Research Article

C-Reactive Protein as a Marker of Response to Treatment of Ventilator Acquired Pneumonia

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Abstract
VAP is the most common nosocomial infection seen in patients in the ICU. High serum CRP concentrations have been reported to be predictive of ICU readmission and in-hospital mortality in heterogeneous populations of Ventilator acquired pneumonia**Patients& methods:** ٤٠ Patients with VAP were selected(٢٠ surviving and ٢٠ non surviving) during the period from December ٢٠١١ to December ٢٠١٣. All patients were followed up in the period from day of clinical diagnosis (D٠) to the day ١٠ (D ١٠) by CRP titre, ratio, core temperature, White cell count, SOFA score, PaO_2/FiO_2 ratio and APACHE score on the day of admission to ICU. **Results:**Mean age for the study was٤٢.٩٥ ± ١١.٨٣for surviving group and٤٦.٧ ± ١٧.٢٥for non surviving group**.** There were a significant difference as regard CRP ratio in two groups from day ٠ to day ١٠ with high sensitivity (١٠٠٪) and specificity ٦٠٪ at day ٤ on analysis of receiver operating curve. **Conclusions:** We concluded that daily CRP measurement with ventilator acquired pneumonia is a good marker for VAP resolution with good prognostic value for the outcome of VAP treatment and VAP survival as early as possible.
Keywords: C-reactive protein, marker, response, treatment and Ventilator acquired pneumonia

Introduction
Ventilator-associated pneumonia (VAP) is a complication of mechanical ventilation and is defined as the occurrence of pneumonia in patients undergoing mechanical ventilation for at least ٤٨ hours[١].Ventilator-associated pneumonia (VAP) is among the most common infections acquired by adults in ICUs. Preventive strategies, early suspicion of VAP, rapid diagnostic workup, and immediate administration of adequate antimicrobial treatment active against the potential pathogens, followed by deescalation according to clinical progress and culture results are imperative[٢].The accurate diagnosis of VAP remains difficult and challenging, with no universally accepted 'gold standard,' leading to both under and over diagnosis of the condition. Prevention of any nosocomial infection in the ICU requiresmulti-disciplinary approach, with staff education, infectioncontrol programmes, adequate staffing and antibiotic controlstrategies. Prompt initiation of adequate antibiotic therapy is ssociated with a reduced mortality in patients suspected of VAP. [٣]

In recent years, many indicators (biomarkers) are present in scenarios where infectious pathogens invade into the body. These biomarkers, as reflected in specific biological responses to infections, have been reported to demonstrate the ability to facilitate the diagnosis, risk stratification, and management of pneumonia.[٤]Physicians frequently use serum biomarkers to assist in the clinical decision making process, namely in the assessment of clinical response to antibiotic therapy. C-reactive protein (CRP) is one of these biomarkers and probably the most widely used. In different infections and clinical settings, CRP discriminates, early in the clinical course, survivors from non-survivors. In addition, the

course of relative CRP variations, the CRP ratio, after prescription of antibiotic therapy, can be classified in different patterns as fast response, slow response, and non-response.[٥]

The clinical use of CRP measurement had been largely ignored for many years. During the last ١٥ years, the ready commercial availability of automated CRP immunoassay, with greater sensitivity than those previously in routine use, led to increased application of this test to clinical medicine. The availability of this new technology revealed that increased CRP values, even within the range previously considered normal, strongly predict future coronary events and this triggered widespread interest.Also, during recent years, the interest on CRP in pneumonia appeared to be born again.[٦] Measurement of C reactive protein at onset and the fourth day of treatment can predict the survival of patients with VAP. A decrease in either of these marker values predicts survival. The identification of those with good outcome as early as on day four could possibly help to ensure the adequacy of antimicrobial therapy necessary to establish whether a combination of marker kinetics can be usedto guide antimicrobial therapy, especially incases in which microorganisms are not identified.[٧]

Patients and Methods

Following departmental approval and informed consent, this study was initiated in El-Minia University Hospital in the period from December ٢٠١١ to December ٢٠١٣. The study involved ٤٠ patients received mechanical ventilation and diagnosed to have ventilator acquired pneumonia in ٨-bed intensive care unit.

