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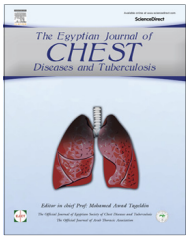

ORIGINAL ARTICLE

Platelet count and level of $paCO_2$ are predictors of CAP prognosis

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KEYWORDS

Community acquired pneumonia;
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Pneumonia severity index;
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Abstract *Objective:* The purpose of our study was to examine patients hospitalized with CAP association between abnormal platelet count and levels of $paCO_2$ and ICU admission and 30 days mortality.

Methods: This retrospective study was conducted on 173 patients diagnosed as CAP admitted to Mansoura University Hospital. Arterial blood gases and CBC were obtained at admission with the measurement of platelet count and $paCO_2$. Data were collected and analyzed.

Results: Patients with abnormal platelet count thrombocytopenia (19%) or thrombocytosis (28%) had a higher length of hospital stay, were more in the need for ICU admission, more use of mechanical ventilation invasive or non invasive more 30 days mortality rate with more association of pulmonary complication like pleural effusion.

Both groups of hypercapnia (13%) and hypocapnia (42%) had a higher ICU admission and higher 30 day mortality rate.

Conclusion: Patients with abnormality in platelet count and levels of $paCO_2$ were associated with an increase in ICU admission and higher 30 day mortality.

They should be considered for inclusion in future severity criteria to identify patients who are in need for a higher level of care.

Introduction

Community-acquired pneumonia (CAP) represents one of the most common causes of ICU admission [1]. Prior investigations of CAP in the ICU have shown that the requirement for mechanical ventilation is associated with increased mortality compared with non-ventilated patients [2–8].Platelets have been increasingly recognized as an important component of innate and adaptive immunities [9–11].

Platelet response in antimicrobial host defense is similar, in many ways, to the leukocyte response: both cell types contain antimicrobial peptides that act against a broad range of pathogens. After platelets and neutrophils are activated, they accumulate at the site of infection to produce a direct contact between their antimicrobial peptides and invading bacteria. Leukocytes need to phagocytize bacteria to achieve interaction with intracellular peptides; platelets can also internalize microorganisms into phagosomelike vacuoles, enhancing pathogen clearance.

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Antimicrobial peptides from both cells exert a rapid, potent, and direct antimicrobial effect that contributes to limiting the infection [12].

Clinicians have always evaluated the degree of leukocytosis in patients with pneumonia as an indication of systemic inflammatory response and severity of disease. Thrombocytopenia is also a recognized marker of poor outcomes in patients with pneumonia, due to the association of low platelet counts with disseminated intravascular coagulation and severe sepsis [13].

Hypoxemic respiratory failure is well recognized as a prognostic marker in different severity-of-illness scores to predict poor clinical outcomes in hospitalized patients with CAP [14].

By contrast, ventilatory abnormalities reflected by an alteration in $PaCO_2$ have not been considered a poor prognostic marker unless arterial pH changes are observed [15–17].

$PaCO_2$ is widely accepted as an indicator of ventilator adequacy. Abnormally high levels may indicate severe respiratory fatigue and impending cardiopulmonary arrest [18].

We hypothesized that an abnormal platelet count may be an important marker to assess severity of disease in patients with CAP. The primary objective of this study was to investigate the association of platelet count at the time of hospitalization with mortality at 30 days in patients with CAP. The secondary study objective was to examine the association between abnormal $PaCO_2$ and the need for invasive mechanical ventilation, ICU admission, and 30-day mortality in patients hospitalized with CAP.

Materials and methods

Study design and patient data

This was a retrospective cohort study of 173 patients admitted with CAP to the Mansoura University Chest Department between June 2010 and March 2013.

Patients enrolled were a part of the community-acquired pneumonia. Clinical and laboratory data were collected for each patient. These include a total of 36 variables regarding patient's demographic, co-morbidity, physical examination, laboratory, and chest radiographic findings.

Collected data were used to estimate patient's CAP severity using the pneumonia severity index (PSI) and CRB-65 (confusion, respiratory rate, blood pressure, 65 years of age and older). We excluded patients with previous use of oral corticosteroids ($\geqslant$10 mg prednisone equivalent per day for at least 2 weeks); other immunosuppressive therapy; active solid or hematologic neoplasms; HIV infection; active TB; hematologic disease involving platelets and/or leukocytes, such as essential thrombocytosis or myelodysplastic syndrome; and patients hospitalized within the preceding 21 days due to chronic obstructive pulmonary disease.

