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Original Article

Thrombocytopenia as a predictor of acute kidney injury in patients with emphysematous pyelonephritis

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Abstract: Objective: The goal of this study was to investigate the relationship between thrombocytopenia and acute kidney injury (AKI) in patients with emphysematous pyelonephritis (EPN). Methods: A retrospective study was conducted in three university hospitals, and early hematological biomarkers were detected to predict the development of AKI in EPN patients. Results: Of 56 EPN patients, 32 (59%) developed AKI. Spearman correlation analysis showed that the nadir platelet count was negatively associated with the peak leukocyte count (r=-0.354, P<0.001), peak serum creatinine (r=-0.429, P<0.001), peak blood urea nitrogen (r=-0.317, P<0.001), and the length of hospital stay (r=-0.442, P<0.001). Furthermore, the area under the receiver-operating-characteristic curve (AU-ROC) was used to evaluate the accuracy of thrombocytopenia for the diagnosis of AKI in EPN patients, and the accuracy of nadir platelet count (AU-ROC: 0.92, 95% CI: 0.85-0.99, P<0.001) predicted AKI was significantly higher than admission platelet count (AU-ROC: 0.84, 95% CI: 0.73-0.94, P<0.001). Multivariate analysis demonstrated that the nadir platelet count (Odds Ratio [OR]: 0.92, 95% CI: 0.87-0.97, P=0.003), the presence of proteinuria (OR: 0.25, 95% CI: 0.01-0.41, P=0.005) and shock (OR: 1.21, 95% CI: 0.02-2.05, P=0.01) were independently associated with the development of AKI in EPN patients. Conclusions: Thrombocytopenia is independently correlated with the development of AKI in patients with EPN.

Keywords: Thrombocytopenia, platelet count, acute kidney injury, emphysematous pyelonephritis

Introduction

Emphysematous pyelonephritis (EPN) is a rare necrotic infection of the kidney characterized by production of air in the renal collecting system, parenchyma, and perinephric tissue. In 1898, Kelly et al. [1] reported the first case of EPN, which is usually associated with diabetics, urinary obstruction and severe infection, the mortality rate is more than 80% [2, 3]. Severe infection of kidney and perirenal tissue may cause sepsis and even multiple organ dysfunction in EPN patients, and acute kidney injury (AKI) is one of the most common complications of EPN patients [6].

Computed tomography (CT) as the gold standard for the diagnosis of EPN has been widely used in clinical practice, but it is difficult to be used for the diagnosis of AKI [7]. The serum creatinine (Scr), blood urea nitrogen (BUN) and urine output are important indicators to evaluate kidney function. Additionally, we found that thrombocytopenia had a better predictive value for the development of AKI in patients with EPN. In this study, we aimed to investigate the relationship between thrombocytopenia and the development of AKI in patients with EPN. To the best of our knowledge, no such study has been reported previously.

Methods

Study population

A retrospective non-interventional cohort study was performed in three university hospitals in China from October 2012 to March 2018. Inclusion criteria: 1. Age >18 years old; 2. High fever (>38.0°C) with pyuria or a positive urine culture; 3. CT scan confirmed air accumulation in the renal collecting system, parenchyma, and

Table 1. Characteristics of patients by severe AKI status

	AKI (n=32)	Non-AKI (n=24)	*P* value
Demographic characteristics			
Age (yr)	51 (33-74)	44 (24-59)	0.021
Female sex	28 (87.5%)	11 (45.8%)	0.106
Hematological markers			
Admission platelet count ($\times10^9$/L)	103 (76-132)	128 (93-175)	<0.001
Nadir platelet count ($\times10^9$/L)	56 (18-113)	98 (69-134)	<0.001
Admission leukocyte count ($\times10^9$/L)	17 (10-25)	11 (7-14)	<0.001
Peak leukocyte count ($\times10^9$/L)	23 (12-35)	14 (12-21)	<0.001
Renal function			
Peak blood urea nitrogen (mmol/L)	33 (19-53)	16 (6-28)	<0.001
Peak serum creatinine (μmol/L)	302 (278-412)	109 (175-243)	<0.001
Clinical records			
Shock	10 (31.3%)	4 (16.7%)	0.216
Proteinuria	30 (93.8%)	11 (45.8%)	<0.001
Hematuria	25 (78.1%)	18 (75%)	0.786
Percutaneous drainage	11 (34.4%)	7 (29.2%)	0.891
Urinary tract obstruction	15 (46.9%)	8 (33.3%)	0.216
Dialysis required	22 (68.8%)	0 (0%)	
Nephrectomy	18 (56.3%)	3 (12.5%)	0.034
Length of hospital stay (days)	19 (11-36)	11 (8-18)	0.016
Hospital mortality	7 (21.9%)	2 (8.3%)	0.109

Data are median (IQR) or number (%).

perinephric space. Exclusion criteria: 1. patients with a history of urethral fistula, urethral trauma, urethral drainage, or catheter insertion; 2. patients with end-stage of renal disease need long-term hemodialysis or those waiting for renal transplantation. Our study was approved by the Ethics Committee of Ningbo First Hospital, and the written informed consent was obtained from the patients or their relatives.

