The clinical utility of pentraxin 3 for the early diagnosis of infection in mechanically ventilated patients

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Background
Ventilator-associated pneumonia (VAP) is one of the most common ICU-acquired infections; however, its diagnosis is still a challenge.
Objectives
To evaluate the diagnostic performance of pentraxin 3 (PTX3) in early detection of patients with VAP.
Patients and methods
In the period from the first of January 2019 up to December 2021, 45 adult patients who underwent mechanical ventilation more than 48 h and developed VAP were enrolled in this longitudinal descriptive hospital-based study, Assiut University Hospital, Assiut, Egypt. Diagnosis of VAP depends on positive culture, in addition to a clinical pulmonary infection score more than or equal to 7. To measure the level of PTX3, the first sample was taken on the first day of the endotracheal intubation, and the second sample was taken on the third day from the patients who developed VAP.
Results
The study showed that the mean age of enrolled patients was 55.98 ± 14.54 years (range, 30–80 years). Overall, 60% were males and 40% were females. The most common causative pathogen was *Pseudomonas aeruginosa*, followed by *Staphylococcus aureus*. Only PTX3 showed significant increase during follow-up, whereas no significant difference was observed in either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) during the follow-up period. Moreover, it was observed that PTX3 had a significant positive correlation with CRP; however, it did not show correlation with ESR, whereas CRP had a significant positive correlation with ESR.
Conclusions
PTX3 was superior to both ESR and CRP as a biomarker to diagnose patients with VAP and also for follow-up of disease progression.

Keywords:
early diagnostic marker, pentraxin 3, ventilator-associated pneumonia

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Introduction

Ventilator-associated pneumonia (VAP) is a type of hospital-acquired pneumonia that develops more than 48 h after endotracheal intubation [1]. It is frequent seen in critical ill patients and accounts for about half of antibiotics received by patients in ICU [2].

Patients who are intubated have a reduced level of consciousness, which makes voluntary clearance of secretions difficult [3]. This results in macroaspiration and microaspiration of contaminated oropharyngeal secretions rich in pathogens [4].

The clinical pulmonary infection score (CPIS) is based on the following items: tracheal aspirates, leukocytosis, fever, and oxygenation radiographic infiltrates [5]. Although CPIS is useful in the diagnosis of VAP patients, it is insufficient for a conclusive diagnosis [6,7].

The difficulty of accurately diagnosing VAP in children and adults is still disputed, and patients with VAP may experience worse outcomes if the disease is diagnosed late and proper medication is not started right at once [5]. Antibiotic overuse increases clinical hazards such antibiotic resistance and colitis caused by *Clostridium difficile* [8].

Pentraxins (PTXs) are phylogenetically conserved proteins with a multimeric structure that are classified as short [C-reactive protein (CRP) and serum amyloid *P* component] and long PTX [9]. PTX3 is the first member identified from the long subfamily of PTX [5]. Acute respiratory distress syndrome (ARDS) has been linked to elevated PTX3 levels, which show positive correlation with the lung injury severity and were found to be a helpful predictor of patient survival [10]. Therefore, the primary goal of this study

was to compare the diagnostic performance of PTX3 with other inflammatory markers in the early detection of patients with VAP.

Patients and methods

Sample size calculation

The sample size was calculated using Epi-Info7. According to results of previous study of Bilgin *et al.* [2], PTX3 plasma level is present in 85% of patients with pneumonia admitted in ICU. Based on this percentage, confidence limits of 7%, and a confidence level of 80%, the sample needed for the study was estimated to be about 43 patients.

Study design and setting

This was a longitudinal descriptive hospital-based study conducted at one of the major tertiary health care hospitals, Assiut University, Egypt, in the period from the first of January 2019 up to December 2021. The study included 45 critically ill adult patients who were mechanically ventilated and intubated during their admission into the ICU Department of Assiut University Hospital. Patients with pulmonary embolism, those with lung cancer, those with mechanical ventilation less than 48 h, and pregnant patients were excluded from the present study.

