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ORIGINAL ARTICLE

Urinary Intestine Fatty Acid Binding Protein is Associated with Poor Outcome of Pneumonia Patients in Intensive Care Unit

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SUMMARY

Background: **Urinary intestine fatty acid binding protein (U-IFABP) is a biomarker for gut injury. Previous studies showed that enterocyte damage in critically ill patients was common and appeared to be associated with poor prognosis. However, the impact of enterocyte damage on the outcome of critically ill patients with pneumonia has not yet been well investigated. The aim of the study is to evaluate the prognostic value of U-IFABP in critically ill patients with pneumonia.**

Methods: **A prospective observational study was performed in the intensive care unit (ICU) from September 1, 2013 to April 30, 2014. Pneumonia patients were divided into survival and non-survival groups. U-IFABP was measured using enzyme linked immunosorbent assay for 7 consecutive days after admission to ICU and expressed as U-IFABP/urine creatinine ratio. The prognostic value was tested by Receiver Operator Characteristic (ROC) curves and Kaplan-Meier curves.**

Results: **A total of 32 pneumonia patients with endotracheal intubation were enrolled. U-IFABP/Cr levels were significantly higher in non-survivors than in survivors at day 1 ($p = 0.033$), day 4 ($p = 0.018$), day 5 ($p = 0.008$), day 6 ($p = 0.006$) and day 7 ($p = 0.008$) after ICU admission. The areas under ROC curve in predicting mortality were 0.755 (D1), 0.781 (D4), 0.812 (D5), 0.823 (D6), and 0.812 (D7). Moreover, pneumonia patients with day 7 U-IFABP/Cr above the cutoff of 28.9 pg/100 µL had a significantly lower survival rate ($p = 0.043$).**

Conclusions: **Enterocyte injury was common in critically ill patients with pneumonia. The severity of enterocyte injury, as evidenced by the U-IFABP/Cr, was associated with the patient's mortality. U-IFABP/Cr may serve as a significant prognostic factor for patients with pneumonia admitted to ICU. Further studies with larger populations are needed to verify these issues.**

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KEY WORDS

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INTRODUCTION

Pneumonia is an inflammatory process of the alveolar portions of the lung [1-4]. It is the leading cause of morbidity and mortality in the intensive care unit (ICU) and

the second ranking cause of global deaths in 2013 [5,6]. Patients with severe pneumonia usually require inotropic agents and endotracheal intubation with assisted mechanical ventilation that always direct admission to the ICU for high-level monitoring and management of the unstable hemodynamic condition [7]. Previous studies demonstrated that enterocyte injury in critically ill patients was associated with poor prognosis [8,9]. However, the cause-effect between pneumonia and enterocyte damage is not clear. Respiratory and intestinal epithelia originate from common embryonic origin which integrated as a network of the common mucosal immune system in humans. It is perhaps not surprising that disruption of one mucosal compartment can directly impact the immunity of distant mucosal sites [10].

Intestine fatty acid binding protein (IFABP) is a 12 -15 kDa protein located at the mature enterocytes of the small intestinal and is usually undetected in blood circulation. IFABP diffuses through the interstitial space into the circulation when enterocyte membrane integrity is lost [11,12]. Because of its small size, IFABP can rapidly pass through the glomerular apparatus and can be detected in urine, making it an early and sensitive non-invasive marker of enterocyte injury [13-15].

The usefulness of urinary IFABP (U-IFABP) in predicting outcomes of patients with pneumonia in the ICU has not yet been investigated. Furthermore, to our knowledge, there is a lack of reliable biomarkers to predict the outcome of the critically ill patients with pneumonia. It can be clinically relevant and attractive if and when U-IFABP is shown to be of value in predicting the outcomes of patients with pneumonia admitted to the ICU. In this study we evaluated the prognostic value of U-IFABP in patients with pneumonia admitted to the respiratory ICU.

MATERIALS AND METHODS

Study setting and patients

We performed a prospective observational study on pneumonia patients who were admitted to the respiratory ICU at Taipei Veterans General Hospital from September 1, 2013 to April 30, 2014. It is a tertiary care medical center in Taipei, Taiwan. Patients age > 20 years old who were diagnosed to have severe pneumonia (community-acquired pneumonia and health care-associated pneumonia) with an indwelling urinary catheter and admitted to the respiratory ICU were eligible for this study. Severe pneumonia was defined as follows: pneumonia with one of two major criteria (the need of invasive mechanical ventilation or inotropic agents) or three of nine minor criteria (respiratory rate ≥ 30 breaths/min, $PaO_2/FiO_2 \leq 250$ mmHg, multilobar infiltrates, confusion, serum urea nitrogen level ≥ 20 mg/dL, white blood cell count < 4000 cell/mm^3, platelet count < 100,000 cells/mm^3, core temperature < 36°C, and hypotension requiring aggressive fluid resuscitation) [7]. Written informed consent was obtained from the patients or their families before participating in the study, and the study was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No: 2013-04-030BC). Exclusion criteria were pregnancy, chronic renal failure, chronic gut disease, intra-abdomen infection, and history of gut resection surgery.

