (ALI) predisposing conditions. Patients who developed ALI based on standard definition according to the American–European consensus conference were examined for C-reactive protein levels measured in serum (mg/dl) collected within 48 h after fulfillment of criteria.

Results: CRP levels were the highest in patients with complete recovery ranging between 190 and 233 mg/dl with a mean of 211.5 ± 30.406 mg/dl, modest in patients who recovered with residual complications ranging between 107 and 120 with a mean of 111.33 ± 7.506 mg/dl, and lowest in patients who died ranging between 35 and 106 with a mean of 79.55 ± 24.007 mg/dl. Higher CRP levels were significantly associated with better survival (P = 0.000). There was an inverse relationship between CRP levels and duration of mechanical ventilation while ICU stay increased as the CRP levels increased. The relationships between CRP levels and both mechanical ventilation days and ICU stay were statistically non significant (P = 0.710 and 0.801 respectively). CRP levels were lower in patients who developed multiorgan dysfunction syndrome (MODS) with a mean of 76.6 ± 28.778 mg/dl compared to a mean of 111.43 ± 59.332 mg/dl in patients who didn’t develop MODS, this relationship was not statistically significant (P = 0.060).

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Conclusions: Although CRP has widely been considered to be a marker of systemic inflammation, our findings show that higher levels of CRP are associated with decreased mortality, organ failure, and need for mechanical ventilation among patients with ALI.

Introduction

Acute lung injury (ALI) and its severe form acute respiratory distress syndrome (ARDS) are terms used to describe the pulmonary response to a wide range of insults that lead to abnormalities in oxygenation with refractory hypoxemia and diffuse radiographic shadowing of the lungs, and usually necessitate invasive mechanical ventilation. These insults can be direct or indirect; they are listed in Table 1 [1].


Definition


ARDS is considered to be present in the setting of bilateral infiltrates on a chest radiograph, a PaO2/FiO2 <200, and a pulmonary artery occlusion pressure ≤18 mmHg or no clinical evidence of elevated left atrial pressure. ALI is defined similarly, with the difference being that the PaO2/FiO2 is < 300. Unlike earlier definition of ARDS, the PaO2/FiO2 is defined regardless of the level of positive end expiratory pressure (PEEP) [4].

Although AECC definitions allowed for a concerted ALI/ARDS research effort, the validity of the definition has been criticized. For example, the vague nature of the term “acute,” vide intraobserver variation in ascertaining “bilateral radiographic infiltrates”, [5] and sensitivity of the PaO2/FiO2 ratio criteria to small changes in positive end-expiratory pressure (PEEP) [6] led to the recent revisiting of the AECC definition and drafting of the Berlin definition of ARDS [7] (Table 2).

The Berlin criteria were unique in that they were iteratively drafted and then empirically evaluated in order to provide a definition that would be feasible, reliable, and prognostic. Major changes to the AECC definition included:

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical disorders associated with ALI and ARDS [1].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct precipitating cause</td>
<td>Indirect precipitating cause</td>
</tr>
<tr>
<td>Pneumonia (Bacterial, viral, pneumocystis carinii)</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Inhalational injury</td>
<td>Shock (irrespective of etiology)</td>
</tr>
<tr>
<td>Reperfusion pulmonary edema</td>
<td>Reperfusion lung injury (post transplant, post cardiopulmonary bypass)</td>
</tr>
<tr>
<td>Embolic events (fat, amniotic fluid or air)</td>
<td>Drug overdose</td>
</tr>
<tr>
<td>Chest trauma with lung contusion</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Near drowning</td>
<td>Multiple trauma</td>
</tr>
<tr>
<td>Aspiration of gastric contents</td>
<td>Transfusion of blood products</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>American–European Consensus Conference (AECC) definition of acute lung injury and the Berlin definition of acute respiratory distress syndrome (ARDS).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>The AECC definition 1994</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
</tr>
<tr>
<td>Radiographic abnormality</td>
<td>Bilateral infiltrate on frontal chest radiograph</td>
</tr>
<tr>
<td>Noncardiogenic source of pulmonary edema</td>
<td>No clinical evidence of elevated left atrial pressure, or, a pulmonary capillary wedge pressure, 18 mmHg</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>PaO2/FiO2 ratio ≤300</td>
</tr>
<tr>
<td></td>
<td>Acute lung injury: ≤300</td>
</tr>
<tr>
<td></td>
<td>Acute respiratory distress syndrome: ≤200</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Predisposing condition</td>
<td>Not specified</td>
</tr>
</tbody>
</table>
(1) Elimination of the term “acute lung injury” as the umbrella term and replacing it with three levels of ARDS severity based on PaO$_2$/FiO$_2$ measured with at least 5 cm H$_2$O of applied PEEP,
(2) Defining “acute” as ≤7 days from the predisposing clinical insult, and
(3) Eliminating pulmonary wedge pressure cutoff values that discriminate ARDS from cardiogenic edema. The Berlin criteria provide a slight improvement in predictive ability for mortality (area under the curve [AUC] 0.577) when compared to the AECC (0.536).