The study adhered to the regulations of Assiut University's Ethical Committee (IRB No. 17100892), and all patients' relatives provide written informed consent.

Data collection and assessment

Eligible patients who accept to participate in the current study were subjected to detailed history taking including age, sex, length of ICU stay, duration of mechanical ventilation, diagnosis on admission, and the presence other comorbid medical conditions.

The severity of illness was calculated within 24 h of admission to ICU using acute physiologic and chronic health evaluation II score (APACHE II) [11].

We used CPIS after 48 h of mechanical ventilation to help in diagnosis of development of VAP (≥7) [12].

Two venous blood samples were obtained from all studied participants: the first sample was used to measure the baseline laboratory data, namely, complete blood count, which was obtained using CELL-DYN Ruby analyzer [13]; liver function tests (albumin, total protein, alkaline phosphatase, total and direct bilirubin, aspartate transaminase and alanine transaminase) and kidney function (urea and creatinine), which were analyzed using Advia 1800 based on photometry [14]; and inflammatory markers [erythrocyte sedimentation rate (ESR) was measured by standard Westergren method (mm/h), and CRP was performed by Advia method (mg/l) by rate nephelometry].

The level of human PTX3 in serum samples of all studied participants was assessed using a double-antibody sandwich enzyme-linked immunosorbent assay purchased from SinoGeneClon Biotech Co. Ltd (catalog No. SG-10465) USA.

Moreover, endotracheal aspirate specimens were collected before the start of antimicrobial therapy. The cultures were graded as +1 (light), +2 (few), +3 (moderate), and + 4 (heavy) [15]. Then, identification of the organism was done using the Vitek identification system [16].

Follow-up

The second blood sample was obtained after 48 of admission into ICU and starting the antibiotic therapy for reevaluation of the studied inflammatory markers (ESR and CRP) and to reevaluate the serum level of PTX3.

Statistical analysis

SPSS version 22 (statistical package for the social science; SPSS Inc., Chicago, IL, USA) was used for data entry and analysis. The Shapiro–Wilk test was used to determine the normality of the data. Continuous variables were statistically described by mean and SD and compared by Student *t* test, whereas categorical variables were described by number (%) and compared by χ^2 or Fisher exact tests. To assess the relationship between continuous variables, Pearson correlation or Spearman's coefficient was used. Significance level was set at *P* value of 0.05.

Results

The mean age of the enrolled patients was 55.98 ± 14.54 years, with range between 30 and 80 years. Of 45 studied patients, 27 (60%) patients were males and 18 (40%) patients were females. The most frequent diagnoses among the studied patients were chronic obstructive pulmonary disease (62.3%) and coronavirus disease 2019 (33.3%), and two patients had bronchial asthma. The mean duration of mechanical ventilation was 8.89 ± 1.79 days (range; 6–12 days), whereas the mean duration of ICU stay was 12.13 ± 2.44 days (range, 6–15 days). The most frequent comorbidities among the studied patients

were hypertension (60%) and diabetes mellitus (37.8%). Overall, 13 (28.9%) cases, 10 (22.2%), and three (6.7%) patients had renal, hepatic, and cardiac diseases, respectively, whereas 10 (22.2%) patients had no comorbidities (Table 1).

A total of 26 (57.8%) cases had positive pus in sputum. Regarding semiquantitative sputum culture, seven (15.6%), 19 (42.2%), and 19 (42.2%) patients had few, moderate, and heavy growth, respectively. The mean CIPS was 7.80 ± 0.96 (range, 7–10), whereas the mean APACHE II score was 22.56 ± 2.73 (range, 18–28). Regarding the culture growth, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, Klebsiella spp, Candida spp, and Proteus spp were reported in 17 (37.8%), 13 (28.9%), five (11.1%), eight (17.8%), four (8.9%), and two (4.4%) patients, respectively (Table 1).

