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Does C-Reactive Protein, Mean Platelet Volume and Red Cell Distribution width predict ventilator-associated events in mechanically ventilated patients?

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Abstract

Background: To investigate the role of C-reactive protein, procalcitonin, mean platelet volume (MPV), red cell distribution width (RDW), neutrophil–lymphocyte ratio (NLR) and other parameters of complete blood count on predictive value in patients with ventilator association events (VAE).

Materials and Methods: Seventy-six patients admitted to the intensive care unit of our institute -a tertiary center- with required mechanical ventilation between March 2019 and July 2019 were retrospectively recruited in the study. Demographic and clinical data including age, gender and laboratory test results were retrospectively collected from medical records and electronic databases. The study population was divided into two groups according to the development of VAE as VAE group or non-VAE group.

Results: Twenty-nine subjects developed of VAE during the in hospital course (VAE group) and 47 subjects didn't develop of VAE (non-VAE group). MPV, RDW, NLR, CRP and procalcitonin were significantly higher in the VAE group compared to that of the non-VAE group. Multiple logistic regression revealed that CRP, MPV and RDW were independent predictors of development of VAE in patients with mechanical ventilated. ROC curve analysis indicated a cut-off value 8.46 mg/dL for CRP (sensitivity 76%, specificity 74%), a cut-off value of 9.35 fl for MPV (sensitivity 69%, specificity 70%) and a cut-off value of 14.80 % for RDW (sensitivity 59%, specificity 58%) to predict development of VAE in patients with mechanical ventilated.

Conclusions: CRP, acute phase reactant, MPV, as an emerging indicator of preexisting inflammation, and RDW, indicative of systemic inflammation might have predictive diagnostic value invivo of VAE.

Key words: *Ventilator-association events, mean platelet volume, red blood cell distribution width, C reactive protein, procalcitonin.*

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Introduction

Mechanical ventilation (MV) is an important life-saving treatment method in patients with respiratory failure. MV has a lot of fatal complication including sepsis, barotrauma, pulmonary edema and ventilator association events (VAE). This complications might increase MV duration, hospital stay, healthcare cost and death.

VAE incidence range from 0.0-4.4 per 1000 ventilator days in various studies (1). VAEs are identified by using different clinical parameters including deterioration in respirator status after of period stability, evident of infection or inflammation and laboratory evident of respiratory infection (2) (Table 1). Preventive strategy focusing on VAE is essential to decrease morbidity, mortality and health care cost. Early obtaining high risk VAE patients might be beneficial in critical care settings.

Different biomarkers including white blood cell (WBC), neutrophil-to-lymphocyte ratio (NLR), red cell distribution width (RDW), platelets count, mean platelet volume (MPV), C-reactive protein (CRP) and procalcitonin levels are associated with inflammatuar conditions in critically care settings.

In this study, we aimed to find out the difference of these parameters in mechanically ventilated critical care patients with or without VAE, and we also focused on the predictive value of these markers in obtaining high risk patients in view of VAE.

Materials and Methods

Study population

All consecutive patients admitted to the intensive care unit of our institute -a tertiary center- between March 2019 and July 2019 were retrospectively recruited in the study. Informed consent was obtained from all subjects and the study protocol was approved by the local Ethics Committee. Patients admitted to intensive care unit with diagnosis of VAE, was defined using CDC's NHSN new definitions (2). We included subjects who were ≥ 18 years old and required mechanical ventilation for ≥ 4 days. Patients treated with extracorporeal membrane oxygenation or high frequency oscillatory ventilation were excluded. Exclusion criteria were also evidence of diabetes mellitus, hypercholesterolemia, coronary artery disease, congestive heart failure, renal or hepatic dysfunction, chronic lung disease, arterial or venous thrombotic disease, haematological disease, cancer, hypo and hyperthyroidism, auto-immune disease, antithrombotic agents or serotonin reuptake inhibitor drug use, blood transfusion within the last three months, chronic or systemic inflammatory diseases such as asthma bronchial, rheumatoid arthritis and psoriasis.

