



## Mean platelet volume can predict subsequent *Candida* spp. airway colonization in mechanically ventilated subjects

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### Abstract

**Background:** Despite the association between the airway colonization with *Candida* spp and impaired ICU outcomes of critically ill patients, little is known whether *Candida* colonization in respiratory tracts could be predicted with simple blood tests. The present study aims to investigate whether admission blood tests could provide information regarding the further *Candida* spp airway colonization in patients admitted to the ICU for MV.

**Materials and Methods:** A hundred patients who were admitted to the ICU of our institute for invasive MV for more than 4 days were enrolled in this retrospective study. Venous blood samples were drawn upon admission for measurement complete blood count, procalcitonin, and C-reactive protein (CRP). Endotracheal aspirates were also obtained by 7 days intervals to identify *Candida* spp. airway colonization. Rapid assimilation or agglutination tests and API 20C AUX were performed for the identification of *Candida* spp.

**Results:** Mean platelet volume was significantly higher in subjects who developed *Candida* spp. airway colonization compared to subjects without *Candida* spp. airway colonization during the ICU stay ( $10.5 \pm 1.3$  fl vs.  $9.4 \pm 1.4$  fl,  $p < 0.001$ ). Logistic regression analysis revealed that among the parameters studied, only MPV was a significant predictor for the development of *Candida* spp. airway colonization during the ICU stay (OR: 1.992, 95%CI: 1.289-3.078,  $p = 0.002$ ).

**Conclusions:** Mean platelet volume, a simple and readily available marker of the inflammatory state, can be used in the prediction of the subsequent *Candida* spp. airway colonization in mechanically ventilated subjects.

**Key words:** *Candida*, airway colonization, mean platelet volume.

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## Introduction

Positive-pressure mechanical ventilation (MV) has long been the standard of care in the management of acute or chronic respiratory failure due to pulmonary or systemic insults. About 1 to 3 million patients are estimated to receive mechanical ventilator support each year in intensive care unit (ICU) settings of the United States (1). Mechanical ventilation provides tissue oxygenation and carbon dioxide elimination by maintaining adequate tidal volumes and respiratory rates (2). However, patients receiving mechanical ventilation are at substantial risk for complications, including barotraumas, acute respiratory distress syndrome, and ventilator-associated pneumonia (VAP), which often lead to prolonged hospital stays and increase mortality and morbidity (3, 4).

*Candida* species ordinarily take place in the normal flora of mouth, gastrointestinal tracts and respiratory tracts in healthy adults (5). Since pneumonia caused directly by the *Candida* spp is relatively rare, isolation of the *Candida* spp from respiratory tracts is often considered as airway colonization (6). Mechanical ventilation is a major risk factor for *Candida* colonization in respiratory tracts. Although *Candida* spp airway colonization was previously considered as innocent, recent evidence indicates that *Candida* colonization in respiratory tracts is associated with prolonged MV, prolonged ICU stay, and higher ICU mortality (7). The identification of *Candida* spp. in respiratory tract of the ICU subjects has been shown to be an independent risk factor for *A. baumannii* VAP (8).

Despite the association between the airway colonization with *Candida* spp. and impaired ICU outcomes of critically ill patients, little is known whether *Candida* colonization in respiratory tracts could be predicted with simple blood tests. The present study aims to investigate whether admission blood tests could provide information regarding the further *Candida* spp. airway colonization in patients admitted to the ICU for MV.

## Materials and Methods

This retrospective study enrolled all consecutive patients who were admitted to the ICU of our institute for invasive MV for more than 4 days between September 2019 and January 2020. The study was approved by the local ethics committee and was performed in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants or their proxies. In situations of impaired decision-making capacity and absence of surrogates, informed consent was obtained later on from the patient. Subjects with neutropenia, recent solid organ transplant, and bone marrow transplant recipients, and patients receiving corticosteroid therapy of > 2 mg/kg of methylprednisolone or equivalent were excluded. Patients with *Candida* spp. airway colonization an admission and those on prior antifungal treatment were also excluded from the study.

Venous blood samples were drawn upon admission for measurement complete blood count, procalcitonin, and C-reactive protein (CRP). Endotracheal aspirates were also obtained by 7 days intervals to identify *Candida* spp. airway colonization. For this purpose, specimens were inoculated onto CAN2 chromogenic isolation plates and/or into Sabouraud chloramphenicol tubes and incubated for 3–6 days at 35 °C. Rapid assimilation or agglutination tests (Glabrata RTT, Bichro-Latex Albicans and Krusei-Color; Fumouze Diagnostics, Levallois-Perret, France) and API 20C AUX (bioMérieux, Lyon, France) were performed for identification of *Candida* spp. The primary outcome measure of this study was the difference in admission CBC parameters, procalcitonin, and CRP in subjects with and without *Candida* spp. airway colonization during the ICU stay.

### Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Shapiro-Wilk test was used. Data are given as mean  $\pm$  standard deviation for continuous variables and as frequency (percentage) for categorical variables. Student t-test was used for the comparison of the CBC parameters, procalcitonin, and CRP in subjects with and without *Candida* spp. airway colonization. Logistic regression analysis was performed to identify the factors significantly associated with *Candida* spp. airway colonization. P-value  $< 0.05$  accepted as statistically significant result.

### Results

A total of 100 subjects were enrolled in this study (mean age  $62.7 \pm 21.6$ , 61% male). The demographic features and admission laboratory test are presented in Table 1. The groups were similar with respect to age, gender, CRP, leukocyte count, hemoglobin level, neutrophil to lymphocyte ratio, platelet count, and procalcitonin level. However, mean platelet volume was significantly higher in subjects who developed *Candida* spp. airway colonization compared to subjects without *Candida* spp. airway colonization during the ICU stay ( $10.5 \pm 1.3$  fl vs.  $9.4 \pm 1.4$  fl,  $p < 0.001$ ).

**Table 1.** Demographic features and laboratory measurements of the subjects with and without *Candida* spp. airway colonization during the ICU stay.

	<b>Candida (-) n=58</b>	<b>Candida (+) n=42</b>	<b>P value</b>
<b>Age (years)</b>	63.3 $\pm$ 22	61.9 $\pm$ 21.3	0.763
<b>Gender (male)</b>	35 (60.3%)	26 (61.9%)	0.521
<b>CRP (mg/l)</b>	214.7 $\pm$ 128.5	216.5 $\pm$ 93.2	0.938
<b>Procalcitonine (ng/m)</b>	15.7 $\pm$ 3.9	16.8 $\pm$ 2.6	0.858
<b>Leukocyte count (x1000/mm<sup>3</sup>)</b>	19.0 $\pm$ 4.2	17.0 $\pm$ 3.8	0.357
<b>Neutrophil (x1000/mm<sup>3</sup>)</b>	12.4 $\pm$ 3.7	11.3 $\pm$ 2.9	0.437
<b>Lymphocyte (x1000/mm<sup>3</sup>)</b>	1.2 $\pm$ 0.2	1.1 $\pm$ 0.3	0.454
<b>NLR</b>	13.9 $\pm$ 4.3	11.8 $\pm$ 2.7	0.306
<b>Hemoglobine (g/dl)</b>	9.9 $\pm$ 2.3	10.9 $\pm$ 3.1	0.090
<b>Platelet count (x1000/mm<sup>3</sup>)</b>	228.9 $\pm$ 64.3	217.9 $\pm$ 45.2	0.689
<b>MPV (fl)</b>	9.4 $\pm$ 1.4	10.5 $\pm$ 1.3	<b>&lt;0.001</b>
<b>Length of ICU stay (days)</b>	20.8 $\pm$ 2.4	22.3 $\pm$ 2.7	0.761

Data are presented as mean  $\pm$  Standard deviation for continuous variables and as frequency for categorical variables.

Table 2 demonstrates the predictive role of selected variables on *Candida* spp. airway colonization. Logistic regression analysis revealed that among the parameters studied, only MPV was a significant predictor for the development of *Candida* spp. airway colonization during the ICU stay (OR: 1.992, 95%CI: 1.289-3.078,  $p = 0.002$ ).

**Table 2.** Logistic regression analysis demonstrating value of the variables for predicting *Candida* spp. airway colonization during the ICU stay.

	OR	95%CI	P value
<b>Age</b>	0.999	0.978-1.021	0.959
<b>Gender</b>	1.124	0.447-2.831	0.803
<b>CRP</b>	1.000	0.996-1.004	0.926
<b>Procalcitonine</b>	1.000	0.985-1.016	0.993
<b>Lekocyte count</b>	0.988	0.945-1.032	0.583
<b>NLR</b>	0.981	0.933-1.031	0.444
<b>Hemoglobine</b>	1.092	0.924-1.290	0.302
<b>Platelet count</b>	1.001	0.997-1.004	0.676
<b>MPV</b>	1.992	1.289-3.078	<b>0.002</b>
<b>Length of ICU stay</b>	1.011	0.991-1.032	0.275

## Discussion

Our findings demonstrate that admission mean platelet volume, one of the complete blood count subtests, is significantly higher in subjects who develop *Candida* spp. airway colonization the ICU stay compared to those without colonization. The results of this study also show that admission mean platelet volume is a significant predictor of subsequent *Candida* spp. airway colonization in subjects receiving MV in the ICU.

