Prognostic role of serum uric acid in acute respiratory distress syndrome patients: A preliminary study

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Abstract  Background: ARDS mortality is still high, many biomarkers had been used to predict the mortality but they may have many drawbacks because of its validity, complications and cost.

Study design: Observational study was planned to evaluate the predictive role of serum uric acid level in ARDS outcome. Mortality was the primary end-point while secondary endpoints included total ICU stay, duration of mechanical ventilation and the presence or absence of complications.

Aim: The aim of this work is to study the role of serum uric acid level as an outcome predictor in ARDS patients.

Patients and methods: Thirty three ARDS patients were enrolled in this study according to Berlin 2012 definition. Patients with diabetes mellitus, chronic renal failure, cardiovascular disorders, decompensated liver disease and known malignancies were excluded from the study. On admission to ICU serum uric acid level was investigated.

Results: Sensitivity and specificity of uric acid as an outcome predictor at a cut off of 8.4 mg/dl were 89% and 80% respectively; the area under curve was 0.88 with p value <0.001, mortality in a high uric acid group that reported to be 86.7% was statistically significant higher than the normal uric acid group 38.9%.

Conclusion: Serum uric acid level at 8.4 mg/dl cut off point predicts mortality in ARDS patients with 89% sensitivity and 80% specificity.

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Introduction

The acute respiratory distress syndrome (ARDS) was defined in 1994 by the American-European Consensus Conference (AECC) [1]. Since then, issues regarding the reliability and validity of this definition have emerged. Using a consensus process, a panel of experts convened in 2011 (an initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine) developed Berlin definition, focusing on feasibility, reliability and validity [2]. Recent consensus group made a number of changes to the previous American-European Consensus Conference definition of ARDS which includes: timing within one week of a known clinical insult or new or worsening respiratory symptoms, chest imaging of bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules, the origin of edema and respiratory failure are not fully explained by cardiac failure or fluid overload which needs objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor is present; and lastly oxygenation: mild PaO₂/FIO₂ ≤300–200 mmHg with PEEP or CPAP ≥5 cmH₂O; moderate: ≤200–100 mmHg with PEEP ≥5 cmH₂O and severe: PaO₂/FIO₂ ≤100 mmHg with PEEP ≥5 cmH₂O [3].

ARDS is a life threatening respiratory condition characterized by hypoxemia and stiff lungs, without mechanical ventilation most patients would die [4]. A complex network of cytokines and other pro-inflammatory compounds initiate and amplify the inflammatory response in acute respiratory distress syndrome. New evidence indicates that it is not only the production of pro-inflammatory cytokines that is important, but also the balance between pro-inflammatory and anti-inflammatory mediators [4]. Since its first description in 1967, there have been a large number of studies addressing various clinical aspects of the syndrome (risk factors, epidemiology and treatment) as well as studies addressing its pathogenesis (underlying mechanisms, biomarkers and genetic predisposition). The lack of therapeutic modalities is certainly related to the complex pathogenesis of this syndrome with multiple signaling pathways activated depending on the type of lung injury. In addition, the lack of sensitive and specific diagnostic criteria to diagnose ARDS has hampered progress [3]. Serum uric acid is the final product of purine degradation [5], which increases significantly during hypoxia [6]. Increased level of uric acid in respiratory disorders, including obstructive sleep apnea, pulmonary hypertension and COPD was reported in several studies [7,8].

Impaired pulmonary function reduces oxygen intake resulting in tissue hypoxia which is more prominent during acute exacerbation in COPD, this may lead to increased circulating uric acid levels originating from both lung and peripheral tissue damage [9]. Elevated uric acid levels have been associated with the presence of systemic inflammation [10] and increased cardiovascular risk [11]. Elevated uric acid levels have been associated with increased levels of inflammatory markers (e.g. CRP and interleukin-6) [12].