Data collection

Age, gender, and co-morbidities such as diabetes mellitus, cerebrovascular disease, chronic heart disease, chronic respiratory disease, chronic liver disease, and malignancy were recorded on the designed form. Laboratory data at admission including leukocyte count, platelets, hematocrit, prothrombin time, creatinine, alanine aminotransferase, blood sugar, C-reactive protein (CRP), lactate, procalcitonin, and arterial blood gas were also collected. Sequential Organ Failure Assessment score, Acute Physiology and Chronic Health Evaluation (APACHE) II score and Pneumonia Severity Index were calculated and documented by one investigating nurse. Sepsis, severe sepsis, and sepsis shock was defined according to the criteria proposed by the Surviving Sepsis Campaign Guidelines Committee [16]. Shock index was defined as heart rate over systolic blood pressure. The main outcome was all-cause in-hospital mortality.

Measurement of urinary IFABP

24-hour urine samples were collected every day in early morning for 7 consecutive days after ICU admission. Samples were centrifuged and the supernatants were stored at -80°C within 1 hour of urine collection. Urinary IFABP was measured using commercially available enzyme-linked immunosorbent assay kits (R&D systems; Minneapolis, MN, USA) and expressed as U-IFABP/urine creatinine ratio (U-IFABP/Cr, pg/100 μL).

Statistical analysis

Data were expressed as mean ± standard deviation, median, and interquartile ranges (IQR) or number and percentages. Categorical variables were compared using chi-square or Fisher's exact test where appropriate. For normally distributed data, continuous variables were compared using Student's *t*-test. Otherwise, Mann-Whitney *U* test was used for nonparametric variables. Spearman's rank correlation for nonparametric data was used to test the association of U-IFABP/Cr with clinical parameters. The diagnostic performance of U-IFABP/Cr in predicting mortality was tested by Receiver Operator Characteristic (ROC) Curve and the area under the curve (AUC) was estimated. To demonstrate the capacity of U-IFABP/Cr for risk stratification in pneumonia patients, a comparison of survival using Kaplan-Meier survival curves was performed. Statistical analysis was performed using SPSS version 19 (SPSS, Chicago, IL, USA). Statistical significance was determined as $p < 0.05$.

Table 1. The demographic and clinical characteristics of the pneumonia patients.

Variable	n = 32
Age (year)	83 [70 - 88]
Gender Male	 26 (81)
Co-morbidities Diabetes mellitus Cerebrovascular disease Chronic heart disease Chronic respiratory disease Chronic liver disease Malignancy	 7 (22) 10 (31) 13 (41) 14 (44) 3 (9) 7 (22)
Nursing home	5 (16)
SOFA score	8 [5 - 9]
APACHE II score	23 [19 - 28]
Pneumonia Severity Index	141 [121 - 171]
Mechanical Ventilation	32 (100)
Length of stay in ICU, day	17 [13 - 22]
Length of stay in hospital, day	40 [2 3 - 60]
Mortality	8 (25)

n (%) - median [interquartile range], APACHE II - Acute Physiology and Chronic Health Evaluation II, SOFA - Sequential Organ Failure Assessment, ICU - Intensive Care Unit.

RESULTS

Between September 1, 2013 and April 30, 2014, a total of 32 patients were included for this study. The demographic and clinical characteristics of the study population are summarized in Table 1. The median age was 83 years old and 90% of the patients had at least one comorbidity. All of them were intubated and assisted with a mechanical ventilator. The median Pneumonia Severity Index was 140 and the mortality rate was 25% (8 of 32).

Analysis of the risk factors associated with mortality is shown in Table 2. The severity and clinical parameters between survival and non-survival groups were comparable. The median duration (IQR) of ICU stay was 17 (13 - 22) days in survivors and 18 (11 - 26) days in non-survivors. Among the variables related to mortality due to pneumonia were higher U-IFABP/Cr at days 1 and 4 - 7 and lower hematocrit levels. Figure 1 shows the trend of U-IFABP/Cr values of survivors and non-survivors. The U-IFABP/Cr level was always higher in non-survivors during the first 7 days of ICU admission. Table 3 demonstrates that U-IFABP/Cr levels are not significantly correlated with the common clinical severity score or shock parameters at day 1 except for CRP levels ($r = 0.392$, $p = 0.026$).

