C-Reactive Protein: A Potential Biomarker for Length of Stay Prediction in Critically Ill Patients

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Abstract

Background: Intensive care units (ICU) are a cornerstone component of hospital resource utilization. Expected length of ICU stay is important in patient flow management within the healthcare facility. We intended in this study to evaluate the role of admission CRP as a predictor of ICU length of stay (ICU-LOS).

Methods: We included 56 critically ill patients admitted to the medical ICU of Assalam International Hospital, Cairo, Egypt from March 2013 to October 2013 in this study. Patient assessment on admission stressed on Acute Physiology and Chronic Health Evaluation II (APACHE II) score and/or sequential organ failure assessment (SOFA) score. Beside the routine laboratory investigations and routine cultures of suspected infection sites, CRP assay on admission was done. According to presence or absence of infection identified within 48 hours of admission, our patients were divided into sepsis group and non-sepsis group.

Results: Patient population of the current study had mean age of 57.3±18.3 year old, including 26 males (46.4%) and 30 females (53.6%). The CRP and SOFA score were positively correlated with the ICU-LOS ($r=0.27$, $p=0.04$ and $r=0.48$, $p<0.001$ respectively) however, there was no correlation between APACHE II score and the ICU-LOS ($r=0.05$, $p=0.85$). The admission CRP and SOFA score were significantly higher in the patients with ICU-LOS more than 7 days than in the shorter stay group (CRP was 56.5±16.7mg/L vs 47.9±8.7mg/L, $p=0.02$ and SOFA score was 6.9±3.5 vs 4.4±2.8, $p=0.006$ in long and short stay groups respectively). We found an admission CRP level of 51mg/L to be 80% sensitive and 73% specific to predict more than 7 days ICU stay. The sepsis group comprised 27 patients (48.2%). The SOFA score was positively correlated with the ICU-LOS ($r=0.48$, $p=0.01$) however, the admission CRP revealed no significant correlation with the LOS ($r=0.28$, $p=0.16$). Both CRP and SOFA score revealed no significant difference between long and short stay in septic patients (CRP of 60.5±10.8mg/L vs 50.2±11.2mg/L, $p=0.06$ and SOFA score of 7.2±3.6 vs 4.4±3.4, $p=0.1$ for long and short stay respectively).

Conclusion: We concluded that the admission CRP and SOFA scores can predict ICU length of stay yet their sensitivity and specificity for detecting more than 7 days ICU stay is fair.

Key Words: ICU length of stay – CRP – SOFA score – APACHE II score.

Introduction

THE intensive care units (ICUs) represent an important component in patient flow within the hospital. A large proportion of critically ill patients require a prolonged ICU stay [1-3], causing more than 25% of ICU occupancy [2,4] and accounts for a significant contribution of resource utilization within healthcare organization [5-7]. Precise prediction of ICU discharges therefore results in a more organized and predictable patient flow process not only in the ICU but also throughout the patient care pathway within the hospital. Accurate prediction of ICU length of stay (ICU-LOS) is a critical key performance indicator to assess ICU outcome. This outcome measure is supposed to improve resource management and therefore cost-effectiveness of hospitals.

In addition to its benefits in managerial perspectives and resource management, predicting ICU-LOS has clinical implications. It has been reported to be associated with increased mortality and morbidity [3,8]. Prolonged ICU stay was reported to be associated not only with intra-hospital mortality, but also with long term mortality within 1 year after discharge [1,5-7,9].

Another advantage of predicting the ICU-LOS is the information required for patient and family counseling. In 2001, it was recommended that healthcare delivery becomes patient-centered rather than clinician or disease-centered, with treatment recommendations and decision making tailored to patients’ preferences and beliefs [10]. In this patient-centered model, patients and families are kept informed and actively involved in medical decision
Aim of the study:

For all cases the following were performed:

- Routine cultures of blood, sputum, urine, and suspected sites of infection were obtained. Three ml of venous blood were taken through a venipuncture and sent coded by the patient’s number to the laboratory for admission CRP assay. The lab was blinded to the samples.
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Within 48 hours of admission, patients included in the study were categorized to either sepsis or non-sepsis groups. Septic patients were identified by the presence of SIRS based on the 1991 ACCP/SCCM Sepsis Definition Conference [18] and the diagnostic criteria advanced by the 2001 International Sepsis Definition Conference [19], exhibiting two or more of the following signs: 1- Temperature of >38°C or <36°C, 2- Pulse rate of >90 beats/min, 3- Respiratory rate of >20 breaths/min or hyperventilation with a partial pressure of arterial carbon dioxide (PaCO2) of <32mmHg, or 4- White blood cell (WBC) count of >12,000µL⁻¹ or <4000µL⁻¹, or >10% immature cells. Within the SIRS identified patients, the presence of infection was defined according to the clinical and microbiological criteria of the CDC definitions [20] and was held as a gold standard and determined by three independent experts who were blinded to the CRP results and examined the patients daily for the first 48 hours of admission. According to presence or absence of infection, our patients were divided into two groups; group A included patients with sepsis (sepsis group) and group B included patients with no sepsis (non-sepsis group).

The study protocol was approved by the Ethical Committee of Assalam International Hospital. A written informed consent to participate was obtained from all participating patients or first degree relatives.

Material and Methods

We included in this study a cohort of 56 critically ill patients admitted to the medical ICU of Assalam International Hospital, Cairo, Egypt from March 2013 to October 2013.

We excluded patients received anti-inflammatory drugs or corticosteroids before admission, patients who had immunosuppressive illness, and patients who had received massive blood transfusion from our study.

For all cases the following were performed:

- Full history taking and meticulous physical examination, with Acute Physiology and Chronic Health Evaluation II (APACHE II) score and/or sequential organ failure assessment (SOFA) score to be assessed on admission.
- Routine laboratory investigations (e.g. complete blood count, blood urea nitrogen, blood sugar, serum sodium, potassium, calcium, aspartate aminotransferase, alanine aminotransferase, INR, albumin) were done to the patients. Routine cultures of blood, sputum, urine, and suspected sites of infection were obtained. Three ml of venous blood were taken through a venipuncture and sent coded by the patient’s number to the laboratory for admission CRP assay. The lab was blinded to the samples.

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Statistical methods:

Data were prospectively collected and coded prior to analysis using the professional statistical Package for Social Science (SPSS version 16). Continuous variables were expressed as mean and standard deviation (SD). Categorical variables were expressed as frequency and proportion. Student-t Test (t) was used for comparison between two groups as regards normally distributed (parametric) quantitative data. Chi-Square Test (χ²) was used for comparison between two groups as regards qualitative data. Results were considered statistically significant if p<0.05. A receiver operating characteristic (ROC) analysis was performed to define a cutoff value of different markers.

Results

During the period between March 2013 and October 2013, fifty six critically ill patients with expected length of stay more than 24 hours in the medical ICU in Assalam International Hospital, Cairo, Egypt were enrolled in the study. Our patients had mean age of 57.3±18.3 year old, including 26 males (46.4%) and 30 females (53.6%).

Patients’ demographics and baseline clinical data are shown in Table (1) and the causes of ICU admission are illustrated in Table (2).
Table (1): Baseline demographic and clinical data.

<table>
<thead>
<tr>
<th>Age (Year old)</th>
<th>57.3±18.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender [N (%)]:</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (46.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (53.6%)</td>
</tr>
<tr>
<td>Co-morbidity:</td>
<td></td>
</tr>
<tr>
<td>1 Co-morbidity</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>2 Co-morbidities</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>More than two co-morbidities</td>
<td>28 (50%)</td>
</tr>
<tr>
<td>Cause of admission:</td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>46 (82.1%)</td>
</tr>
<tr>
<td>Surgical</td>
<td>10 (17.9%)</td>
</tr>
</tbody>
</table>

Table (2): Causes of admission.