ARDS related mortality is still high, many biomarkers had been used to predict mortality but they may have many drawbacks because of its validity, complications and cost. To date, as far as we know, no studies have evaluated the role of serum uric as an outcome predictor in ARDS patients. Therefore, this cohort observational study was conducted to evaluate the possible role of serum uric acid as a biomarker for outcome prediction in ARDS patients. Mortality was the primary endpoint while secondary endpoints included total ICU stay, duration of mechanical ventilation and presence or absence of complications.

Patients and methods

After approval from the departmental ethics committee, this cohort observational study was conducted in the pulmonary critical care unit, Mansoura University Hospitals during the period from July 2013 to August 2014 including 11 females and 22 males with ages ranging from 18 to 50 years suffering from ARDS according to the Berlin 2012 definition, which is based on history, X-ray opacities, exclusion of cardiac causes of pulmonary edema and PaO₂/FIO₂ ratio [1]. Patients with diabetes mellitus, chronic renal failure, cardiovascular disorders, decompensated liver disease and known malignancies were excluded from the study. Plain chest X-ray, trans-thoracic echocardiography was done to exclude patients with cardiovascular disorders.

Admission APACHEII score was calculated. Blood samples were collected from each patient on admission and prior to initiation of any treatment for basic serum uric acid and standard laboratory measurements (complete blood count, serum creatinine and blood gases). Uric acid was measured using enzymatic colourimetric method. Uric acid values above or equal to 6.4 mg/dl were considered the high uric acid group and below it were the normal uric acid group. Mortality rate was reported. Total ICU stay, duration of mechanical ventilation and presence or absence of complications were also reported, consent was taken from first-degree patient relative.

Statistical analysis

Statistical analysis was conducted by using SPSS (version 17, Chicago, IL). For continuous variables, data were tested for normal distribution using the Kolmogorov–Smirnov test. The description of the data was done in the form of mean ± SD for quantitative data and frequency and proportion for qualitative data. The analysis of the data was done to test statistically significant difference between groups. For quantitative data, unpaired Student’s t-test was used to compare between two groups. Chi square test was used for qualitative data. Receiver operating characteristics (ROC) curve analysis was performed for the evaluation of the sensitivity and specificity of serum uric acid level and PaO₂/FIO₂ ratio in predicting ARDS mortality. Correlations were performed with Pearson’s rank correlation coefficient. For all tests, statistical significance was considered when p < 0.05.

Results

Comparing data in high and normal uric acid groups, there was no statistically significant difference as regards age in both high (≥6.4 mg/dl) and normal uric acid (<6.4 mg/dl) groups 32.6 ± 8 and 32.7 ± 9 respectively, p value of 0.97 (Table 1). Statistically significant lower APACHEII was reported in high uric acid group 27.1 ± 3.8 in comparison with normal uric
Comparing data between survived versus dead, there was no statistically significant difference for age in both survived and dead 32.0 ± 8.6 and 33.2 ± 8.4 respectively p value of 0.684 (Table 2). While the APACHEII was statistically significant lower in dead one (29.6 ± 6.3) than survived one (42.3 ± 8.5); p was < 0.001 (Table 2). Furthermore, the PaO₂/FIO₂ was statistically significant lower 87.7 ± 28.1 in died group than 179.9 ± 44.8 in the survived group p was < 0.001 (Table 2). On the other side, the uric acid level in dead one 8.8 ± 2.8 mg/dl was statistically significant higher than 5.0 ± 1.8 mg/dl in survived one p was < 0.001 (Table 2). As regards the etiology of ARDS, near drowning represents 92.30% in survived compared to (35%) died groups, gastric aspiration represents 20% in dead and no one survived had gastric aspiration. Pneumonia was found in 45% of died group compared to only 7.69% in survived group (Table 2). In spite of the duration of ventilation being shorter in dead one (9.9 ± 3.2) days compared to survived (12.1 ± 3.4) it was non-significant p = 0.06 (Table 2). In addition, the total ICU stay was statistically significant shorter in died group (10.1 ± 3.2) compared to (15.4 ± 3.7) survived p value was 0.01 (Table 2). Multiple organ dysfunction syndrome was encountered more in dead 60% than survived 15.4% it was statistically significant; p value was < 0.001 (Table 2). There was a statistically significant negative correlation between uric acid and APACHEII r = -0.84 p value < 0.001 and the same negative correlation between uric acid and PaO₂/FIO₂ r = -0.68; p value was < 0.001 (Table 3 and Figs. 2a and 2b).