Data collection

Standardized data collection forms were used to collect laboratory and clinical data daily throughout hospitalization, including patients' age, gender, clinical features, imaging results, platelet counts, leukocyte counts, Scr, BUN, percutaneous drainage, nephrectomy, hemodialysis, culture (blood and urine) results, length of hospital stay, and presence of hematuria, proteinuria, shock, and adverse outcomes. All patients were monitored daily from admission to discharge.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables were presented as medians with interquartile range (IQR). Pearson's χ^2 test was used to compare the categorical variables, and the nonparametric *Mann-Whitney U* test was used to compare the continuous variables. Spearman correlation analysis was used to assess the relationship between the nadir platelet count and other laboratory and clinical findings. The area under the receiver-operating-characteristic curve (AUROC) was structured to evaluate the specificity and sensitivity of nadir platelet count in predicting the development of AKI. Multivariate logistic regression models were calculated to confirm the relationship between thrombocytopenia and the development of AKI. All analyses and calculations were done using SPSS 16.0 (Inc, Chicago, USA), and $P<0.05$ was considered significant.

Results

Characteristics of EPN patients

A total of 56 EPN patients were enrolled, and females (66.1%) were more than half, 53 cases of diabetics (94.6%). The most common symptom was fever (100%), and other symptoms were loin pain (53.6%), vomiting (21.4%), and hematuria (10.7%). Pathogens were found in urine cultures of 54 (96.4%) EPN patients, 32 (57.1%) of Escherichia coli, 20 (35.7%) of pneumonia Klebsiella, 2 (3.6%) of Escherichia coli infection mixed with Pseudomonas aeruginosa.

Thrombocytopenia (the nadir platelet count $<80\times10^9$/L) emerged in 31 (55.4%) EPN patients, and severe thrombocytopenia (the nadir platelet count $<50\times10^9$/L) in 21 (37.5%) EPN patients. Leukocytosis (the peak leukocyte count $>10\times10^9$/L) emerged in all patients, and