**Frequency**

The incidence of ARDS varies greatly, partly because of differing and changing definitions of this disease [8].

Within intensive care units, approximately 10–15% of admitted patients and up to 20% of mechanically ventilated patients meet criteria for ALI or ARDS [9–12]. The incidence of ALI may be somewhat higher in the United States than in other countries [13].

The incidence of ARDS may be decreasing. A prospective cohort study from a single institution reported that the incidence of ARDS decreased from 82.4 cases per 100,000 person-years in 2001 to 38.9 cases per 100,000 person-years in 2008 [14]. This was attributable to a decline in hospital-acquired ARDS, since the incidence of ARDS at hospital presentation did not change. These findings may reflect changes in the delivery of care at this institution only; studies from other institutions are necessary before it can be concluded that the incidence of ARDS is declining in general.

**Risk factors**

A number of single-center prospective cohort studies that enrolled patients at risk for ARDS have identified risk factors for the development of ARDS (Table 3). Non-modifiable risk factors for ARDS include a history of alcohol abuse [16], obesity, and admission severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] > 16) [15]. Prospective studies have shown either no association [15] or a protective association [16,17] between older age and ARDS development. Potentially modifiable risk factors for ARDS include increased use of red blood cell transfusion [18], admission hypoproteinemia [17], failure to achieve resuscitation goals within 6 h of septic shock onset, and failure to provide adequate antibiotics within 3 h of septic shock [19]. Interestingly, patients with diabetes have approximately half the risk of developing ARDS as at-risk patients without diabetes [20]. Determining mechanisms for these risk factors may allow for the development of therapies that prevent ARDS.

**Outcome**

The outcome for ALI and ARDS has improved during the past two decades with mortality rates of 35–45% [22]. However, it is not clear whether this reduction is due to any specific intervention because these improvements occurred before the large NIH trials [23].

**Mortality**

ALI and ARDS are associated with appreciable mortality, with estimates ranging from 26% to 58% [24,25]. The underlying cause of the ALI or ARDS is the most common cause of death among patients who die early [26,27]. In contrast, nosocomial pneumonia and sepsis are the most common causes of death among patients who die later in their clinical course [28]. Patients uncommonly die from respiratory failure [25].

Numerous studies suggest that survival has improved over time [27,29]. As an example, an observational study of 2451 patients who had enrolled in ARDSNet randomized trials found a fall in mortality from 35% to 26% between 1996 and 2005 [30].

Although encouraging, several issues should be considered with respect to trends in ARDS-related mortality:

- The improved mortality may be attributable to patients who have ARDS related to risk factors other than sepsis, such as trauma [27]. To the extent that mortality has decreased, the

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**Table 3** Multivariable-adjusted predisposing conditions and clinical risk factors for acute lung injury (Lung injury prediction study) [21].