Inclusion criteria:**(١)** Aged more than ١٨ yrs. **(٢)** Received mechanical ventilation for more than ٧٢h will be enrolled**.(٣)**Clinical and microbiological diagnosis of pneumonia**. (٤)** Pneumonia was considered ventilator associated when it occurred after ٤٨ hours of mechanical ventilation and will be judged to not have been incubating before starting mechanical ventilation.

Exclusion criteria: (١) Patients with a clinical diagnosis of VAP but without microbiological documentation will be excluded in the final analysis.**(٢)**Life expectancy less than ٤ days. **(٣)**The presence of uncontrolled infection in another site. **(٤)**The presence of contraindications for respiratory secretion sampling, such as hemo-dynamic instability, severe hypoxemia, risk of bleeding, uncontrolled intracranial hypertension and severe liver disease. **(٥)**Prior antimicrobial treatment before the hospital admission. **(٦)**No evidence of another medical condition to which the presenting symptoms, signs or radiological findings could be attributed.

The data have been collected are (from day ٠ to day ١٠)

For the purposes of time-dependent analysis, day ٠ (D٠) was defined as the day of VAP clinical diagnosis, as well as when the empirical antibiotic therapy for VAP was started.Data collected as **(١)**Name, age and sex. **(٢)**Cause of admission diagnosis. **(٣)**Arterial partial pressure of oxygen/fraction of inspired oxygen ($PaO_٢/FiO_٢$) from day ٠ to day ١٠.**(٤)**Nasopharyngeal body temperature from day ٠ to day ١٠.**(٥)**White cell count (WCC) from day ٠ to day ١٠.**(٦)** SOFA score (Sequential assessment of organ dysfunction).**(٧)** APACHE II ("Acute Physiology and Chronic Health Evaluation II") on admission

Clinical diagnosis of ventilator acquired pneumonia was suspected when it occurred after ٤٨ h on mechanical ventilation and was therefore judged not to have been incubating before the initiation of the mechanical ventilation anddiagnosed by a new and persistent radiographic infiltrate plus two of the following:**(١)** Body temperature more than ٣٨°C or lessthan ٣٦°C in absence of antipyretic therapy. The highest axillary temperature recorded during the ٢٤ h preceding inclusion in the study will be registered.**(٢)** White blood cells more than ١١,٠٠٠ or less than٤,٠٠٠/$mm^٣$.**(٣)**Macroscopically purulent tracheal aspirate. Purulent endotracheal aspirate will be defined on inspection by the assistant team.**(٤)**Rales on chest examination.**(٥)** Decrease of at least ١٠٪ in arterial oxygen tension/fractional inspired oxygen ratio.

After clinical VAP diagnosis, all patients received empirical antibiotic therapy. Patients with a clinical diagnosis of VAP but without micro-

biological documentation were not included in the final analysis.

In the presence of a clinical diagnosis of VAP, samples were collected for bacteriological culture from day ٠, before antimicrobial treatment is started by:
Sterile quantitative and qualitative endotracheal aspirates were obtained with a suction catheter dapted to a mucus collector without saline instillation. Tracheal aspirate cultures yielding≥ ١٠^{٥} CFU/mL (colony forming unit per ml) will be considered positive. Modifications to the empirical therapy were based on the results of tracheal aspirate culture.

From day ٠, we calculated the ***clinical pulmonary infection score(CPIS),*** adding points for microbiological results at day ٤.All patients with a clinical suspicion of VAP, later confirmed by a CPIS (clinical pulmonary infection score) of at least ٧ and fulfilling inclusion criteria, will be included and received empirical antimicrobial therapy on day ٠. The choice of antibiotics and changes will be rested solely with the critical care team or primary service caring for the patient. Modifications to empirical therapy will be based on the results of endotracheal aspirates.