Table 4 shows the AUC of ROC curves of U-IFABP/Cr in predicting mortality at day 1 and day 4 - 7 after ICU admission. The optimum cutoff points to discriminate survivors and non-survivors were assessed as the maximum sum of sensitivity and specificity using ROC curves. The optimum cutoff points, sensitivity, specificity, positive predictive value, and negative predictive value are summarized. To demonstrate the capacity of U-IFABP/Cr for risk stratification in pneumonia patients, a comparison of all-cause hospital survival using Kaplan-Meier survival curves was performed. Pneumonia patients with day 7 U-IFABP/Cr levels above the cutoff of 28.9 pg/100 μL had significantly lower survival rates compared with patients with levels below this cutoff (Log-rank test = 0.043) (Figure 2).

DISCUSSION

To the best of our knowledge, our research is the first to study the clinical relevance of the urinary biomarker I-FABP in pneumonia patients in the ICU. The major results indicated that the patients with marked elevation of U-IFABP/Cr had higher mortality. In this research, we demonstrated the optimum cutoff point of U-IFABP/Cr for predicting all-cause hospital mortality at day 1 and day 4 - 7. The specificity ranged from 83% to 96%. Moreover, the study also revealed a prognostic cutoff value of day 7 U-IFABP/Cr for risk stratification in all-cause in-hospital mortality.

The human intestinal tract acts as a major physical barrier between the microflora and internal host tissues and responds to the mucosal innate system through the commensal microflora [17]. A failure of gut barrier function as a result of a major stress insult permits bacterial and endotoxin translocation, which triggers systemic cytokines and exacerbates a systemic immunoinflammatory response that results in organ dysfunction [18]. A previous study found that enterocyte destruction was due to the reduction of splanchnic perfusion in shock, a common condition in patients admitted to the ICU [19]. Our study found that the U-IFABP/Cr showed a trend of positive correlation to several shock parameters such as lactate and systolic blood pressure but did not reach statistical significance. The shock index in both survivors and non-survivors were comparable (0.95 [0.73 - 1.15] vs. 0.85 [0.83 - 1.1]). However, the U-IFABP/Cr was significantly different between the two groups. This phenomenon implied that shock might be one of the factors that caused gut failure. Our results supported that pneumonia itself might be an important risk factor responsible for injury of the gut barrier. The influence of the gut-lung axis on lung injury and immunity has been known for many years [20]. Recently, patients with COPD have been found to have altered intestinal permeability at rest. The performance of daily activity led to significantly increased plasma IFABP concentrations in patients with COPD but not in control subjects [21]. Moreover, previous animal study demonstrated that commensal microflora in gut could increase immunity through the stimulation of the toll-like receptor and

Table 2. Univariate analysis of the variables related to mortality.

Variables	Survivors (n = 24)	Non-survivors (n = 8)	p-value
Age (year)	85 [72 - 89]	82 [54 - 87]	0.285
Gender, male	21 (87.5)	5 (62.5)	0.148
Co-morbidities			
Diabetes mellitus	5 (20.8)	2 (25)	1.0
Cerebrovascular disease	9 (37.5)	1 (12.5)	0.38
Chronic heart disease	11 (45.8)	2 (25)	0.42
Chronic respiratory disease	11 (45.8)	3 (37.5)	1.0
Malignancy	4 (16.7)	3 (37.5)	0.327
Nursing home	3 (12.5)	2 (25)	0.578
Glasgow Coma Scale	10 [7 - 15]	12 [5 - 15]	0.873
Use of vasopressor	5 (20.8)	2 (25)	1.0
Leukocyte count, 10^9/L	11.6 [7.5 - 16.3]	14.3 [9.5 - 22.1]	0.542
Platelets, 10^9/L	268 [185 - 346]	175 [124 - 366]	0.147
Hematocrit, g/dL	34.7 [29 - 36.7]	25.4 [21.9 - 32.8]	0.033
Prothrombin time, seconds	10.8 [10.8 - 11.4]	10.8 [2.6 - 12.2]	0.919
C-reactive protein, mg/L	11.6 [6.8 - 18.6]	14.7 [10.6 - 17.4]	0.254
Creatinine, mg/dL	1.14 [0.87 - 2.2]	1.3 [0.9 - 1.7]	0.983
Blood sugar, mg/dL	119 [119 - 168]	174 [98 - 307]	0.261
PaO_2/FiO_2, mm Hg	186 [120 - 259]	203 [134 - 263]	0.749
Arterial pH	7.4 [7.3 - 7.46]	7.36 [7.34 - 7.48]	0.983
Systolic blood pressure, mm Hg	122 [111 - 144]	120 [75 - 148]	0.815
Shock index	0.95 [0.73 - 1.15]	0.85 [0.83 - 1.1]	0.815
SOFA score	8 [5 - 9]	7 [6 - 9]	0.983
APACHE II score	22 [19 - 28]	24 [18 - 30]	0.564
Pneumonia Severity Index	143 [123 - 170]	130 [114 - 170]	0.623
Severe sepsis/septic shock	6 (25)	3 (38)	0.654
U-IFABP/Cr, pg/100 µL			
Day 1	4.9 [2.5 - 11.3]	61.6 [3.4 - 115.2]	0.033
Day 2	10.7 [1.9 - 20.5]	25.3 [8.5 - 83.6]	0.057
Day 3	8 [2 - 10.9]	20.5 [4.1 - 94.8]	0.078
Day 4	8.9 [3.3 - 20.4]	29.3 [10.4 - 121.8]	0.018
Day 5	8.2 [0.9 - 20.6]	48.6 [10.1 - 159.2]	0.008
Day 6	6.9 [2.4 - 21.9]	35 [9.5 - 155.5]	0.006
Day 7	9.1 [1.8 - 20.2]	30 [9.6 - 75.7]	0.008