<table>
<thead>
<tr>
<th>Predisposing conditions</th>
<th>Proportion of patients with condition who develop ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>18%</td>
</tr>
<tr>
<td>Aspiration</td>
<td>17%</td>
</tr>
<tr>
<td>Aortic surgery</td>
<td>17%</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>17%</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>10%</td>
</tr>
<tr>
<td>Acute abdomen</td>
<td>9%</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>9%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8%</td>
</tr>
<tr>
<td>Risk modifiers</td>
<td>Odds ratio for developing ARDS</td>
</tr>
<tr>
<td>Obesity (body mass index &gt; 30)</td>
<td>1.75</td>
</tr>
<tr>
<td>Diabetes (only in sepsis; associated with decreased risk)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1.58</td>
</tr>
<tr>
<td>FIO$_2$ &gt; 0.35</td>
<td>2.77</td>
</tr>
<tr>
<td>pH &lt; 7.35</td>
<td>1.73</td>
</tr>
<tr>
<td>Tachypnea (respiratory rate &gt; 30)</td>
<td>1.99</td>
</tr>
</tbody>
</table>
Many studies have sought to identify factors during the acute illness that predict mortality. Such factors can be categorized as patient-related, disease-related, or treatment-related. No single factor has proven to be superior to the others.

**Patient-related.** Older patients appear to be at an increased risk of death [30,18]. This was illustrated by a multicenter cohort study that followed 1113 patients with ALI for 15 months [33]. The mortality rate increased progressively with age, ranging from 24% among patients 15–19 years of age to 60% among patients 85 years of age or older. The overall mortality rate was 41%.

**Disease-related.** Disease-related predictors of mortality include failure of oxygenation to improve, increased dead space, infection, high severity of illness score, non-traumatic cause of the ARDS, and certain biomarkers and gene polymorphisms.

In recent years, a number of studies have focused on defining the role of plasma mediators or markers of inflammation and their association with phenotype and outcome in this disease [34–36]. However, despite the body of literature connecting CRP with prognosis in other diseases little is known about the characteristics of CRP levels in patients with ARDS and acute lung injury (ALI).

**C-reactive protein (CRP).** C-reactive protein (CRP) is an acute phase protein produced primarily from the liver and is stimulated by the release of cytokines, such as interleukin-6 [37]. CRP is a marker of systemic inflammation that is elevated during a wide variety of diseases [38,39], and is widely used at numerous emergency departments. The severe inflammatory process of the lung in ALI/ARDS patients occurs in response to various etiologies, including pulmonary or extrapulmonary injury [40].

Although there have been a few reported studies regarding CRP levels [34,41] in critically ill patients with ALI/ARDS, the prognostic value of CRP for these conditions has not been determined. In addition, in vitro and animal model studies have suggested that CRP may play a pathogenic role by inhibiting neutrophil chemotaxis or modulating vascular permeability in ways that could potentially be protective in patients with these diseases [42–44].

Several studies have sought factors during acute illness that predict long-term sequelae [45,46]. Persistent symptoms one year after recovery correlate with duration of mechanical ventilation and the lowest static thoracic compliance during acute illness [45].

Abnormal lung function one year after recovery correlates with the following factors measured during acute illness: lowest static thoracic compliance, mean pulmonary artery pressure, positive end-expiratory pressure (PEEP), initial intrapulmonary shunt fraction, and requirement of an FiO\textsubscript{2} > 0.6 for more than 24 h [47,48].

A better functional outcome at one year correlates with absence of steroid treatment, absence of illness acquired during ICU stay, and rapid resolution of multiple organ failure and lung injury [46]. There is no known correlation between ventilatory strategies and either long-term pulmonary function or health-related quality of life [49,50].

**Aim of the work**

1. To examine plasma level of C-reactive protein (CRP) in patients with acute lung injury (ALI) and its relationship to outcome and severity of illness.

**Patients and methods**

The study was carried out on 100 consecutive patients, who were admitted to both the Emergency and Critical Care Medicine Departments in Alexandria Main University Hospital. Approval of the medical ethics committee of Alexandria Faculty of Medicine, and an informed consent from the patients or their next of kin were taken before conducting the study.

Inclusion criteria were:

- All patients who aged > 18 years who have one or more of the acute lung injury (ALI) predisposing conditions (Table 4) will be included in the study.