Study definitions

CAP was defined as the presence of a new pulmonary infiltrate on the chest radiograph at the time of hospitalization associated with at least one of the following: (1) new or increased cough, (2) an abnormal temperature ($<$35.6 °C or 37.8 °C), (3) an abnormal serum leukocyte count (leukocytosis, left shift, or leukopenia defined by local laboratory values). Hypotension was defined as a systolic blood pressure, $<$90 mm Hg or diastolic blood pressure, $<$60 mm Hg. Alteration of gas exchange was defined as, $PaCO_2$ values from the arterial blood gas measured in the first 24 h of admission with CAP, the patients were stratified into 3 groups: normal $PaCO_2$ (35–45 mm Hg), hypocapnic ($PaCO_2 \leqslant 35$ mm Hg), and hypercapnic ($PaCO_2 > 45$ mm Hg).

Thrombocytopenia and thrombocytosis were defined as platelet counts $\leqslant$100,000/L or $>$400,000/L, respectively. Significant leukopenia and leukocytosis were defined here as WBC counts of $\leqslant$4000 and $>$25,000 respectively.

The study outcome, 30-days mortality, was defined as death by any cause during the period of 30 days after hospital admission.

Statistical analysis

Categorical variables were described as frequencies and percentages and compared with x2 or fisher exact test when appropriate.

Continuous variables were expressed as mean ± SD and compared between groups using one way analysis of variance, for data not normally distributed.

Data were processed with the SPSS (Statistical Package for Social Science) version (16).

The level of significance.

$p < 0.05$ significant.
$p < 0.01$ highly significant.
$p < 0.001$ very highly significant.

Results

During the study period, we evaluated 173 patients (94 males (54%) and 79 females (46%)) with community acquired pneumonia who met inclusion criteria and in whom the platelet count was taken at admission was available (see Tables 1 and 2).

33 patients (19%) were with thrombocytopenia **(group I)**, 49 patients (28%) with thrombocytosis **(group III)** and 91 patients (53%) with normal platelet **(group II)**.

All group patients' age and sex matched without a significant difference.

There was no difference between groups in antibiotic receiving prior admission, active smoking history, the presence of comorbidity like heart failure, renal failure, liver failure and other chronic illnesses like diabetes mellitus and neurological disease.

There was no significant difference between the studied group as regards the leukocytic count and heamatocrit value.

Patients with thrombocytosis had a higher heart rate at the admission.

Patient with thrombocytosis and thrombocytopenia were more in need for I.C.U admission and more in need for invasive mechanical ventilation as p value between groups less than 0.001.

The mortality rate within 30 days of hospital admission and length of hospital stay were higher in patients with thrombocytosis and thrombocytopenia than in patients with normal platelet count, and p value less than 0.01.

Table 1 Characteristics of study patients at admission divided into 3 groups according to levels of platelet.