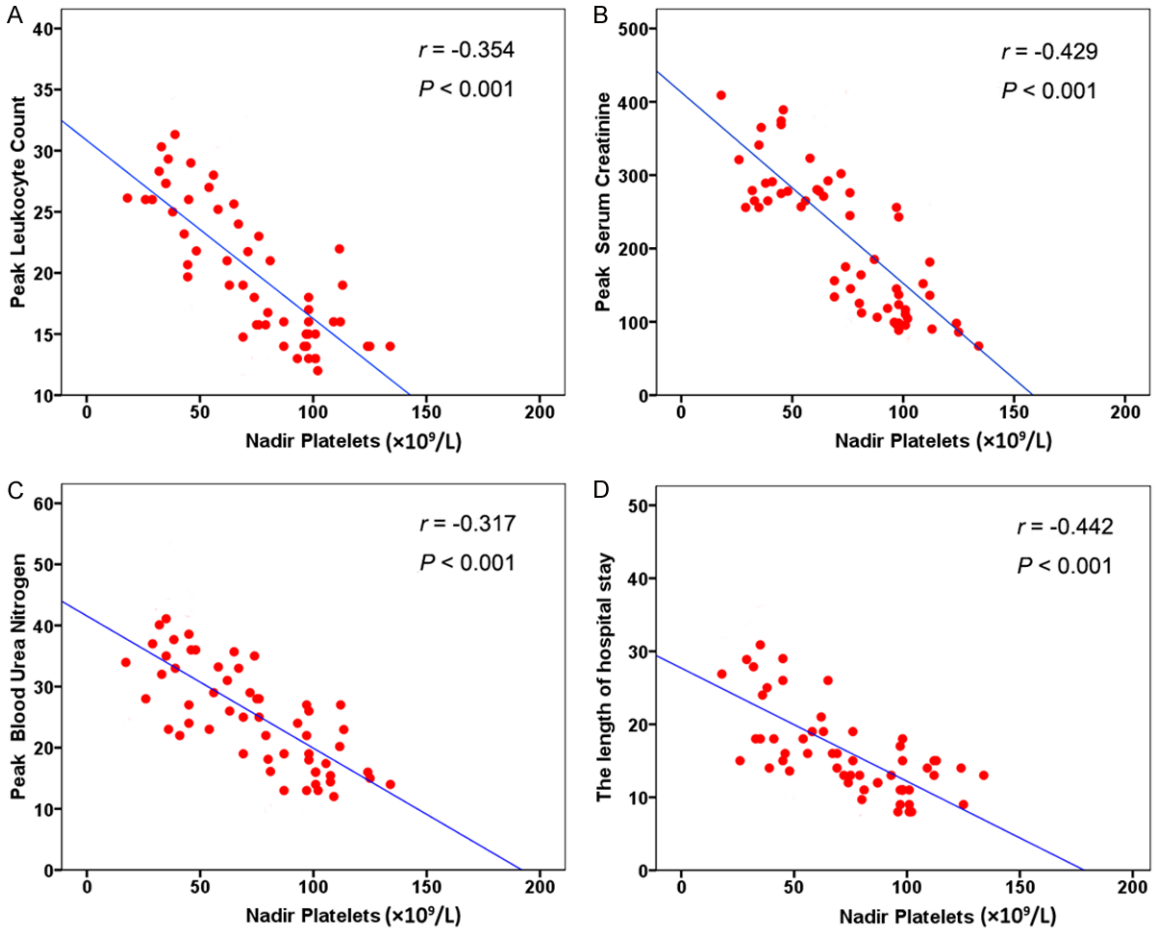

Figure 1. Relationship between nadir platelet count and other laboratory or clinical findings. Shown are the level of peak leukocyte count (A), peak serum creatinine (B), peak blood urea nitrogen (C), and lengths of hospital stay (D) plotted against the nadir platelet count. The *r* denotes the Spearman correlation coefficient, and the line the linear regression for each comparison.

severe leukocytosis (the peak leukocyte count >20×10^9/L) in 22 (39.3%) EPN patients. Moreover, the increased Scr (>134 μmol/L) occurred in 39 (69.6%) EPN patients, and 32 (82.1%) developed AKI, which was defined as increased Scr >344 μmol/L or need emergency hemodialysis at stage 3 of Acute Kidney Injury Network criteria [8]. EPN patients who developed AKI were older, and more probability to suffer thrombocytopenia, leukocytosis, proteinuria, or shock, required emergency hemodialysis, and longer hospital stay compare to those patients without AKI (**Table 1**).

The relationship between thrombocytopenia and AKI development

Admission and nadir platelet count were significantly lower in EPN patients with AKI than those without AKI. In contrast, admission and peak leukocyte count were significant higher in EPN patients with AKI compare to those without AKI (**Table 1**). Spearman correlation analysis results showed that the nadir platelet count was negatively associated with peak leukocyte count (r=-0.354, *P*<0.001), peak Scr (r=-0.429, *P*< 0.001), peak BUN (r=-0.317, *P*<0.001), and the length of hospital stay (r=-0.442, *P*<0.001) (**Figure 1**).

AU-ROC was used to predict the development of AKI, and the results revealed that the nadir platelet count was significantly higher than admission platelet count (AU-ROC: 0.92, 95% CI: 0.85-0.99 vs AU-ROC: 0.84, 95% CI: 0.73-0.94, *P*<0.001) (**Figure 2**), and at a cut-off of 35×10^9/L, 95% sensitivity and 78% specificity to predict the development of AKI. After adjust-

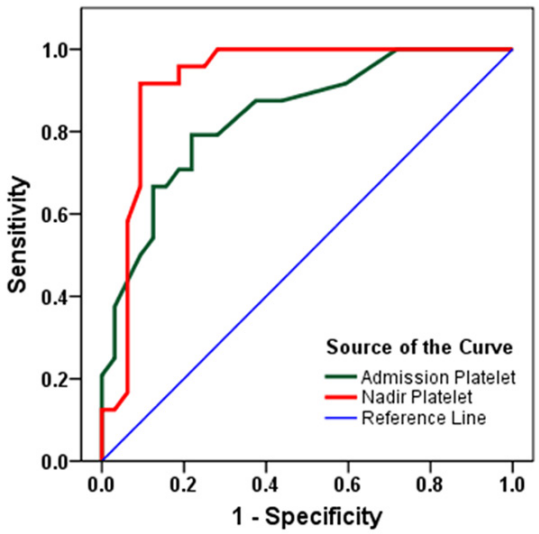

Figure 2. Receiver-operating-characteristic (ROC) curves for admission and nadir platelet count to predict the development of AKI.

Table 2. Multivariable logistic regression for the prediction of AKI combining nadir platelet count with other variables

	Adjusted odds ratio	95% CI	*P* value
Age (per year)	1.09	0.96-1.24	0.166
Gender	1.37	0.04-3.29	0.374
Presence of shock	1.21	0.02-2.05	0.010
Presence of proteinuria	0.25	0.01-0.41	0.005
Presence of hematuria	1.26	0.03-2.49	0.240
Nadir platelet counts	0.92	0.87-0.97	0.003
Peak leukocyte counts	1.27	1.00-1.61	0.053
Nephrectomy	0.26	0.01-0.51	0.116
Percutaneous drainage	4.65	0.33-8.24	0.541

ment, the nadir platelet count (OR: 0.92, 95% CI: 0.87-0.97, $P<0.001$), the presence of proteinuria (OR: 0.25, 95% CI: 0.01-0.41, $P=0.005$), and shock (OR: 1.21, 95% CI: 0.02-2.05, $P=0.01$) were independent risk factors for predicting the development of AKI (**Table 2**).