CRP concentration and CRP ratio (The ratio of the CRP level during therapy to the level at the start of antimicrobial therapy) were calculated from the day of antibiotic prescription from day ٠ until day ١٠.Measurement of CRP was performed by means of an immunoturbidimetric method using a commercially available kit (BioMed-CRP; BIOMED Diagnostics, Hannover, Germany).Patients were followed-up to day ١٠. The progression of CRP concentration,CRP ratio, body temperature, WCC, Pao٢/fio٢, CPIS and SOFA score throughout the course of VAP were analyzed in **surviving** and **non surviving** patients groups. Patients were retrospectively divided into two groups according to the pattern of response of the CRP ratio after antimicrobial prescription to **surviving** and **non surviving** group. Patient's response to VAP treatment classified into **rapid response** occurred when the CRP ratio at D٤ < relative to D٠ CRP, **slow response** was characterized by a continuous and slow decrease in CRP ratio, **biphasic response** was characterized by an initial CRP ratio decrease to low levels followed by secondary rise to high value and **non response.** Patients with fast and slow response pattern survived, whereas those showing non response and a biphasic response not survived.

Results

This study included ٤٠ patients admitted to intensive care unit and diagnosed clinically and microbiologically to have VAP. Patients were divided into two groups: surviving group included ٢٠ patients and non surviving group included ٢٠ patients.

Patient characteristics and cause of admission: The two groups were comparable as regard age, sex and cause of admission without any significance.

APACHE II score: Significance decrease was seen as regard APACE II on admission with surviving group and significant increase in non surviving group.

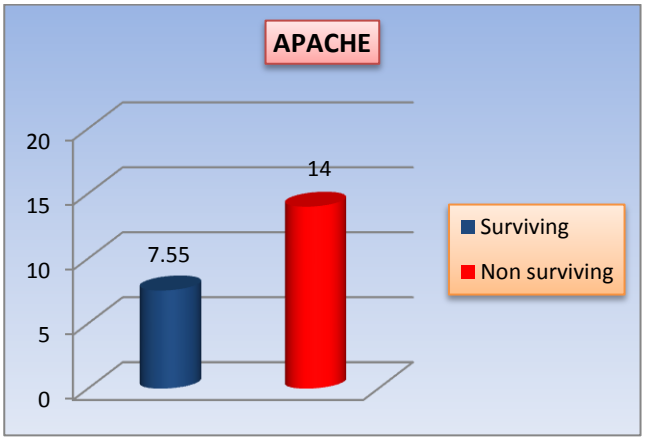

Chart (١):APACHE II on day of admission in two groups.

C-reactive protein titre (CRP titre) There was significant difference between two groups starting at day ٢.There was significant difference within group in surviving group starting at day ٣ and non significant changes in non surviving group.There

was statistically significant steady difference as regard bed time test from day ٠ to day ١٠.

C- reactive protein ratio (CRP ratio) There was a statistically significant difference in comparing between two groups from day ٠ to day ١٠.There was a statistically difference within surviving group started from day ٣ to day ١٠ and within non surviving from day ٧ to day ١٠.There was a highly statistically significant difference as regard time based test for CRP ratio from day ٠ to day ١٠.

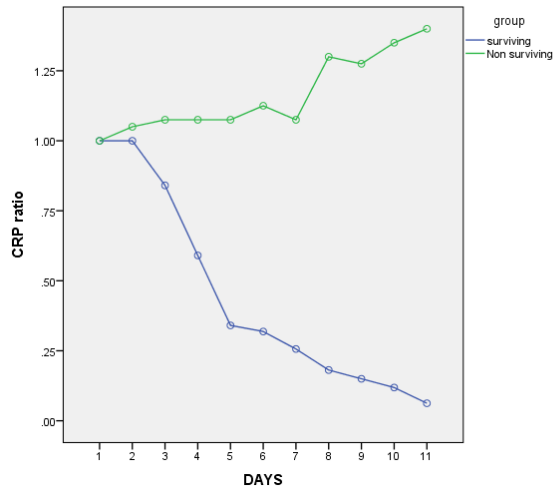

Chart (٢): C-reactive protein ratio (CRP ratio) from day o to day ١٠ within surviving and non surviving group.

CRP ratio analysis at D٤:

By using receiver-operating characteristics curve was plotted for CRP ratio on day ٤ of VAP treatment. The indicative accuracy of this variable at D٤ was assessed by calculation of the area under the curve (AUC) and in medical practice; a diagnostic test with an AUC of < ٠.٧٥ is regarded as non contributive.In our study ROC curve analysis in D٤ show AUC of ٠.٩٦٨ which is statistically significant with sensitivity of ١٠٠٪, specificity of ٦٠٪, positive predictive value of ٧١.٤ and negative predictive value of ١٠٠. The cutoff of the CRP ratio used was found as the best value in discriminating between survivors and non survivors using the highest area under the receiver-operating curve (AUC) from the curves constructed for the ten days.