<table>
<thead>
<tr>
<th>Respiratory distress:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>19 (33.9%)</td>
</tr>
<tr>
<td>Acute lung injury</td>
<td>4 (7.1%)</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>2 (3.6%)</td>
</tr>
<tr>
<td>Acute Pulmonary edema</td>
<td>2 (3.6%)</td>
</tr>
<tr>
<td>CRF with volume overload</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Suspected central line infection</td>
<td>3 (5.4%)</td>
</tr>
<tr>
<td>Soft tissue infection</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (3.6%)</td>
</tr>
<tr>
<td>DKA</td>
<td>6 (10.7%)</td>
</tr>
<tr>
<td>Post-operative</td>
<td>10 (17.9%)</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Abdominal sepsis</td>
<td>2 (3.6%)</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Melena</td>
<td>1 (1.8%)</td>
</tr>
</tbody>
</table>

We found that the serum CRP level on admission is positively correlated with the SOFA score ($r=0.49, p<0.001$) (Fig. 1). We could not elucidate any correlation between CRP and APACHE II score in 16 of our patients for whom APACHE II score was done ($r=0.09, p=0.7$) (Fig. 1).

We evaluated the correlation between the admission CRP, APACHE II score and the SOFA score and the ICU-LOS. The CRP and SOFA score were positively correlated with the ICU-LOS ($r=0.27, p=0.04$ and $r=0.48, p<0.001$ respectively) (Fig. 2). Meanwhile, we didn’t find any correlation between APACHE II score and the ICU-LOS ($r=0.05, p=0.85$) (Fig. 3).

The ICU-LOS was then categorized into group of patients with short stay (less than or equal to 7 days for ICU LOS) and a long stay group (more than 7 days).

The admission CRP and SOFA score were significantly higher in the long stay group than in the short stay group (CRP was 56.5±16.7 mg/L vs 47.9±8.7 mg/L, $p=0.02$ and SOFA score was 6.9±3.5 vs 4.4±2.8, $p=0.006$ in long and short stay groups respectively) (Fig. 4). The APACHE II score revealed no significant difference between both groups (13.1±5.7 vs 12.9±6.1, $p=0.9$ in long and short stay groups respectively) (Fig. 4). We found an admission CRP level of 51 mg/L to predict more than 7 days ICU stay with a sensitivity of 80%, specificity of 73%, 70% positive predictive value (PPV), and 81% negative predictive value (NPV).
The admission CRP was higher in the sepsis group compared to the non-sepsis group (58.6±11.4mg/L vs 45.7±12.8mg/L, p<0.001) (Fig. 6). The SOFA score was also higher in the sepsis group (6.7±3.7 vs 4.5±2.6, p=0.01) (Fig. 6). The SOFA score was positively correlated with the ICU-LOS in septic patients (r=0.48, p=0.01) however, the admission CRP revealed no significant correlation with the LOS (r=0.28, p=0.16) (Fig. 7). Both CRP and SOFA score revealed no significant difference between long and short stay in septic patients (CRP of 60.5±10.8mg/L vs 50.2±11.2mg/L, p=0.06 and SOFA score of 7.2±3.6 vs 4.4±3.4, p=0.1 for long and short stay respectively).

Intensive care units consume a considerable portion of hospital budgets. Problems with ICU capacity are nevertheless common. Many studies documented high rates of lack of empty ICU beds representing a problem with ICU capacity [21,22]. Optimizing patient planning is critical to improve the efficiency of ICU capacity management. Availability of reliable information regarding the expected date of patient discharge, when known on patient admission, is a cornerstone in ICU planning by anticipating the date at which the ICU bed will be once again available.
It was shown that the ICU-LOS is the most important variable that affects ICU resource use [23]. A small proportion of ICU patients with longer stay contributes to the highest resource utilization [6] and the highest financial burden during the whole hospital stay [24].

Another important issue in predicting ICU-LOS is achieving an answer to an important and common question of the patient and/or family during family counseling which is “when the patient will be discharged?”. The answer of this question is challenging. There is a gap between the patients families’ optimistic expectation and the ICU clinicians’ professional judgment and choice of treatment.