	Group I N = 33 (19%)	Group II N = 91 (53%)	Group III N = 49 (28%)	
Sex				
Male	16 (48%)	51 (56%)	27 (55%)	$p > 0.05$
Female	17 (52%)	40 (44%)	22 (45%)	
Age	48 ± 1.5	42 ± 1.5	44 ± 1.9	$p > 0.05$
Length of hospital stay	10.5 ± 5.2	4.6 ± 1.6	10.9 ± 5	$p < 0.001$
Antibiotic prior admission	8 (24%)	41 (45%)	20 (40%)	$p > 0.05$
Active smoking	8 (24%)	32 (35%)	13 (27%)	$p > 0.05$
Heart failure	9 (27%)	23 (25%)	13 (26%)	$p > 0.05$
Renal failure	8 (24%)	20 (22%)	10 (20%)	$p > 0.05$
Liver failure	3 (1%)	13 (14%)	5 (10%)	$p > 0.05$
Diabetes mellitus	10 (30%)	35 (38%)	20 (41%)	$p > 0.05$
Neurological disease	2 (06%)	14 (15%)	11 (22%)	$p > 0.05$
Respiratory rate	21(64%)	57 (63%)	35 (71%)	$p > 0.05$
Heart rate	21 (64%)	58 (64%)	41 (84%)	$p < 0.05$
Shock	17 (51%)	39 (43%)	29 (59%)	$p > 0.05$
Temperature > 39	17 (52%)	40 (44%)	22 (45%)	$p > 0.05$
Leukocytic count				
Leukopenia	14 (42%)	17 (19%)	13 (27%)	$p > 0.05$
Leukocytosis	6 (18%)	20 (22%)	10 (20%)	
Normal	13 (40%)	54 (59%)	26 (53%)	
Hematocrit value	7 (21%)	32 (35%)	20 (41%)	$p > 0.05$
Pao2	24 (73%)	56 (62%)	33 (67%)	$p > 0.05$
Na level	10 (30%)	30 (33%)	16 (33%)	$p > 0.05$
Mental state	11 (33%)	27 (29%)	16 (32%)	$p > 0.05$
ICU	31 (94%	64 (70%)	43 (88%)	$p < 0.001$
Non invasive MV	16 (48%)	37 (41%)	16 (33%)	$p > 0.05$
Invasive MV	15 (45%)	17 (19%)	24 (49%)	$p < 0.001$
30 days mortality	8 (24%)	9 (1%)	14 (29%)	$p < 0.01$
Pneumothorax	7 (21%)	18 (20%)	11 (22%)	$p > 0.05$
Pleural effusion	18 (55%)	31 (34%)	24 (49%)	$p < 0.05$
Empyema	6 (18%)	14 (15%)	10 (20%)	$p > 0.05$
Lung abscess	5 (15%)	11 (12%)	6 (12%)	$p > 0.05$
Chest X-ray				
Alveolar	5 (15%)	19 (21%)	13 (26%)	$p > 0.05$
Interstitial	6 (18%)	25 (27%)	3 (6%)	
Cavitation	9 (27%)	19 (21%)	19 (39%)	
Multilobar	13 (40%)	28 (31%)	14 (29%)	
CRB-65 2, 3, 4	19 (58%)	31 (34%)	31 (63%)	$p < 0.001$
PSI class VI, V	25 (76%)	45 (49%)	37 (76%)	$p < 0.001$

Table 2 Relation between the leukocytic count and 30 day mortality and length of hospital stay.

	Group I N = 44 (25%)	Group II N = 93 (54%)	Group III N = 36 (21%)	
30 days mortality	10 (22%)	14 (15%)	7 (19%)	$p > 0.05$
Length of hospital stay	9.5 ± 5.2	7.1 ± 3.7	6.1 ± 3	$p > 0.05$

There was no significant difference between studied groups as regards the levels of paO_2, Na levels and mental state.

There was no association between leukocytic count and platelet count.

There was no significant relation between the leukocytic count and length of hospital stay and 30 days mortality.

Patient with pulmonary complication like pleural effusion was higher in patients with thrombocytopenia than thrombocytosis or normal platelet count patients. p value less than 0.05.

There was no difference between groups in the occurrence of lung abscess, empyema or pneumothorax.

There was no significant difference between groups in the chest X-ray presentation P values were more than 0.05, while patients with thrombocytosis showed higher incidence of cavitation.

Patients with thrombocytosis and thrombocytopenia had higher PSI and CRB-65 scores at admission than patients with normal platelet count.

As regards the levels of $paCO_2$, the distribution among the group was 73 patients (42%) with hypocapnia ($paCO_2$ < 35 mm Hg) **Group I***, 87 patients (50%) with normal $paCO_2$ (35–45 mm Hg) **Group II*** and 13 patients (8%) with hypercapnia $paCO_2$ (>45 mm Hg) **Group III***.

Table 3 showed demographic characteristics of the studied group. Patients with abnormal levels of $paCO_2$ higher or lower were more likely to have liver diseases, diabetes mellitus and

neurological disease, there was a high significant difference between studied groups regarding p values.

There was a significant difference between the studied group regarding body temperature above 38 °C and hyponatreamia.

As regards clinical outcomes over all 30 day mortality was higher in patients with hypercapnia and hypocapnia compared with the reference group with normal $paCO_2$ (54%, 18% and 13% respectively) with p value < 0.001.

Both groups (hypercapnic and hypocanic) patients had significantly higher ICU admission and more in need for invasive mechanical ventilation.