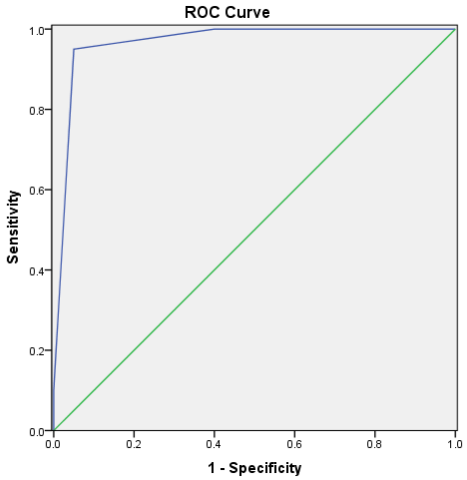

Chart (٣): Receiver-operating characteristics (ROC) for D ٤ of CRP ratio

SOFA score:

There was a statistically significant difference in surviving group when compared to non surviving group from day ٠ to day ١٠ as regard SOFA score.There was a statistically significant reduction in SOFA score in surviving groups started at day ٦ to day ١٠. And on the other hand there was a significant increase in SOFA score in non surviving group started in day ٣ to day ١٠.Statistically significant difference occurred in SOFA score within two groups as regard time based test.

Temperature:

There was no statistically significant difference as regard temperature within surviving and non surviving group and between two groups from day ٠ to day ١٠.

White cell count (WCC):

There was no statistically significant difference within surviving and non surviving group and between two group from day ٠ to day ١٠.

$Pao_{٢}/Fio_{٢}$

There was a statistically significant difference within a surviving group started at day ٦ to day ١٠ as compared to day ٠.There was a statistically difference within non surviving group started at day ٤ to day ١٠ as compared to day ٠.There significant difference within two groups as regard time based test from day ٠ to day ١٠.

Discussion

This study designed compare different patterns of C-reactive protein (CRP) ratio response to antibiotic therapy in ٤٠ patients with ventilator acquired pneumonia and evaluate it as a marker of outcome and in the prediction of clinical course. We compared CRP titre, CRP ratio, APACHE II score, SOFA score, temperature, WCC and $PaO_٢/FiO_٢$ ratio between and within surviving and non surviving group admitted to intensive care unit. In our study we observed that there was a significant decrease in CRP titre in surviving group started at day ٣ to day ١٠ compare to day ٠ and in CRP ratio started at day ٣ to day ١٠ compared to day ٠ associated with statistically significant difference in time based test for both CRP titre and ratio from day ٠ to day ١٠. And we concluded in our study that there was significant difference as regard to CRP ratio from day ٧ to day ١٠ compared to day ٠ and the difference was comparable as regard to CRP titre with significant difference in time based test from day ٠ to day ١٠ for CRP titre and ratio.With ROC curve analysis of CRP ratio at day ٤ we found significant AUC of ٠,٩٦٨ with a high sensitivity of ١٠٠٪, specificity of ٦٠٪, positive predictive value of ٧١.٤ and negative predictive value of ١٠٠ with cut off value more than zero. The cutoff of the CRP ratio used was found as the best value in discriminating between hospital survivors and non-survivors using the highest area under the receiver-operating curve (AUC) from the curves constructed for the ten days.