Acute lung injury will be defined based on the standard definition according to the American–European consensus conference [3]. The definition is based on:

1. Acute onset of an insult known to cause ALI,
2. Chest radiograph appearance,
3. Ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen (PaO\textsubscript{2}/FiO\textsubscript{2} hypoxic index),
4. Assessment of left atrial filling and pressure by means of a wedged pulmonary artery catheterization or clinical assessment.

**Exclusion criteria were:**

1. Acute lung injury or pulmonary edema already present at the time of hospital admission,
2. Admitted for comfort or hospital care only,
3. Patients admitted for cardiac telemetry, coronary care unit, and low risk elective surgery,
4. Hospital readmission,
5. Hospital transfer,
6. Patients less than 18 years of age.

All patients who will have any acute lung injury (ALI) risk factors before or 6 h after hospital admission will be subjected to lung injury predictive score (LIPS).

Patients will be categorized into two groups based on lung injury predictive score (LIPS):

1. Group I: (LIPS > 3) patients at high risk of developing acute lung injury.
2. Group II: (LIPS ≤ 3) patients at low risk of developing acute lung injury.

Patients who develop acute lung injury (ALI) with fulfillment of the criteria of acute lung injury (ALI) based on the standard definition according to the American–European consensus conference will be examined for C-reactive protein levels in serum collected within 48 h after fulfillment of criteria.
All patients included in the study will be subjected to the following:

1. Demographic data: age and sex.
2. History taking: as regards the risk factors for acute lung injury.
3. Complete clinical examination.
4. Routine laboratory investigations including: complete blood count, serum sodium, serum potassium, serum creatinine, blood urea, random blood sugar, total protein, serum albumin, and serum bilirubin.
5. Electrocardiogram (ECG) on admission and when needed.
6. Chest X-ray on admission, every 24 h and when needed.
7. Arterial blood gas analysis through direct arterial puncture or inserted arterial line for measurement of \( \text{PaO}_2 \) to calculate \( \frac{\text{PaO}_2}{\text{FiO}_2} \).
8. Continuous arterial oxygen saturation (SpO\text{\textsubscript{2}}) monitoring by pulse oxymetry (Dash 4000 monitor, General Electric Medical System, Nell Cor) to detect any acute changes in oxygen saturation.
9. Continuous end tidal carbon dioxide (\( P_{\text{ET}} CO_2 \)) monitoring using capnography (Dash 4000 monitor, General Electric Medical System, Marquette) to detect any acute changes in mechanical ventilation.
10. Hemodynamic parameters:
   * Continuous monitoring of heart rate and mean systolic blood pressure using bedside monitor (Dash 4000 monitor, General Electric Medical System) and this will be recorded every hour.
   * Central venous pressure monitoring (cm H\text{\textsubscript{2}}O) every 6 h, will be measured during connection to mechanical ventilator.

12. Sampling for level of CRP in serum collected within 48 h of developing acute lung injury (ALI).

All patients fulfilling the criteria of acute lung injury (ALI) included in the study will be mechanically ventilated according to the same protocol recommended by ARDS network lung protective strategy [32].

All mechanically ventilated patients will be managed with the same protocol for sedation and fluid management.

Outcome variables:

2. Duration of mechanical ventilation.
3. Intensive care unit (ICU) length of stay.
5. Prognosis (complete recovery, recovery with residual complications, and 28 day mortality).

Results

Demographic data

Gender

In our study most of our study population were male (64 patients) which represent 64% of our study population while 36% were female with sex distribution (male:female ratio) of 1.77:1 (Table 5).

Age

Age of patients in the study ranges between 18 and 90 years with a mean of 48.38 ± 19.49 (Fig. 1).
Etiology of ALI

Table 6 demonstrates the frequency and percentage of the different predisposing factors for ALI in our study:

Pneumonia and sepsis were the most frequent predisposing factors for ALI in our study, accounting for 60% (9 patients) of each. This was followed by shock accounting for 53.4% (8 patients). Other etiological factors include aspiration (3 patients), high risk trauma (2 patients) and pancreatitis (1 patient).

Table 7 shows the relationship between patient sex and development of ALI: among 64 males constituting 64% of all patients only 10 patients developed ALI and among 36 females constituting 36% of all patients only 5 patients developed ALI.