Patients with hypercapnic and hypocapnic were more liable to the occurrence of pneumothorax as a complication of pneumonia, but there was no significant difference between the studied groups as regards the lung abscess, pleural effusion and empyema.

Patients with abnormal $paCO_2$ had higher PSI and CRB-65 scores at admission than patients with normocapnia.

There was no significant difference between studied groups regarding the length of hospital stay.

Patient with abnormality in $paCO_2$ had more liability to multilobar affection in chest X-ray without a significant difference between studied groups.

Discussion

The main findings of our study were as follows: that patients at the time of hospitalization, abnormalities in platelet count are better predictors of clinical outcomes in patients with CAP, as follows

1. Patients with thrombocytosis and thrombocytopenia had a higher 30 day mortality rate, more length of hospital stay, more in need of ICU care, more in need for mechanical ventilation invasive or non invasive and higher PSI and CRB-65.
2. As regards the pulmonary complication of pneumonia pleural effusion was high in patients with thrombocytopenia with a significant difference, while empyema was high in patients with thrombocytosis without a significant difference.

Table 3 Characteristics of study patients at admission divided into 3 groups according to the levels of $PaCO_2$.

	Group I* N = 73(42%)	Group II* N = 87 (50%)	Group III* N = 13 (8%)	
Sex				
Male	39 (53%)	50 (57%)	5 (38%)	$p > 0.05$
Female	34 (47%)	37 (43%)	8 (62%)	
Age	43 ± 1.2	45 ± 1.8	43 ± 2.2	$p > 0.05$
Length of hospital stay	6 ± 3.2	8.2 ± 4.1	7.9 ± 5	$p > 0.05$
Antibiotic prior admission	34 (47%)	28 (32%)	7 (54%)	$p > 0.05$
Active smoking	23 (32%)	28 (32%)	2 (15%)	$p > 0.05$
Heart failure	14 (19%)	25 (29%)	6 (46%)	$p > 0.05$
Renal failure	17 (23%)	17 (20%)	4 (31%)	$p > 0.05$
Liver failure	15 (21%)	2 (2%)	4 (31%)	$p < 0.001$
Diabetes mellitus	34 (47%)	21 (24%)	10 (77%)	$p < 0.001$
Neurological disease	10 (6%)	11 (13%)	6 (46%)	$p < 0.01$
Respiratory rate	45 (62%)	59 (68%)	9 (69%)	$p > 0.05$
Heart rate	47 (64%)	64 (74%)	9 (69%)	$p > 0.05$
Shock	31 (42%)	25 (29%)	6 (46%)	$p > 0.05$
Temperature	23 (32%)	43 (49%)	4 (31%)	$p < 0.01$
Leukocytic count				
Leukopenia	16 (22%)	22 (25%)	6 (46%)	$p > 0.05$
Leukocytosis	15 (21%)	18 (21%)	3 (23%)	
Normal	42 (57%)	47 (54%)	4 (31%)	
Hematocrit value	31 (42%)	24 (28%)	4 (31%)	$p > 0.05$
PaO_2	54 (74%)	52 (60%)	9 (69%)	$p > 0.05$
Na level	23 (32%)	31 (36%)	2 (15%)	$p < 0.001$
Mental state	24 (33%)	21 (24%)	9 (69%)	$p < 0.01$
ICU	61 (84%)	64 (74%)	13 (100%)	$p < 0.05$
Non invasive MV	32 (44%)	37 (43%)	0 (0%)	$p < 0.01$
Invasive MV	24 (33%)	21 (24%)	11 (85%)	$p < 0.001$
30 days mortality	13 (18%)	11 (13%)	7 (54%)	$p < 0.001$
Pneumothorax	22 (30%)	10 (11%)	4 (31%)	$p < 0.05$
Pleural effusion	30 (41%)	39 (45%)	4 (31%)	$p > 0.05$
Empyema	13 (18%)	13 (15%)	4 (31%)	$p > 0.05$
Lung abscess	6 (8%)	12 (14%)	4 (31%)	$p > 0.05$
Chest X-ray				
Alveolar	12 (16%)	25 (29%)	0 (0%)	$p > 0.05$
Interstitial	11 (15%)	19 (22%)	4 (31%)	
Cavitation	22 (31%)	22 (25%)	3 (23%)	
Multilobar	28 (38%)	21 (24%)	6 (46%)	
CRB-65 2, 3, 4	36 (49%)	33 (38%)	12 (92%)	$p < 0.001$
PSI class VI, V	49 (67%)	47 (54%)	11 (85%)	$p < 0.01$