Our results closely related to the results postulated by Povaoet al., in ٢٠٠٥ in cohort study of ٤٧ VAP patients and concluded that daily C-reactive protein concentration measurement after prescription of antibiotic therapy is useful in the identification, as early as day ٤, of ventilator-associated pneumonia patients with poor outcome, and performs better than the commonly used markers of infection, such as body temperature and white cell count.[٨]Similar results were reported by Renatoet al., in ٢٠٠٦ in study of ٧٥ patients consecutively admitted to the intensive care unit that developed VAP and concluded that measurement of CRP at onset and on the fourth day of treatment can predict survival of VAP patients. A decrease of this marker values predicts survival and postulated that the identification of those with good outcome as early as on day four could possibly help to ensure the adequacy of antimicrobial therapy.[٧]

Our results were supported by Povoa P in ٢٠٠٢ who reported that CRP is a good marker to help the clinical in the decision making process in patients with suspected VAP and CRP have demonstrated potential value in monitoring the clinical course and in guiding antibiotic therapy.[٩]

Our results go hand with hand with Coelhoet al., in ٢٠٠٧ who found that CRP is useful for assessing the clinical severity of pneumonia and showed that in patients with a good outcome the CRP concentration fell sharply, whereas in patients who died of pneumonia there was a progressive rise in the CRP level prior to death and about ٧٦٪ of patients with fast and slow response patterns survived, whereas the combined mortality rate of the patients sowing the nonresponse and biphasic response patterns was ٧٥%.[١٠]

The results of our study agree with the finding of Lisboaet al., in ٢٠٠٨ reported that CRP is a useful biochemical surrogate of bacterial burden in patients with ventilator associated pneumonia and follow-up measurements of serum CRP anticipate the appropriateness of antibiotic therapy in sixty eight intubated patients with ventilator associated pneumonia.[١١]The results of Marcelo et al., in ٢٠١٠ revealed that daily CRP in ٤٧ patients with VAP as a type of hospital acquired pneumonia in a ٢٤-beds intensive care unit may be useful in identification of patients with poor outcome, as early as day ٤, and detect patients with inappropiate antimicrobial therapy and reported difference in mortality rate between groups with no deaths in the good response group and a ٧٥٪ mortality rate in patients with a poor response which in consistence with the present study.[١٢]

Agustin and his collegues in ٢٠١٠, in the study of behavior of plasma CRP in hospitalized patients with CAP reported that Changes in CRPlevels are useful to discriminate between true treatment

failure and slow response to treatment and can help clinicians in management decisions when CAP patients fail to improve which match well with our results.[١٣]Our results were supported with the results of Coelho et al., in ٢٠١٢ who reported that in severe CAP, sequential evaluation of CRP-ratio was useful in the early identification of patients with poor outcome. The evaluation of CRP-ratio pattern of response to antibiotics during the first week of therapy was useful in the recognition of the individual clinical evolution and patients were classified according to an individual pattern of CRP-ratio response into fast response, slow response and nonresponse and comparison between ICU survivors and non-survivors was performed. [٥]

Ulrish and his collegues in ٢٠٠٩ reported that CRP is not good predictor of prognosis of community acquired pneumonia in hospitalized elderly patients and data did not reveal any association between CRP and mortality.[١٤]

By using APACHE II score on admission we found a significant decrease with surviving group associated significant increase in non surviving group.

Similar results were found by Brunkhorstet al., in ٢٠٠٢ showed that APACHE score was significantly high in patients with poor outcome and low in patients with good outcome in study of risk evaluation in patients with severe pneumonia in nonsurgical intensive care unit.[١٥] Marcelo and his colleagues in ٢٠١٠ found that there was significantly higher APACHE II scores in a poor response group than a good response group in study used CRP as a tool in the follow up of nosocomial pneumonia which match will with our study. [١٢]

Michael et al., in ١٩٩٩ found that there was strong associatin of high biomarkers of sepsis with APACH II and indicates tha not only sepsis-related score system, but also a MODS- related evaluation of the severity of the disease should be considered when CRP or PCT concentration of different types of disease were compared.[١٦]

Regarding SOFA score we found a significant in surviving group decrease started at day ٦ to day ١٠ compared with day ٠ and observed a significant increase in non surviving group started at day ٣ to day ١٠ compared to day ٠ . There was a statistically significant difference as regard to time based test in two groups.