Data collection and outcome measurements

Demographic and clinical data including age, gender, accompanying chronic diseases and laboratory test results (Beckman Coulter LH 780 Haematology Analyzer) were retrospectively collected from medical records and electronic databases. In our intensive care unit, CBC is performed daily as part of routine care. WBC count, neutrophil counts, lymphocyte counts, red blood cell count (RBC), hemoglobin (Hb) level, erythrocyte mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RDW, platelets count, platelet distribution width (PDW) and MPV were recorded. The neutrophil-to-lymphocyte ratio (NLR) was determined from the blood cytology by dividing the neutrophil count by the lymphocyte count. C-reactive protein (CRP) and procalcitonin levels also were recorded.

The outcomes of patients with VAE were compared with patients who were mechanically ventilated for at least 4 days but who did not develop VAE.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v22 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using the Kolmogorov-Smirnov test. Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Independent samples t-test was used to compare the groups. Categorical variables were analyzed using Pearson chi-square test. Logistic regression analysis was carried to identify the contributors to VAE. ROC curve analyses were performed to determine the cut-off values for selected variables to predict development of VAE. A p-value < 0.05 was assumed statistically significant.

Table 1. Ventilator-Associated Events (VAE) Surveillance Algorithm (2).

Patient has a baseline period of stability or improvement on the ventilator, defined by ≥ 2 calendar days of stable or decreasing daily minimum* FiO2 or PEEP values. The baseline period is defined as the 2 calendar days immediately preceding the first day of increased daily minimum PEEP or FiO2.
*Daily minimum defined by lowest value of FiO2 or PEEP during a calendar day that is maintained for > 1 hour.

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After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:
1- Increase in daily minimum* FiO2 of ≥ 0.20 (20 points) over the daily minimum FiO2 of the first day in the baseline period, sustained for ≥ 2 calendar days. 2- Increase in daily minimum* PEEP values of ≥ 3 cmH2O over the daily minimum PEEP of the first day in the baseline period†, sustained for ≥ 2 calendar days.

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Ventilator-Associated Condition (VAC)

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On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets both of the following criteria:
1- Temperature > 38 °C or < 36°C, **OR** white blood cell count ≥ 12,000 cells/mm3 or ≤ 4,000 cells/mm3.
2- A new antimicrobial agent(s) (see Appendix for eligible antimicrobial agents) is started, and is continued for > 4 qualifying antimicrobial days

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Infection-related Ventilator-Associated Complication (IVAC)

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On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met (**taking into account organism exclusions specified in the protocol**):

Criterion 1: Positive culture of one of the following specimens, meeting quantitative or semi-quantitative thresholds as outlined in protocol, without requirement for purulent respiratory secretions: Endotracheal aspirate, ≥ 105 CFU/ml or corresponding semi-quantitative result
Bronchoalveolar lavage, ≥ 104 CFU/ml or corresponding semi-quantitative result
Lung tissue, ≥ 104 CFU/g or corresponding semi-quantitative result
Protected specimen brush, ≥ 103 CFU/ml or corresponding semi-quantitative result

Criterion 2: Purulent respiratory secretions (defined as secretions from the lungs, bronchi, or trachea that contain >25 neutrophils and <10 squamous epithelial cells per low power field [lpf, x100]) **PLUS** organism identified from one of the following specimens (to include qualitative culture, or quantitative/semi-quantitative culture without sufficient growth to meet criterion #1):
Sputum
Endotracheal aspirate
Bronchoalveolar lavage
Lung tissue
Protected specimen brush

Criterion 3: One of the following positive tests:
Organism identified from pleural fluid (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
Lung histopathology, defined as: 1) abscess formation or foci of consolidation with intense neutrophil accumulation in bronchioles and alveoli; 2) evidence of lung parenchyma invasion by fungi (hyphae, pseudohyphae or yeast forms); 3) evidence of infection with the viral pathogens listed below based on results of immunohistochemical assays, cytology, or microscopy performed on lung tissue
Diagnostic test for *Legionella* species
Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

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Possible Ventilator-Associated Pneumonia (PVAP)

Results

A total of 76 patients with required mechanical ventilation were enrolled in this retrospective study. Twenty-nine subjects developed of VAE during the in-hospital course (VAE group) and 47 subjects didn't develop of VAE (non-VAE group). The group of VAE comprised 12 (41.3%) male and 17 (58.7%) female, with a mean age of 61.97±12.47 years. The group of non-VAE comprised 22 (46.8%) male, 25 (53.2%) female, with a mean age of 62.17±11.56 years. There were no significant differences between two groups regarding age and gender distribution. The patient characteristics for groups of VAE and non-VAE are presented in table 2.