There was no statistically significant relationship between sex difference and development of ALI, \( P = 0.531 \).

Table 8 shows the relation between LIPS risk factors and CRP levels.

In patients with pneumonia who developed ALI, CRP levels ranged between 50 and 190 with a mean of 90.29 ± 43.296. There was no significant relationship between pneumonia and CRP levels in the study group (\( P = 0.848 \)) (see Fig. 2). In patients with sepsis who developed acute lung injury CRP levels ranged between 65 and 233 with a mean of 110.56 ± 61.299. There was no significant relationship between sepsis and CRP levels in the study group (\( P = 0.114 \)).

In patients with aspiration who developed ALI, CRP levels ranged between 100 and 225 with a mean of 143.67 ± 70.501. There was no significant relationship between aspiration and CRP levels in the study group (\( P = 0.310 \)).

In patients with pancreatitis who developed ALI, CRP levels were 107 and 225 with a mean of 143.67 ± 70.501. There was no significant relationship between pancreatitis and CRP levels in the study group (\( P = 0.792 \)).

In patients with trauma who developed ALI, CRP levels were 35 and 225 with a mean of 130.00 ± 134.35. There was no significant relationship between trauma and CRP levels in the study group (\( P = 0.652 \)).

In patients with shock index > 1.5 who developed ALI, CRP levels were 50 and 93 with a mean of 74.40 ± 20.369. There was no significant relationship between shock index and CRP levels in the study group (\( P = 0.325 \)).

In patients with high RR > 30 cycle/min who developed ALI, CRP levels were 35 and 233 with a mean of 83.97 ± 49.665. There was no significant relationship between high RR and CRP levels in the study group (\( P = 0.116 \)).

In patients with low serum albumin < 3.5 who developed ALI, CRP levels were 35 and 225 with a mean of 86.82 ± 49.858. There was no significant relationship between serum albumin and CRP levels in the study group (\( P = 0.306 \)).

In patients with smoking who developed ALI, CRP levels were 76 and 190 with a mean of 119.75 ± 48.992. There was no significant relationship between smoking and CRP levels in the study group (\( P = 0.757 \)).

In patients with diabetes who developed ALI, CRP levels were 66 and 232 with a mean of 101.80 ± 134.35. There was no significant relationship between diabetes and CRP levels in the study group (\( P = 0.655 \)).

Table 9 illustrates the relationship between CRP levels and the 2ry end point: CRP levels were the highest in patients with complete recovery ranging between 190 and 233 with a mean of...
Higher CRP levels were significantly associated with better survival ($P = 0.000$).

Table 10 illustrates the correlation between CRP levels and both mechanical ventilation days and ICU stay:

There was an inverse relationship between CRP levels and mechanical ventilation days while ICU stay increases as the CRP levels increase.

Relationships between CRP levels and both mechanical ventilation days and ICU stay are statistically non significant ($P = 0.710$ and $0.801$ respectively).
Table 9  Endpoint in relation to CRP level.

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. deviation</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered</td>
<td>190</td>
<td>233</td>
<td>211.50</td>
<td>30.406</td>
<td>28.194</td>
<td>.000</td>
</tr>
<tr>
<td>Residual complication</td>
<td>107</td>
<td>120</td>
<td>111.33</td>
<td>7.506</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>35</td>
<td>106</td>
<td>79.55</td>
<td>24.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>233</td>
<td>103.50</td>
<td>50.336</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10  Correlations between CRP, MV days and ICU stay.

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>MV days</th>
<th>p</th>
<th>N</th>
<th>ICU stay</th>
<th>r</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>.105</td>
<td>.710</td>
<td>15</td>
<td>.071</td>
<td>.801</td>
<td>15</td>
</tr>
</tbody>
</table>

Correlation is significant at the 0.01 level (2-tailed).

Table 11 illustrates the relationship between CRP levels and development of MODS.

CRP levels were lower in patients who developed MODS ranging between 35 and 106 with a mean of 76.6 ± 28.778 and were higher in patients who didn’t develop MODS ranging between 66 and 233 with a mean of 111.43 ± 59.332. This relationship was not statistically significant ($P = 0.060$).