No significant changes was observed in ESR (44.64 ± 43 vs. 38.57 ± 32.75 ml/h; $P = 0.038$) and CRP (51.25 ± 45.56 vs. 58.09 ± 54.87 mg/l; $P = 0.16$) during follow-up, whereas PTX3 showed significant increase during follow-up (from 3.13 ± 1.97 to 7.71 ± 4.76 ng/ml; $P < 0.001$) (Table 2).

PTX3 had a significant positive correlation with CRP ($r = 0.34$, $P = 0.02$), and CRP had a significant positive correlation with ERS ($r = 0.59$, $P < 0.001$). No significant correlation was observed between PTX3 and ESR, CPIS, and APATCH-II score ($P > 0.05$, for all) (Table 3 and Fig. 1).

Table 1 Demographic and clinical characteristics of the studied participants

Variable names	*N*=45
Age (years) (mean±SD)	55.98±14.54
Range	30–80
Sex [*n* (%)]	
Male	27 (60)
Female	18 (40)
Diagnosis [*n* (%)]	
COPD	28 (62.3)
COVID-19	15 (33.3)
Asthma	2 (4.4)
Mechanical ventilation (days) (mean±SD)	8.89±1.79
Range	6–12
ICU stay (days) (mean±SD)	12.13±2.44
Range	6–15
Associated comorbidities [*n* (%)]	
None	10 (22.2)
Hypertension	27 (60)
Diabetes mellitus	17 (37.8)
Renal disease	13 (28.9)
Hepatic disease	10 (22.2)
Cardiac disease	3 (6.7)
Pus in sputum [*n* (%)]	26 (57.8)
Semiquantitative sputum culture [*n* (%)]	
Few growth	7 (15.6)
Moderate growth	19 (42.2)
Heavy growth	19 (42.2)
Culture [*n* (%)]	
Pseudomonas aeruginosa	17 (37.8)
Staphylococcus aureus	13 (28.9)
Escherichia coli	5 (11.1)
Klebsiella spp.	8 (17.8)
Candida spp.	4 (8.9)
Proteus spp.	2 (4.4)
CIPS (mean±SD)	7.80±0.96
Range	7–10
APACHE II (mean±SD)	22.56±2.73
Range	18–28

APACHE II, acute physiologic and chronic health evaluation II score; CIPS, clinical infection pulmonary score; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019.

Table 2 Baseline and follow CRP, ESR and pentraxin 3 among studied patients

	Baseline	Follow-up	*P*
ESR (ml/hour)	44.64±43	38.57±32.75	0.28*
Range	3–130	5–140	
CRP (mg/L)	51.25±45.56	58.09±54.87	0.16*
Range	1.1–206.2	3.2–299.3	
PTX-3 (ng/ml)	3.13±1.97	7.71±4.76	<0.001*
Range	1–11.7	3.3–24.4	

Data are expressed mean ± SD and range. CRP, C-reactive protein; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; PTX-3: Pentraxin3. Data are expressed mean ± SD and range. *P* value was significant if < 0.05. *Paired *t* test was used for comparison.

Discussion

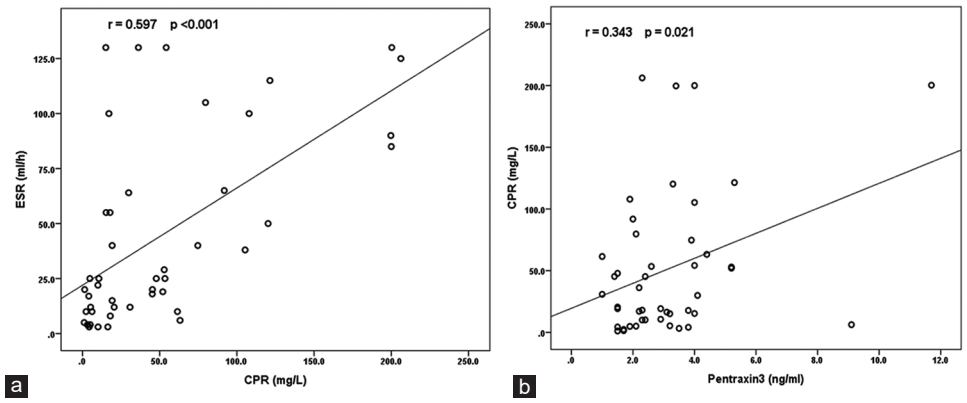
VAP is one of the most common ICU-acquired infections. Based on the diagnostic and setting criteria, reported incidences of VAP range from 5% up to 40%. VAP is associated with more mechanical ventilation and ICU stay. It is estimated that VAP has a 10% attributable mortality rate [17].