The laboratory characteristics of study populations are presented in table 1. Mean values of WBC counts, RBC counts, Hb level, MCV, MCH, MCHC, platelets counts and PDW were similar among the groups. However, CRP (16.11 ±9.04 mg/dL vs. 5.79±5.31 mg/dL, $p < 0.001$), procalcitonin (6.77±7.21 ng/mL vs. 1.39±2.30 ng/mL. $p < 0.001$), MPV (10.08±1.15 fl vs. 8.77±0.87 fl, $p < 0.001$), RDW (15.91±2.30 % vs. 14.57±1.55 %, $p= 0.003$) and NLR (18.42±13.38 vs. 9.40±6.61, $p = 0.002$) were significantly higher in the VAE group compared to the non-VAE group (Table 2).

Multiple logistic regression analysis revealed that CRP (OR: 1.188, 95 % CI: 1.024-1.377, p=0.023), MPV (OR: 4.007, 95 % CI: 1.558-10.306, p=0.004) and RDW (OR: 1.772, 95 % CI: 1.090-2.881, p=0.021) were independent predictors of development of VAE in patients with mechanical ventilated (Table 3).

ROC curve analysis indicated a cut-off value of 8.46 mg/dL for CRP (sensitivity 76%, specificity 74%), a cut-off value of 9.35 fl for MPV (sensitivity 69%, specificity 70%) and a cut-off value of 14.80 % for RDW (sensitivity 59%, specificity 58%) to predict development of VAE in patients with mechanical ventilated (Figure 1).

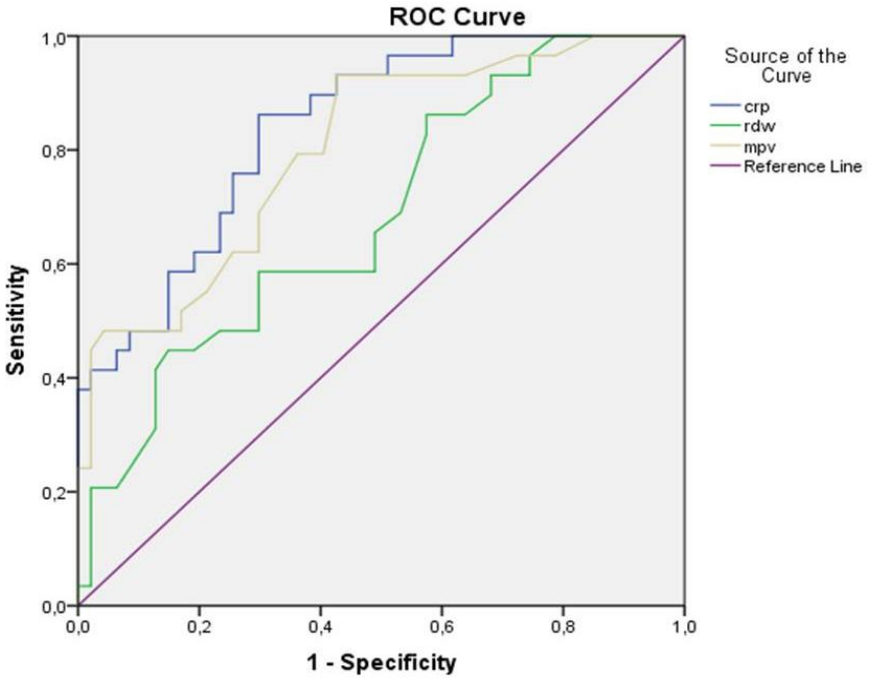

Figure 1. Receiver operating characteristic (ROC) curves demonstrating the predictive value of CRP, MPV and RDW for development of VAE. The area under curve (AUC) of CRP, MPV and RDW were 0.841, 0.802 and 0.685, respectively.

Table 2. Demographic characteristics and laboratory parameters of study groups.