n (%) - median [interquartile range], APACHE II - Acute Physiology and Chronic Health Evaluation II, SOFA - Sequential Organ Failure Assessment, U-IFABP/Cr - ratio of urinary Intestine fatty acid binding protein to urinary creatinine.

nuclear factor κB DNA-binding activity in the intestinal tract [22]. Taken together, lung injury may cause gut barrier dysfunction and vice versa, and may explain in part why the severity of enterocyte injury is associated with the mortality of pneumonia patients as shown in our study. Further studies with larger populations are needed to verify these issues.

Another interesting finding was that the hematocrit level was significantly lower in non-survivors (25.4 [21.9 - 32.8] vs. 34.7 [29 - 36.7], p = 0.033). The clinical relevance of anemia in critically ill patients had been widely studied [23,24]. The intestinal epithelium is dependent on sufficient oxygen and energy supply for both its absorptive and barrier functions. During severe sepsis and septic shock, the circulatory abnormalities lead to an imbalance between systemic oxygen delivery and oxygen demand in tissue, resulting in multiple organ dysfunction and death. Early goal-directed therapy is a resuscitation strategy to achieve a targeted central venous pressure, mean arterial pressure, urine output, and central venous oxygen saturation and proves to increase survival rates in patients with severe sepsis and septic

Table 3. The correlations between U-IFABP/Cr and laboratory and clinical parameters in all patients (n = 32) at day 1.

	r	p-value
Leukocyte count	-0.096	0.602
Platelets	-0.125	0.497
Hematocrit	-0.29	0.113
Creatinine	0.069	0.707
C-reactive protein	0.392	0.026
Procalcitonin	0.3	0.624
Serum lactate	0.385	0.194
PaO_2/FiO_2	-0.008	0.965
Systolic blood pressure	0.004	0.983
SOFA score	0.053	0.773
APACHE II score	0.042	0.818
Pneumonia Severity Index	-0.085	0.643

APACHE II - acute physiology and chronic health evaluation II, SOFA - Sequential Organ Failure Assessment.

Table 4. Goodness criteria of U-IFABP/Cr in predicting mortality of severe pneumonia during the first week of ICU admission.

	AUC	Cutoff, pg/100 µL	Sensitivity, %	Specificity, %	PPV, %	NPV, %	p-value
Day 1	0.755	32	63	96	84	89	0.033
Day 4	0.781	24	63	83	55	87	0.019
Day 5	0.812	25	63	83	55	87	0.009
Day 6	0.823	34.6	63	92	73	88	0.007
Day 7	0.812	28.9	63	96	84	89	0.009

AUC - area under the curve, PPV - positive predictive value, NPV - negative predictive value.