Diagnosing of VAP remains a challenge; delayed VAP diagnosis is followed by a delayed starting of appropriate antibiotic therapy, which would result in poorer outcomes in patients with VAP. However, lack of correct diagnosis can result in needless treatment and therapy-related complications [18].

ARDS has been associated with increased levels of PTX3, which have been found to be positively correlated with the severity of lung injury and to be a helpful predictor of survival [10,19].

In the current study, no significant changes were observed for both studied inflammatory markers (ESR and CRP). Only PTX3 showed a significant increase during follow-up. In line with the present study, Afifi *et al*. [20] estimated the serum levels of CRP on days 1, 4, and 7 following the diagnosis of VAP and correlated

Figure 1



Scatter dot diagram showing the correlation between (a) the inflammatory markers (ESR and CRP) and (b) pentraxin 3 and CRP. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 3 Correlation of baseline C-reactive protein, erythrocyte sedimentation rate, and pentraxin 3 with other variables

Variable names	CRP, *r* (*P*)	ESR, *r* (*P*)	PTX3, *r* (*P*)
Age	−0.14 (0.35)	−0.10 (0.91)	−0.23 (0.11)
MV (days)	−0.01 (0.93)	−0.18 (0.25)	0.07 (0.65)
ICU's stay (days)	0.12 (0.45)	−0.04 (0.82)	0.06 (0.70)
CPIS	−0.04 (0.76)	−0.07 (0.62)	0.11 (0.44)
APACHE II	−0.19 (0.19)	−0.06 (0.68)	−0.26 (0.08)
CRP (mg/l)	1	0.59 (< 0.001)	0.34 (0.02)
ESR (ml/h)		1	0.27 (0.06)

APACHE II, acute physiologic and chronic health evaluation II score; CPIS, clinical pulmonary infection score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MV, mechanical ventilation; *r*, correlation coefficient. *P* was significant if less than 0.05.

their level with 28-day mortality and found that the serum CRP levels on these days were comparable between the group of survivors and nonsurvivors. Based on this finding, the authors concluded that among patients with VAP, CRP is beneficial as a diagnostic biomarker but not as a predictive one. Similarly, previous studies [6,21,22] have concluded that CRP did not change in either group.

On the contrary, Seligman *et al.* [23] reported significant decrease in CRP level from onset to the fourth day of VAP and suggested that decreasing CR*P* values could predict survival. This disparity could result from the high patient number (75 patients), measurement of the CRP every day, calculation of the change in the CRP level, and the duration of the study (4 days). However, Povoa *et al.* [24] concluded that CRP was a good tool in assessment of resolution of VAP, not as a predictor of death.

In concordance with the present study, Markanday [25] concluded that ESR increases between 24 and 48 h after inflammation and gradually declines as inflammation resolved. Additionally, it is not illness specific, rather its decline indicates the resolution of any form of inflammation, including infection, and may help clinicians decide when to stop prescribing antibiotics. Moreover, Mosaed *et al.* [26] observed decrease in ESR in the studied patients with VAP. However, in the current study, we did not find significant changes in ESR from baseline to after follow-up. This may be contributed to the effects of red blood cells or fibrinogen levels on the ESR value [25], and also the small sample size could be another cause.