	VAE n=29	non-VAE n=47	p value
Age (years)	61.97±12.47	62.17±11.56	0.943
Gender (Male/Female)	12/17	22/25	0.644
CRP (mg/dL)	16.11 ±9.04	5.79±5.31	<0.001*
Procalcitonin (ng/mL)	6.77±7.21	1.39±2.30	<0.001*
Hb level (g/dL)	10.11±2.59	10.50 ±2.57	0.527
WBC count (x10^3/µl)	13.37± 4.70	11.46± 4.36	0.084
Platelet count (x10^3/µl)	248.24 ±121.87	256.00±121.77	0.788
RBC count(x10^3/µl)	3.60±0.90	3.72±0.88	0.568
RDW (%)	15.91±2.30	14.57±1.55	0.003*
MCV(fl)	88.07±9.56	87.90±7.84	0.938
MCH (pg)	28.50±3.30	28.30±2.83	0.788
MCHC (%)	31.48±3.51	32.22±1.40	0.289
NLR	18.42±13.38	9.40±6.61	0.002*
MPV (fl)	10.08±1.15	8.77±0.87	<0.001*
PDW (%)	16.10±0.60	16.18±0.42	0.519

Abbreviations: CRP, C reactive protein; Hb, hemoglobin; WBC, white blood cell; RBC, red blood cell count; RDW, red cell distribution width; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; NLR, neutrophil-to-lymphocyte ratio; MPV, mean platelet volume; PDW, platelet distribution width. * $p < 0.05$.

Table 3. Predictors of development of ventilator-association events (VAE).

	OR	95% CI	p value
CRP	1.188	1.024-1.377	0.023*
Procalcitonin	1.151	0.936-1.416	0.182
RDW	1.772	1.090-2.881	0.021*
NLR	1.051	0.948-1.164	0.344
MPV	4.007	1.558-10.306	0.004*

Abbreviations: CRP, C reactive protein; RDW, red cell distribution width; NLR, neutrophil-to-lymphocyte ratio; MPV, mean platelet volume. * $p< 0.05$.

Discussion

With the present study, we have tested that different biomarkers might have predictive diagnostic value in VAE. We have shown that 1) CRP, procalcitonin, MPV, RDW and NLR were increased in the VAE group compared to the non-VAE group. 2) CRP, MPV and RDW were independent predictors of development of VAE in patients with mechanical ventilated.

VAE and required implementation of the National Healthcare Safety Network (NHSN), the CDC's new surveillance program in January 2019 (2). In contrast to ventilator associated pneumonia (VAP), VAE include complications related to mechanical ventilation with 3 different tiers of classifications for VAE. The VAE surveillance definition algorithm uses a tiered approach, moving from measures of ventilator-associated conditions (VAC), to infection-related ventilator-associated complications (IVAC), to possible VAP (Figure 1). VAC is defined by a sustained period of worsening oxygenation that immediately follows a baseline period of stability or improvement on the ventilator. IVAC, attempts to identify the subset of VACs that are potentially related to infection, as evidenced by an abnormal

white blood cell count or temperature and initiation of a new antimicrobial agent. Possible VAP, attempts to zero in on the subset of IVAC patients with respiratory infections, as manifested by objective evidence of purulent respiratory secretions and/or positive results of microbiological tests performed on respiratory tract specimens (2).

Increased hospital mortality, prolonged mechanical ventilation, and longer lengths of stay have been reported by numerous groups in patients with VAEs compared with patients without VAEs. Excess fluid balance, deeper levels of sedation, prolonged sedation, and high tidal volumes are risk factors for VAEs. The most common and consistent complications that trigger VAE criteria are pneumonia, pulmonary edema, ARDS, and atelectasis (3). Preventive strategy focusing on VAE is essential to decrease morbidity, mortality and health care cost. Early obtaining high risk VAE patients might be beneficial in critical care settings.

Mean platelet volume (MPV), the most common used measure of platelet size, is a potential marker of platelet reactivity (4). Large platelets contain a greater number of dense granules and are enzymatically and metabolically more active, and thus have greater prothrombotic potential (5).Besides their role in hemostasis, platelets also initiate inflammation by releasing various kinds of cytokines and adhesion molecules directly activating responses for monocytes, neutrophils, and T-lymphocytes. They also activate the complement system that augments the inflammatory responses (6). MPV has emerged as an alternate marker for several clinical conditions which explicit with acute or chronic inflammation. In previous studies, elevated MPV value was associated with poor outcomes and increased mortality rate in diseases such as sepsis, neonatal respiratory distress syndrome, myocardial infarction, pulmonary embolism and chronic obstructive pulmonary disease where inflammation plays a critical role in development and progression of the these diseases(7-11). Zhang et al. showed that a higher MPV level is a significant risk factor for higher mortality in critically ill patients (12). Sezgi et al. showed that discharge MPV levels increased in the non-survivor intensive care unit patients (13). In the present study, MPV levels were found significantly higher in the VAE group compared with in the non-VAE group. Furthermore, we found that the MPV is an independent predictor of development of VAE in patients with mechanical ventilated (cut-off value of 9.35 fl showed sensitivity %69 and specificity %70).