The analysis was carried further in that the relation between CRP ratio patterns of response and the SOFA score was studied by Povoaet al., in ٢٠٠٥ and the patients with a fast response pattern showed less severe VAP than those with a slow response, but the rate of organ failure improve-ment after antibiotic prescription was parallel. In contrast, patients showing non-response and biphasic response patterns exhibited more severe VAP, and their SOFA score remained unchanged or increased even further over time and statistically insignificant.[٨]High SOFA score was found by Marceloet al., in ٢٠١٠ in a poor response group of VAP patients and low scores in good response curve in study used CRP as a tool for follow up VAP resolution which with consistence with our results.[١٢]

Coelho and his colleagues in ٢٠٠٧ found that significant decrease in the SOFA score from day ٠ to a day ٧ was found in survivors, whereas in non survivors the values remain almost unchanged.[١٠]Our results also supported by Selligmanet al., in ٢٠١١ who reported that high SOFA scores associated with mortality and those values increase progressively as patient status worsens and have important clinical implications, because lower SOFA scores signal lower mortality risk.[١٧]

As regard temperature we found no significant difference from day o to day ١٠ compared to day ٠ in surviving and non surviving group and without any difference in time based test for temperature in two groups until day ١٠.

In our study there was no significant as regard WCC as compared to day ٠ and in time based test for WCC from day ٠ to day ١٠ in surviving and non surviving group.

Our findings were in consistence with Povoa and his collegues in ٢٠٠٥ who reveal that

comparisons of ROC curves showed that the prognostic performance of CRP ratio by D٤ was significantly better than that of body temperature and WCC. These results could be explained, at least in part, by the influence of noninfectious factors on body temperature and WCC.(٨)

Pedro et al., in ٢٠٠٥ found that no significant differences were found for changes in WCC and body temperature in a pilot study evaluating C-reactive protein levels in the assessment of response to treatment of blood stream infection.(١٨) PaO_2/FiO_2 ratio was compared between two group and found that there was significant increase in surviving group started at day ٦ to day ١٠ associated with significant decrease in non surviving group started at day ٤ to day ١٠ and found significant difference in time based test for PaO_2/FiO_2 for two groups form day of VAP diagnosis to day ١٠.

Our study also supported by Povoa and his collegues in ٢٠٠٥ who reported that time-dependent analysis of PaO_2/FiO_2 from D٠ to D٧ of antibiotic therapy in survivors and non survivors was not significantly different in a pilot study of VAP patients using CRP as a marker of clinical course.(٨)The results in our study were similar to Marcelo et al., in ٢٠١٠ who showed that the poor response group had significantly lower PaO_2/FiO_2 than in the good response group in the follow up of VAP using CRP level.(١٢)In contrary to the present study Coelhoet al., in ٢٠١٢ reported that PaO_2/FiO_2 ratio was not helpful in distinguishing between the different patterns of CRP ratio response during the first week of antibiotic in patients with community acquired pneumonia in elderly hospitalized patients.(٥)

Summary:This study was carried out in Minia University Hospital in the period from December ٢٠١١ to December ٢٠١٣.Fourty patients in our study were diagnosed clinically by certain clinical parameters then diagnosis of VAP was confirmed after appearance of culture results by clinical pulmonary infection score (CPIS).There was a significant decrease in APACHE II score in surviving group and a significant increase in non surviving group on the day of admission.As regard CRP titre and ratio, there was statistically significant difference related to the outcome of VAP resolution with significant decrease with surviving group and significant increase with non surviving group and as a marker of prognosis of disease associated with significant time based test from day ٠ to day ١٠ of VAP treatment with a good marker of VAP resolution..There was a significant increase in SOFA score in non surviving group and a significant decrease in surviving group until day ١٠ associated with significant time based test from day ٠ to day ١٠.There was statistically insignificant difference as regard temperature and WCC from day ٠ to day ١٠ in relation to VAP prognosis in surviving and non surviving associated with insignificant time based test from day ٠ to day ١٠ with a bad markers of VAP resolution.As regard PaO_2/FiO_2 ratio there was a statistically significant steady increase in surviving group and a statistically decrease with non surviving group associated with significant time based test from day ٠ to day ١٠.

Conclusions

We concluded that daily CRP measurement with ventilator acquired pneumonia is a good marker for VAP resolution with good prognostic value for the outcome of VAP treatment and VAP survival as early as possible, and the CRP level is a better predictor of outcome than are body temperature and WBC count. In addition, the identification of the pattern of CRP-ratio response adds more information about the individual clinical course, as well as the rate of improvement.

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