Several studies looked at the levels of PTX in serum, alveolar, and pleural effusion in patients with pneumonia and found that PTX3 levels are related to the severity of ARDS, acute lung injury, and systemic involvement [27–29].

Another study by Bilgin *et al.* [2] observed that in patients with suspicion of VAP, the PTX3 level was significantly higher compared with non-VAP adults, whereas CRP levels did not differ significantly. The same author stated that PTX3 with a cutoff 2.56 ng/ml had a sensitivity of 85%, a specificity of 86%, a positive predictive value of 75%, and a negative predictive value of 92.9% for VAP diagnosis with area under the curve (AUC) of 0.78.

The goal of Mauri *et al.* [30] was to establish the alveolar PTX3 threshold level for microbiologically confirmed pneumonia and reported that for predicting pneumonia the PTX level shows AUC of 0.815 (95% confidence interval = 0.710–0.921, $P < 0.001$).

The different cutoff points for PTX in the reported studies can be explained by the use of a different enzyme-linked immunosorbent assay kit, different sample size, different types of diagnoses at time of admission, and a difference in patient distribution. In addition, the time of sampling may greatly affect the results.

In the current study, PTX3 had a significant positive correlation with CRP (r = 0.34, P = 0.02) and no correlation with ESR, whereas CRP was significantly correlated with ESR (r = 0.59, P < 0.001).

CRP appears to be a better indicator of an acute-phase response than ESR, and it is also more sensitive to subtle changes in the acute-phase response than ESR [31]. Any illness that affects red blood cells or fibrinogen levels can produce an increase in ESR, as can noninflammatory disorders like ageing, pregnancy, medications, anemia, and obesity [25], which mean that ESR is less sensitive to inflammation than CRP; this could explain the absence of correlation between PTX3 and ESR in the present study.

In line with our study, Lin *et al.* [27] stated that in acute lung injury, the PTX3 level was elevated earlier than CRP. Moreover, the same authors observed a positive correlation between PTX3 and CRP concentration on the first day (r = 0.37, P < 0.001) and on the fourth day (r = 0.46, P = 0.026).

ESR and CRP have both been widely used by clinicians in both outpatient and inpatient settings as markers of inflammatory conditions [25,32]. This explains the positive correlation between them that was observed in the current study. However, up to our knowledge, there have been no prior studies evaluating the correlation between ESR and CRP among patients with VAP to compare our results with.

No significant correlation was found between PTX3 and either CPIS or APACHE II score (P > 0.05). No previous publication had addressed this correlation to compare our result with. However, a previous prospective study of Luyt *et al.* [33] observed that serial CPIS reading on days 1, 3, and 7 was less discriminatory in microbiologically proven patients with VAP who had a poor outcome compared with those who had a good outcome.

Another study reported that 39 of 135 patients with VAP died, with a 30-day mortality rate of 28.9%. Nonsurvivors have significantly higher APACHE II and CPIS compared with survivor patients, additionally APACHE II had better discrimination for predicting 30-day mortality in patients with VAP (AUC = 0.808, 95% confidence interval = 0.704–0.912, P < 0.001). The CPIS score, on the contrary, lacked discrimination power for predicting mortality (AUC = 0.612, 95% confidence interval = 0.485–0.739, P = 0.083) [34]. According to the findings, CPIS was a good diagnostic marker for VAP [6,7] but not for follow-up of its response and its outcome [33]. However, APACHE II could be used as a predictor for outcome among patients with VAP [34].

Conclusions

Based on our finding, we could conclude that PTX3 has a higher efficiency over other studied biomarkers for follow-up of patients with VAP, which may help in the decision for starting antibiotics in patients suspected of having VAP. Further prospective studies are needed to confirm the role of PTX3 in earlier diagnosis and follow-up of a large number of patients with VAP for better outcome among these patients.

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Conflicts of interest

There are no conflicts of interest.

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