Discussion

ALI can represent a devastating pulmonary process associated with increased length of stay, costs, and long-term poor outcomes [61,62]. Moreover, it represents a disease that has the potential to impart a burden across a younger and healthier population than previously recognized [63].

The incidence of ALI in this study was 15%, this finding was supported by Trillo-Alvarez et al. [64] in their study whereof 409 patients with at least one predisposing condition at the time of hospital admission, out of 1707 Olmsted County admissions who required ICU care during the study period, 68 (17%) developed ALI/ARDS. While the incidence was lower in other studies like: Gajic et al. [65] where the incidence was 6.8% and Elie-Turenne et al. [66] where the overall incidence was 7%. This can be explained by the type of collected patients where in the current study and in the study of Trillo-Alvarez et al. the study was done in patients who required ICU admission while in the other two studies with the lower incidence rate they were done to inpatient, ICU and ER patients.

Mean age in the current study was 48 years, in those who developed ALI it was 51.9 years and in those who didn’t develop ALI it was 47.4 years, there was no statistically significant difference between the two groups ($P = 0.410$). While some previous studies reported an increased risk of ALI/ARDS in the elderly [67–69], other studies have not confirmed this association [70–72]. It could be argued that elderly patients seem to have an increased incidence of ALI/ARDS as they tend to have more sepsis, pneumonia and aspiration, and require more medical interventions. However, in patients admitted to the hospital with a risk factor (pneumonia or sepsis), age does not seem to increase the risk of ALI/ARDS development. Indeed, recent work implies that incidence of ALI/ARDS due to community-acquired pneumonia is lower in patients aged $\geq 85$ years [70].

In the current study there was no significant difference with regard to patient gender as a risk factor to develop ALI. This finding was supported by Ferguson et al. [73], Trillo-Alvarez et al. [64] and Elie-Turenne et al. [66] in their studies.

Regarding the risk factors for ALI development, in our study the incidence was higher in pneumonia (60% of the ALI group), sepsis (60% of the ALI group), shock (53% of the ALI group) followed to a lesser degree by aspiration (20% of the ALI group) and trauma (13% of the ALI group), which is consistent with the results of the previous studies.

Review articles on ALI list dozens of potential risk factors for ALI including drugs, burns, inhalation injury, pancreatitis, amniotic fluid embolism, and transfusion. In most cohort studies and clinical trials, the majority of cases are caused by pneumonia followed by extra pulmonary sepsis, traumatic injuries, and shock [74,75].

Studies of risk factors for ALI are limited by varying degrees of rigor in establishing the definition of the risk factor. These studies are challenging because they require not only detailed data on the patients with ALI but on patients at risk of the syndrome who do not acquire it. Furthermore, the association between risk factor and ALI as well as the association between risk factor and death may be distorted by transfer and referral patterns in single center studies.

The likelihood of ALI development depends not only on specific risk factors (from 5% with elective cardiopulmonary bypass [76] to 40% in patients with septic shock [19]), but also on the presence of specific risk modifiers.

These risk modifiers include alcohol abuse [76,19], hypoalbuminemia [17,18], tachypnea [18,19], chemotherapy [19,77] and diabetes mellitus [18,78], although whether these factors are independent of one another is unclear. This was consistent with the results of our study except for alcohol abuse and
chemotherapy as there were no or too few people with these risk modifiers in the study population.

We found that among 15 patients with ALI, plasma CRP levels were significantly higher among patients who survived > 28 days, mean CRP levels among completely recovered patients were 211.5 mg/dl ($P = 0.000$), we had excluded one patient from the statistical analysis as the cause of death was tension pneumothorax as a complication of tracheostomy operation. In keeping with that finding, there was an inverse association between increasing CRP levels and 28-day mortality and requirement for mechanical ventilation. This finding is consistent with Bajwa et al. [79] in a study done on 177 patients with ARDS where 60-day mortality and days of mechanical ventilation were lower among patients with higher CRP levels.