Red cell distribution width (RDW) reflects the variation of red blood cell volume. In general, RDW is reflective of inflammation (14).Some previous research indicates that RDW was an independent prognostic factor in patients with congestive heart failure, sepsis, chronic lower respiratory tract disease, acute pulmonary embolism and critically ill patients (15-18). Any process that results in the release of reticulocytes into the circulation will result in an increase in RDW. Elevations in RDW may have negative impact on patient survival by reflecting the extent of inflammation. In the present study, RDW levels were found significantly higher in the VAE group compared with in the non-VAE group in patients with mechanical ventilated. Furthermore, we found that the RDW is an independent predictor development of VAE in patients with mechanical ventilated (cut-off value of 14.80 % for RDW showed sensitivity 59%, specificity 58 %).

NLR is defined as the number of neutrophils in whole blood divided by the number of lymphocytes in whole blood (19). NLR is an indicator of systemic inflammation and a high NLR may indicate that a patient has severe inflammatory progression (20). High NLR in patients were associated with high levels of inflammation, de Jager et al. showed that NLR

predicted bacteremia was better than conventional inflammation markers like C-reactive protein, white blood cell count and neutrophil count (21). NLR has been found to be a useful biomarker for predicting mortality in various disease ranged from cancers to cardiovascular diseases and other inflammatory related diseases (22-24). In our study, we found that NLR was higher in the group of VAE than that of the non-VAE which is in accordance with their results. However, we haven't found any significant role of NLR levels for on predicting development of VAE. This could have been due to the small sample size.

CRP is an annular protein found in plasma, whose levels rise in response to inflammation. Procalcitonin is a peptide precursor of the hormone calcitonin, the latter being involved with calcium homeostasis. Previous studies have demonstrated that the serum levels of CRP and procalcitonin are elevated in patients with infectious diseases (25-27). CRP and procalcitonin are the most widely studied biomarkers for diagnosis and evaluation of nosocomial infection including VAP (28-30). Povoa et al demonstrated that for patient MV, daily CRP monitoring was useful in VAP prediction, while procalcitonin showed a poor predictive value (31). Habib et al demonstrated positive results of CRP and an insignificant result of PCT in diagnosing CRP (32). However, Jiao et al analyzed the value of procalcitonin in diagnosing VAP for patients undergoing cardiac surgery, and the results showed that serum procalcitonin might be used as diagnostic marker for VAP (33). Tanrıverdi et al demonstrated that the association between CRP, PCT levels and survival condition of VAP patients, and the results were negative (34). In our study, we found that CRP and procalcitonin were higher in the VAE group compared to the non-VAE group. Furthermore, we found that the CRP is an independent predictor development of VAE in patients with mechanical ventilated (cut-off value of 8.46 mg/dL for CRP showed sensitivity 76%, specificity 74 %). However, we haven't found any significant role of procalcitonin levels for on predicting development of VAE.

While the underlying mechanism explaining why elevated MPV and RDW is associated with poor course and outcomes, oxidative stress may also be a contributing factor with increased inflammation in MV patients. High oxidative stress is present in MV patients via the generation of reactive oxygen species by activated leukocytes. High oxidative stress contributing to elevated RDW and MPV by reducing red blood cell and platelet survival, and increasing release of large premature red blood cells and large immature platelets into the peripheral circulation (18,35).

Several limitations of our study should be noted including relatively small sample size, retrospective design, a single center study with a single ethnicity study population, and it remains unclear whether our results could be generalized to other ethnicities.

Conclusion

CRP, acute phase reactant, MPV, as an emerging indicator of preexisting inflammation, and RDW, indicative of systemic inflammation might have predictive diagnostic value invivo of VAE. Simple and common worldwide usage are the many advantages of these promising biomarkers in clinical care settings.

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