The association between thrombocytopenia and adverse outcomes

Of 56 EPN patients, 11 (19.6%) of patients received percutaneous drainage, 26 (46.4%) experienced one or more sessions of hemodialysis, and 21 (37.9%) patients received nephrectomy (**Table 1**). A total of 21 (37.5%) EPN patients with the nadir platelet count was $<50\times10^9$/L, 16 (28.6%) patients complicated with pulmonary infection and respiratory failure, and 8 (14.3%) received more than twice of rescue medications, and 9 (16.1%) patients died. However, of 35 (62.5%) EPN patients with the nadir platelet count was $>50\times10^9$/L, 5 (8.9%) patients complicated with pulmonary infection and respiratory failure, 2 (3.6%) received more than twice the rescue medications, and no deaths. These results show that EPN patients with the nadir platelet count $<50\times10^9$/L suffer more adverse outcomes than if the nadir platelet count was $>50\times10^9$/L.

Discussion

The diagnosis of EPN should be a consideration when pyelonephritis is treated for 3-5 days but high fever (>38.5°C) continues [9]. For similar cases, an early computed tomography (CT) is one of the most sensitive examinations for checking out gas in the kidney [10]. Based on CT examination results, Huang et al. [7] suggested that EPN is able to be divided into four types for guiding treatment, but it does not accurately assess the severity of kidney injury. Therefore, clinicians need a simple and feasible laboratory biomarker which can accurately evaluate kidney function.

In this study, the detailed clinical data of 56 EPN patients was examined throughout the entire period of hospitalization. The main laboratory test results for these EPN patients were characterized by thrombocytopenia, leukocytosis, as well as increased Scr and BUN. Moreover, thrombocytopenia was very common in EPN patients, and more than half of EPN patients (55.4%) suffered thrombocytopenia ($<80\times10^9$/L), and along with increased levels of Scr and BUN. The nadir platelet count was significantly correlated with the development of AKI, and the results were consistent with the results of Lu et al. [11].

Reviewing the studies about EPN, most of the studies defined the admission platelet count as thrombocytopenia, but the nadir platelet count had more sensitivity and specificity to reflect severity of thrombocytopenia [11-13]. In total, 21 EPN patients with the nadir platelet count were $<50\times10^9$/L, and more sensitivity than the previous EPN study by Lu et al. [12]. Our results also show that the nadir platelet count was

inversely associated with high levels of Scr and BUN, and reflecting the severity of renal dysfunction (**Figure 1**). For diagnostic accuracy of AKI, the sensitivity and specificity of the nadir platelet count was significantly higher than that of admission platelet count (**Figure 2**).

Traditionally, early nephrectomy is the primary choice for treatment of EPN, but this approach may require patients to receive hemodialysis for a lifetime. With available better antibiotics and image-guided drainage, conservative therapy is becoming more appealing [6]. Chen et al. [13] suggested that CT-guided percutaneous drainage combined with antibiotic therapy is a successful alternative to nephrectomy. A meta-analysis showed that CT-guided and percutaneous drainage tubes are placed in the retroperitoneum, which significantly improve the cure rate and reduce the rate of nephrectomy in EPN patients [14]. However, our study did not find that percutaneous drainage could significantly improve the prognosis of AKI in EPN patients. A timely hemodialysis might be able to reduce subsequent adverse outcomes in EPN patients with AKI, and detection of routine platelet count made it possible to rule in and rule out the needing of hemodialysis.

Our study has two limitations. First, this was a retrospective cohort study, and it was difficult to recruit more patients because EPN cases are rare. The limited cases lack power to analyze the risk factors. Second, our study did not differentiate the peak Scr and BUN between EPN patients who received nephrectomy or not. Heterogeneity in the nephrectomized EPN patients might limit the statistical analysis and whole values could be underestimated. Thus, a large multicenter cohort study is needed to further investigate the relationship between thrombocytopenia and development of AKI in EPN patients.

In summary, thrombocytopenia was independently associated with the development of AKI in EPN patients. Because platelet count is clinically accessible, dynamic monitoring of early platelet count is valuable for AKI risk stratification and the primary choice of treatment for EPN patients. Further investigation should be focus on whether therapeutic increased platelet count can improve the severity of AKI in EPN patients.

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Disclosure of conflict of interest

None.

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