In our study we found also that CRP levels were lower among patients who developed MODS during hospital stay with a mean CRP value of 76.6 mg/dl ($P = 0.06$). This finding was also compatible with Bajwa et al. [79] in their study. Anyhow this finding failed to reach significance at a statistical test, this may be attributed to the small sample size.

In another study, Kew et al. [80] report that patients with respiratory distress (an inflammatory pathology in its genesis) and elevated levels of CRP show better prognosis compared to patients with ARDS with lower CRP values. This finding was also compatible with the results of the current study regarding mortality and duration of mechanical ventilation.

In contrast with Bajwa et al. [79] findings, length of ICU stay was directly related to the CRP level: a finding consistent with many other studies like Bhattacharya et al. [81], a prospective cohort study on 30 patients > 18 years who required mechanical ventilation and in Lobo et al. [38], a prospective cohort study on 313 patients admitted to the ICU during the 4-month study period.

In the current study there was a significant relationship between ICU length of stay and the final outcome ($P = 0.004$). Shorter ICU stay was associated with better 28 day survival. This finding is supported by Soppa et al. [82] on 2250 patients undergoing adult cardiac surgery between October 2008 and October 2010 who stayed in an ICU for 5–10 days (Group A) or > 10 days (Group B) were studied. They found that patients who have a prolonged ICU stay (> 10 days) following cardiac surgery have high early and late mortalities.

In the current study there was a significant relationship between duration of mechanical ventilation and the final outcome ($P = 0.032$). Mean days of mechanical ventilation in completely recovered patients was $6 \pm 1.414$ days, longer durations of mechanical ventilation were associated with less favorable prognosis. This finding was compatible with Feng et al. [83]. This study suggests that age and duration of MV are strongly associated with mortality and post hospital disposition.

C-reactive protein is a biomarker in common clinical use to delineate the activity of a host of inflammatory conditions such as sepsis, cardiovascular disease and rheumatological disorders. Patients with sepsis-induced acute respiratory distress syndrome (ARDS) have elevated levels of CRP in both plasma and the bronchoalveolar lavage (BAL) [84,85]. Furthermore, patients who survived acute lung injury tended to have more CRP levels in their blood and BAL fluid than those patients who died [80]. Elevation in serum CRP may be a mechanism to control acute inflammation by down-regulating some neutrophil functions. Serum from high-risk and ARDS patients has significantly less neutrophil chemotactic activity than serum from normal subjects [80].

Although clinical data regarding CRP and lung injury are lacking, a protective role is biologically plausible. Neutrophils are known to accumulate in the lungs of patients with ARDS and are thought to play a pivotal role in lung injury [86]. To cause injury, neutrophils must be recruited to the lung, primarily through the effect of chemoattractant molecules [87], and then activated to release a variety of injurious substances [88]. Then, delayed apoptosis prolongs the lifespan of neutrophils in the lung and perpetuates injury leading to ALI/ARDS [89].

CRP does appear to play an important role in neutrophil chemotaxis, but its role may be more complex than serving to act solely as a chemoattractant; more than 25 years ago, Buchta and colleagues [90] showed that CRP stimulated chemotaxis at lower concentrations but inhibits it, along with other characteristic neutrophil functions, at higher concentrations. These data appear to establish a basis for our findings that CRP may play a protective role at high concentrations without contradicting other studies suggesting an association between CRP and worse outcomes. Patients in many of these studies [90,91] typically have CRP levels much lower than those observed in our critically ill population.

Limitations

The main limitation of the study was the limited number of patients, further studies are recommended in the future specially to evaluate the prognostic value of CRP in patients with ALI.

The other limitation was that our study was a single center study.

Conflict of interest

There is no conflict of interest.

References


Predictive value of C-reactive protein


[S. Derdak, Acute respiratory distress syndrome in trauma patients, J. Trauma 62 (Suppl. 6) (2007) S58.]


[B. Bhattacharya, A. Prashant, P. Vishwanath, M.N. Suma, B. Nataraj, Prediction of outcome and prognosis of patients on mechanical ventilation using body mass index, SOFA score, C-reactive protein, and serum albumin, Indian J. Crit. Care Med. 15 (2) (2011) 82–87.]