*Candida* spp. colonization frequently occurs in the respiratory tract of the ICU subjects receiving mechanical ventilation. The prevalence of *Candida* spp. airway colonization reaches 30% in ICU subjects receiving mechanical ventilation, particularly in those with MV duration of > 48 hours. Moreover, in subjects with clinically suspected VAP, the prevalence of *Candida* spp. airway colonization exceeds 50% (9). Except for the subjects with severe immune compromise, the isolation of the *Candida* spp. in lower respiratory is often considered as *Candida* spp. airway colonization rather than true fungal pneumonia (6, 10, 11). Several prospective studies have shown that isolation of the *Candida* spp. in the lower respiratory tract of the subjects with clinically suspected VAP was merely a marker of the immunosuppression or illness severity and its impact on clinical outcomes was not clear (12). However, *Candida* spp. airway colonization does not appear purely innocent since recent evidence suggests that *Candida* spp. airway colonization may act in the development of bacterial pneumonia.

The study conducted by Azoulay et al. has reported that the risk for *Pseudomonas aeruginosa* pneumonia is increased in subjects with *Candida* spp. bronchial colonization (13). Antifungal treatment targeting *Candida* spp. airway colonization has been shown to prevent *P. aeruginosa* VAP (14). A recent study conducted by Tan et al. has revealed that *Candida* spp. airway colonization was an independent risk factor for subsequent *A. baumannii* VAP in ICU patients who were on mechanical ventilation (MV) longer than 48 hours (8). Moreover, a huge amount of data have demonstrated that *Candida* spp. airway colonization impairs the clinical outcomes, including MV duration, ICU stay, and 28-day mortality, and ICU mortality (12, 15, 16).

Despite the evidence indicating poor clinical outcomes in subjects with *Candida* spp. airway colonization, simple and readily available blood tests that could facilitate the prediction of *Candida* colonization are lacking. Currently, the presence of *Candida* spp. airway colonization is recognized by using the rapid assimilation or agglutination tests in bronchoalveolar lavage or endotracheal aspirate specimens. However, these tests are both time-consuming and costly.

This study sought whether simple blood tests such as complete blood count, procalcitonin, or CRP would prove successful in the prediction of the subjects who receive MV and would develop *Candida* spp. airway colonization during the ICU stay. Our findings show that admission mean platelet volume is significantly higher in subjects who develop *Candida* spp. airway colonization during mechanical ventilation. Moreover, our results also indicate that mean platelet volume is a significant predictor of subsequent *Candida* spp. airway colonization in subjects receiving MV in the ICU.

Mean platelet volume has repeatedly shown to be increased in clinical conditions presenting with subclinical inflammation. Recent studies in ICU subjects receiving MV have shown that colonization with *Candida* spp. is associated with an activated immune response. Results of the recent multicenter, randomized, and placebo-controlled CANTREAT trial, which investigated the effect of antifungal therapy in critically ill patients with a clinical suspicion of ventilator-associated pneumonia with positive airway secretion specimens for *Candida* spp., indicate that *Candida* spp. airway colonization in these patients may result from persistent inflammation (17). The presence of *Candida* spp. in the endotracheal secretions of VAP patients was shown to be associated with increased levels of the inflammatory markers, including CRP, IL-6, and PCT. We speculate that the proinflammatory state, indicated by the increased mean platelet volume, is responsible for the subsequent *Candida* spp. airway colonization in subjects receiving MV in the ICU. However, further randomized, prospective studies are required to address the predictive role of the mean platelet volume in subsequent *Candida* spp. airway colonization in mechanically ventilated subjects.

### **Conclusion**

Mean platelet volume, a simple and readily available marker of the inflammatory state, can be used in the prediction of the subsequent *Candida* spp. airway colonization in mechanically ventilated subjects. High admission mean platelet volume may help to identify subjects who will develop subsequent *Candida* spp. airway colonization.

**Ethics Committee Approval:** NA

**Informed Consent:** NA

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