Finally, the sensitivity and specificity of uric acid as an outcome predictor at cut off 8.4 mg/dl were 89% and 80% respectively; the area under curve was 0.88 with a p value of < 0.001, while the sensitivity and specificity of PaO₂/FIO₂ at 99 cut off were 100% and 83% respectively; the area under the curve was 0.97 with a p value of < 0.001 (Table 4 and Fig. 3a and b).

**Discussion**

The findings of this cohort observational study demonstrated that high serum uric acid level was associated with higher
mortality, more severe ARDS and frequent occurrence of multiple organ dysfunction syndrome. Serum uric acid at 8.4 mg/dl cut off point predicts mortality in ARDS patients with 89% sensitivity and 80% specificity.

Uric acid levels are influenced by several factors including cardiovascular disease, food intake, alcohol consumption, renal dysfunction and genetic disorders of purine metabolism [11].

In the evaluation of serum uric acid levels we need to take into account that this metabolite is the end product of purine degradation, which increases in a very sensitive but nonspecific way in several forms of tissue damage and inflammation [13]. It was suggested that tissue injury may cause sterile inflammation and several mediators such as uric acid, ATP, high mobility group box1 protein, heat shock protein 70, lysophosphatidic acid and others have been identified. These danger signals may be produced after lung damage, triggering inflammation, remodeling and fibrosis [14]. ARDS represents a stereotypic response to many different inciting insults. ARDS is a life threatening respiratory condition characterized by hypoxemia [4]. Serum uric acid levels increases significantly during hypoxia [7–9]. Elevated uric acid levels have been associated with the presence of systemic inflammation [12].

APACHEII was statistically significant lower in ARDS patients with uric acid > 6.4 mg/dl group than those with uric acid < 6.4 mg/dl group, besides our finding that APACHEII was statistically significantly lower in patients who died than survived. Not only that but also, the significant negative correlation between uric acid and APACHEII; i.e. lower APACHEII which indicates the more severity of illness in admitted ARDS patients had a higher uric acid level. Data from the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison between survived and died in ARDS patients. Data are expressed as mean ± standard deviation, number and percentage.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived group (n = 13)</td>
<td>Died group (n = 20)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.0 ± 8.6</td>
</tr>
<tr>
<td>APACHEII</td>
<td>42.3 ± 8.46</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.0 ± 1.8</td>
</tr>
<tr>
<td>PaO2/FIO2 (mmHg)</td>
<td>179.9 ± 44.8</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Near drowning</td>
<td>12 (92.30%)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (7.69%)</td>
</tr>
<tr>
<td>Duration/day</td>
<td></td>
</tr>
<tr>
<td>Ventilation</td>
<td>12.1 ± 3.4</td>
</tr>
<tr>
<td>ICU stay</td>
<td>15.4 ± 3.7</td>
</tr>
<tr>
<td>MODS</td>
<td>2 (15.4%)</td>
</tr>
</tbody>
</table>

APACHEII: Acute Physiology and Chronic Health Evaluation; MODS: Multiple Organ Dysfunction Syndrome; FIO2: Fraction of Inspired Oxygen.

* Denotes significant test.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Correlation between uric acid on one side and APACHEII and PaO2/FIO2 on the other side.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid level</td>
<td>r_s coefficient</td>
</tr>
<tr>
<td>APACHEII</td>
<td>−0.84</td>
</tr>
<tr>
<td>PaO2/FIO2</td>
<td>−0.68</td>
</tr>
</tbody>
</table>

* It indicates statistically significant.