Two prior studies, both in pediatric patients, reported an association between thrombocytosis and poor outcomes in patients with CAP [19,20]. The first study reported that pneumonia in children with thrombocytosis seemed to have a more severe and protracted course, whereas the second study suggested that thrombocytosis was associated with a higher likelihood of empyema. Compared with patients with normal platelet counts, both the thrombocytopenia and thrombocytosis groups presented with a worse prognosis but apparently for different reasons:

This finding was in agreement with Prina et al. [21] who concluded that thrombocytosis in patients with CAP associated with poor outcomes, complicated pleural effusion and empyema. The presence of thrombocytosis in CAP should encourage ruling out respiratory complication and could be considered for severity evaluation.

Mirsaeidi et al. [22] analyzed 500 patients with CAP, of whom 65 (13%) presented thrombocytosis and 27 (5%) presented thrombocytopenia. These authors reported that both patients with thrombocytopenia and those with thrombocytosis had a significantly higher mortality and that platelet count was a better predictor of outcome than an abnormal leukocyte count. However, the cause of mortality, complications, etiology, and systemic inflammatory response were not analyzed and the population studied included elderly patients with cancer.

A possible explanation of why patients with thrombocytosis had a poor outcome would be the higher rate of empyema and complicated pleural effusion. In the literature, these types of complications have been associated with a longer length of hospital stay, treatment failure, and higher mortality.

According to our results, we suggest that platelet count should be monitored in patients with CAP: thrombocytopenia or thrombocytosis requires awareness of septic complications and hemodynamic alterations, clinicians should pay attention to local respiratory complications, such as pleural effusion and empyema.

An important limitation of the study includes the fact the investigation was conducted at a single center, the absence of the cause of mortality, searching for the causative organism, link between platelet count and inflammatory marker .We take platelet at the admission serial measurement of platelet count during hospitalization that could differentiate between transient event and sustained derangement in platelet count, we did not evaluate possible difference in the functional activity of platelet among the groups.

The main findings of our study are that patients hospitalized with CAP with abnormal $paCO_2$ levels (hypercapnia or hypocapnia) at the clinical presentation to the hospital were more likely to die within 30 days of admission and require ICU care when compared with those with normal $paCO_2$. This suggests that $PaCO_2$ may play an important role in the clinical outcomes in hospitalized patients with CAP.

A recent meta-analysis suggests that these severity score systems are not accurate to predict ICU admission [23]. These scores include several demographic, co-morbid conditions, physiologic, laboratory or radiologic variables, but none consider $paCO_2$ levels as criteria of severity. In addition, recent new severity scores, such as SCAP [24] or SMART-COP [25], have included low arterial pH as criteria, but $paCO_2$ has not been used as a predictive variable. It is well known that the levels of $paCO_2$ determine arterial pH value, but often pH values can be compensated by bicarbonate levels, especially in patients with chronic disease, and may not reflect an abnormal $paCO_2$ value.

Our results suggest that abnormal $paCO_2$ levels should be considered in severity of illness scores and require further validation.

Both hypocapnia and hypercapnia are independently associated with a greater tendency toward respiratory failure. Hypocapnia can cause or aggravate cellular ischemia by inducing a leftward shift in the oxyhemoglobin dissociation curve and reducing oxygen delivery to tissues [26].

In respiratory disorders such as pneumonia, hypocapnia can worsen ventilation–perfusion matching and gas exchange in the lung via a number of mechanisms, including bronchoconstriction, reduction in collateral ventilation, reduction in parenchymal compliance, and attenuation of hypoxic pulmonary vasoconstriction and increased intrapulmonary shunting [27]. Additionally, hypercapnia can increase sympathetic neural drive, cardiac output, heart rate, and systemic and pulmonary BP [28]. In patients with respiratory disorders, mainly associated with hypoxemia, hypercapnia can increase pulmonary vascular resistance, enhance hypoxic vasoconstriction, mediate large airway constriction, impair contractility of vascular smooth muscles, and limit gas exchange [29–31].We used the decision of ICU admission as the gold standard, because this reflected the actual clinical practice. ICU admission is an important decision that affects outcomes, treatment and costs.

Conflict of interest:

None declared.

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