Prediction of ICU-LOS as a performance outcome is much less studied than mortality prediction. ICU-LOS gained recently more attention in the field of critical care medicine. Severity scores, like the APACHE II score has been used to predict the ICU-LOS [25,26]. We couldn’t elucidate a correlation between the APACHE II score and the LOS in our study neither in the whole population nor on the subgroup of patients with sepsis. Contrary to our results, Siddiqui et al., strongly claimed in their study that APACHE II score on admission is reliable predictor of the length of stay in ICU [27]. The APACHE II score was later modified to the more complex APACHE III and IV scores to improve its predictive accuracy. APACHE III and IV models were widely used to compare ICU stays and its differences among different hospitals [28-31]. These scores are however very sophisticated models.

Another scoring system that was evaluated in predicting LOS is the SOFA score. We found that the SOFA score correlates with the length of stay. SOFA score of 4 can predict more than 7 days ICU stay with 73% sensitivity and 67% specificity. Engle et al., reported correlation of LOS and an admission SOFA similar to our results [32] but they concluded that the maximum SOFA and the change of SOFA over time are better than admission SOFA in prediction of the ICU-LOS [32]. It is well known that the APACHE II score has no adjustments for the use of hemodynamic support, while the SOFA score does [33]. This explains the noticed more accuracy of SOFA score in predicting the ICU-LOS than APACHE II score.

The use of the biomarkers in the field of the critical care medicine is rapidly evolving. CRP is the most widely used biomarker in critically ill patients. It was seen in many studies that CRP can indicate the presence or absence or severity of sepsis [34,35]. Other potential uses of biomarkers include roles in prognostication, guiding antibiotic therapy, evaluating the response to therapy and recovery from sepsis, and predicting sepsis complications. We found in our study that the admission CRP level is positively correlated with both the ICU-LOS ad SOFA score. We found a CRP level of 51mg/L to be 80% sensitive and 73% specific to identify patients who stay more than 7 days in the ICU. Lobo et al., concluded also that patients with high CRP levels had significantly higher SOFA scores, and ICU stays than patients with normal CRP levels [16]. Some other investigators found that high CRP level (>10mg/L) was associated with two fold increase in the LOS [17]. This correlation between serum CRP and ICU-LOS was also evaluated in surgical ICU patients. Perry et al., evaluated preoperative CRP and found that it correlates with LOS in CABG patients [36] and Alaedeen et al., found that the peak and not the admission serum CRP was significantly correlated to LOS in surgical infants [37].

We could not find in the literature a work that evaluated a cutoff value for CRP to predict long ICU stay in critically ill patients. The presence and severity of inflammatory response is a major determinant of the patient course in the ICU. C-reactive protein production being a part of a larger picture of the acute phase response and is principally regulated by the cytokines IL-6, Tumor necrosis factor a, and IL-1ß [38]. it is not surprising that the CRP level may indicate the severity of host immune response that can be translated to its impact on the LOS.

These results about prediction of ICU-LOS were optimistic, however, this enthusiasm faces many obstacles. Differences in response to therapy, the frequency and timing of iatrogenic or disease complications, and unexpected outcomes as deaths among low mortality risk patients and survival among high risk patients might have been influenced, at least in part, the accuracy of ICU length of stay predictions [31].

Our study design has the limitation of studying all critically ill patients without diagnosis categories. A more significant predictive value of the CRP could be higher in certain subgroups of patients. We tried in this contest to evaluate the subgroup of patients with sepsis where we found that despite that the admission CRP is higher in septic than in non-septic patients, there was no correlation between both CRP and SOFA score with ICU-LOS in septic patients. This lack of
correlation was surprising and may be related to the small sample size of the group. We also showed that the admission CRP was higher in septic than in non-septic patients. Many other studies showed that a high serum CRP concentration within 24 hours of admission to hospital is indicative of sepsis and can differentiate septic from non-septic patients [39,40]. Another limitation is depending on one value of CRP level only on admission. Other investigators studied the maximum of many values [37] and others evaluated the trend of CRP level [41]. Our aim of this work was however the early prediction of the LOS on admission.

Conclusion:

We concluded from this study that the admission CRP and SOFA scores have a fair sensitivity and specificity to predict more than 7 days ICU stay.

The concept of using a biomarker for prediction of ICU discharge time is challenging and needs wider scale studies on each subset of patients separately.

References