**Figure 2a** Correlation between uric acid and APACHEII.

**Figure 2b** Correlation between uric acid and PaO2/FIO2.
large ECLIPSE cohort study in COPD exacerbation suggested that the frequent-exacerbation phenotype is more common in more severe disease and this may, in part, explain the association between high serum uric acid levels with disease severity and exacerbation frequency [15].

The PaO$_2$/FiO$_2$ was statistically significant lower in the high uric acid group than in normal uric acid group. Additionally, PaO$_2$/FiO$_2$ was statistically significant lower in dead than in survived one, moreover, there was a statistically significant negative correlation between uric acid and PaO$_2$/FiO$_2$, meaning that ARDS patients with more hypoxemia had a higher serum uric acid level as well as both correlated inversely. These findings were explained by Bartziokas and his associates [7] who found that serum uric acid which is the final product of purine degradation, increases significantly during hypoxia which is a hallmark feature in ARDS patients. Also, Fabbri and Rabe [9] reported that impaired pulmonary function reduces oxygen intake resulting in tissue hypoxia which was more prominent during acute exacerbation in COPD and this may lead to increased circulating uric acid levels originating from both lung and peripheral tissue damage. Elevated uric acid levels had been associated with increased levels of inflammatory markers (e.g. CRP and interleukin-6) [12] which were also increased in ARDS patients. Therefore, not only PaO$_2$/FiO$_2$ triage ARDS patients into mild, moderate and severe, but also predict poor outcome whenever it is low. In our study the sensitivity and specificity of PaO$_2$/FiO$_2$ at 99 cut off were 100% and 83% respectively.

The reported mortality rate of acute respiratory distress syndrome was from 40 to 60% [16] which was almost matched with the results of 20 patients out of 33 mortality in our study (60.6%), that mortality was statistically significant higher in high uric group (86.66%) compared to only (38.88%) in the normal group, also the serum level of uric acid in those who died was statistically significant higher than in survived ARDS patients which may be explained by the study of Filippatos and his coworker, who showed that hyperuricaemia is associated with poor outcomes in heart failure patients without chronic kidney disease but not in those with chronic kidney disease, suggesting that hyperuricaemia may predict poor outcomes when it is related to increased xanthine oxidase activity, but not due to impaired renal excretion of uric acid [17]. As far as we know, no available studies matched hyperuricaemia with mortality in ARDS patients but indirectly most ARDS patients do not die without passing into the journey of heart failure. Patients with pneumonia had higher mortality than near drowning patients. On the other side of the coin, the current study displayed that multiple organ dysfunction syndrome was encountered more in high uric acid group than normal group and its incidence was statistically significant higher in dead compared to survived ARDS patients which may add to the concept of severe ARDS; more hypoxemia; more multiple organ dysfunction syndrome and more death.

The present study was not without limitations; first, a small number of studied ARDS patients (only 33 patients), second, ARDS etiology was mono dimensional; mainly of medical rather than surgical, direct rather than indirect. Third, we did not measure uric acid at different times along the journey of admission for our patient because the notion of mortality prediction circumvents this issue. The previous limitations

| Uric acid | 8.4 | 0.88 | <0.001 | 89% | 80% |
| PaO$_2$/FiO$_2$ | 99 | 0.97 | <0.001 | 100% | 83% |

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Figure 3 (a) ROC curve for uric acid and (b) ROC curve for PaO$_2$/FiO$_2$. |
make back generalization difficult for this preliminary study. Further studies are warranted for more convenience.

The present study concluded that serum uric acid at 8.4 mg/dl cut off predicts mortality in ARDS patients with 89% sensitivity and 80% specificity. The presence of higher mortality, low PaO2/FIO2 and low APACHEII in patients with higher serum uric acid level encourages us to pay attention to the importance of serum uric acid which is one of the routine metabolic profiles in pulmonary critical care practice and because it is a rapid, easy and cheap test sparing money funding costly markers and effort waiting tedious results we can adopt it as one of the valuable outcome predictors for that still fatal ARDS problem.

Conflict of interest

None declared.

References