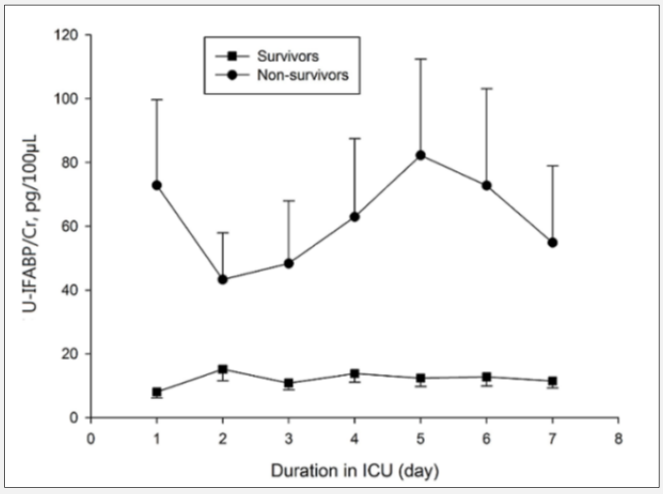

Figure 1. Trends of urinary intestinal fatty acid binding protein values (mean ± SE) in survivors and non-survivor groups after intensive care unit admission.

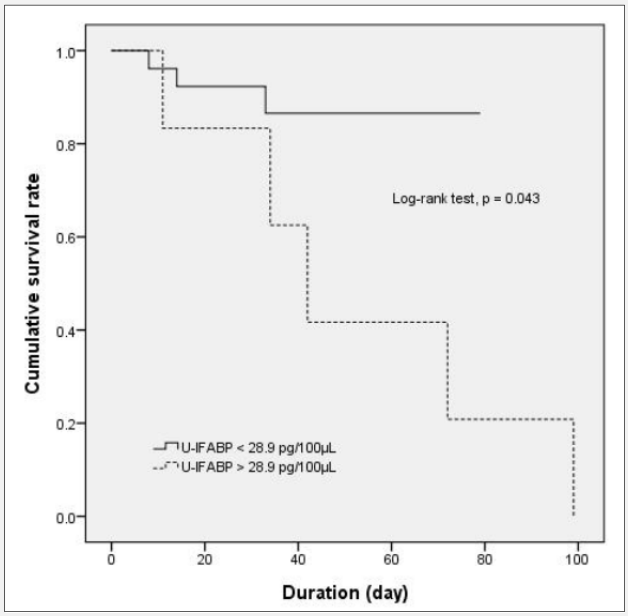

Figure 2. Kaplan-Meier curves showing correlation between value of day 7 U-IFABP/Cr and survival in patients with pneumonia.

The all-cause in-hospital mortality was higher in patients with values of day 7 U-IFABP/Cr greater than 28.9 pg/100 µl than in groups with lower values (p = 0.043).

shock [25]. In this strategy, red blood cell (RBC) transfusion was recommended to achieve a hematocrit level > 30% and central venous oxygen saturation > 70%. However, the usefulness of RBC transfusion in critically ill patients is still controversial [26-28]. Recently, Sadaka et al. showed that RBC transfusion could improve central venous oxygen saturation but not mortality [29]. On the other hand, Mark et al. demonstrated that treatment with RBC transfusion might be independently associated with decreased in-hospital mortality in a retrospective study [30]. Given the results of lower hematocrit level with poor outcome in this study, the clinical relevance of RBC transfusion in pneumonia patients deserves further studies with a larger population to verify.

The third finding in our study was that U-IFABP/Cr showed a positive statistically significant correlation to blood CRP level. CRP is an acute-phase protein synthesized predominately in hepatocytes but also in alveolar macrophages [31,32]. It has been widely used to detect inflammation and infection in the emergency department and ICU. de Hann et al. found a positive correlation between plasma IFABP and day 2 CRP level after severe trauma with the presence of shock. They also demonstrated that enterocyte damage preceded and was related to the subsequent inflammatory response [33]. However, the detailed mechanisms underlying the gut barrier impairment in pneumonia patients need to be elucidated in further studies.

The main limitation is the small sample size that may lower the power of the study. Second, our study included both patients with community-acquired pneumonia and health care-associated pneumonia that might be caused by different bacteria. It is not known whether different micro-bacteria have varying effects on the impairment of the gut barrier. However, only five health care-associated pneumonia patients were enrolled in the study and were distributed equally in both survival (n = 3) and non-survival (n = 2) groups. As a consequence, different bacteria might have limited effects on our results. Third, all of our patients were from a single medical center respiratory ICU. The median age of the study patients was quite high and the vast majority of the patients were male. The results might not be generalizable to other ICUs. Last, not all of our studied patients were treated with standard early goal-directed therapy. This might reduce the survival rate in patients who did not receive that resuscitation strategy. However, all patients with acute respiratory distress syndrome were managed with standard lung protection strategy in our respiratory ICU.

CONCLUSION

Enterocyte injury is common in pneumonia patients. The severity of enterocyte injury is associated with patient's mortality. U-IFABP/Cr may serve as a significant prognostic factor for patients with pneumonia admitted to the ICU.

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

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