Prognostic role of preoperative neutrophil-to-lymphocyte ratio and albumin for 30-days mortality in patients with postoperative acute pulmonary embolism

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**SUBJECT AREAS**

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Abstract

Background This retrospective study aimed to investigate the prognostic value of neutrophil-lymphocyte ratio (NLR) and albumin in 30-days mortality in patients with postoperative acute pulmonary embolism (PAPE).

Methods We retrospectively reviewed the medical records of 101 patients with PAPE admitted from September 1, 2012 to March 31, 2019. The characteristics, surgical information, admission examination data and mortality within 30-days after PAPE were obtained from our electronic medical recording system and follow up. The association between NLR, PLR, and other predictors and 30-days mortality were analyzed with univariate and multivariate analyses. Then, the nomogram include the independent predictors was established and evaluated.

Results 24 patients died within 30 days corresponding to 30-days mortality of 23.8%. The results of the multivariate analysis indicated that both NLR and albumin are independent predictors for 30-days mortality in patients with PAPE. The probability of death increased about 17.1% (OR=1.171, 95% CI: 1.073-1.277, P=0.000) with one unit of increase of NLR, and the probability of death decreased about 15.4% (OR=0.846, 95% CI: 0.762c-0.939, P=0.002) with one unit of increase of albumin. The area under the curve of nomogram was 0.888(95%CI:0.812-0.964).

Conclusion Our findings showed that Elevated NLR and decreased albumin were related with poor prognosis in patients with PAPE. The NLR and albumin were independent prognostic factor for PAPE.

Introduction

Postoperative acute pulmonary embolism (PAPE) is one of the most dangerous complications following operations, with an incidence between 0.9% and 3.1%[1-4].
Although the way of diagnosis and treatment of PAPE have been continuously developed in recent years, including imaging diagnosis, interventional surgery and medicinal chemotherapy, the overall survival rate of patients with PAPE was extremely low. It was reported that the short-term mortality of patients with PAPE was between 10% and 23.1% [5-9]. Therefore, identifying the preoperative risk factors associated with mortality may help to direct more aggressive treatment strategies towards patients who will derive the greatest benefit.

The mechanism of inflammatory reaction is closely related to the occurrence and development of thromboembolism[10]. In recent years, many researches reported that some predictors based on the inflammation are associated with prognosis in patients with pulmonary embolism, such as neutrophil-to-lymphocyte ratio(NLR), lymphocyte to monocyte ratio(LMR), red blood cell distribution width(RDW), and C-reactive protein(CRP) [11-14]. Besides, the relationship between nutritional status and prognosis in patients with pulmonary embolism has also been extensively studied in previous study[15]. Plasma albumin is one of the important indicators reflecting the systemic nutritional status and is associated with prognosis in patients with acute pulmonary embolism[16]. However, previous studies have focused on non-surgical patients, and there were no studies focused the relationship between these predictors and mortality in patients with PAPE. Therefore, this study was performed to investigate the relationship of admission NLR, plasma albumin and other predictors for 30-days mortality in patients with PAPE.

Methods

Patients

We performed a single center, retrospective and case-control study. The medical records of consecutive patients who was diagnosed with pulmonary embolism from September 1, 2012 to March 31, 2019 in our hospital were reviewed, and the patients who diagnosed
with acute pulmonary embolism within 90 days postoperatively were included in this study. Patients were excluded if they underwent cardiac surgery, without complete data, received blood transfusion within 1 month preoperatively, comorbid with infection, comorbid with hematological disease or received immunosuppressive therapy within 1 month preoperatively. Finally, 101 patients met our inclusion criteria. All patients with PAPE meet the diagnostic criteria of 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism[17].

**Data collection**

Data were extracted from the hospital electronic database by two independent doctors. If controversial data was encountered, the two doctors who collected the data will discuss to reach an agreement. All patients' characteristics (sex, age, BMI, smoking history and drinking history), comorbidities (hypertension, diabetes, respiratory diseases, coronary heart disease, arrhythmia, history of stroke and renal failure), surgical information (surgical type and ASA level), admission examination data (neutrophil-to-lymphocyte ratio; platelet to lymphocyte ratio; monocyte-to-lymphocyte ratio; hemoglobin; white blood cell; platelet; mean platelet volume; platelet distribution width; red cell distribution width; glucose; neutrophil; lymphocyte; creatinine and albumin) and situation within 30-days after PAPE were obtained through our electronic medical recording system and follow up. Complete blood count (CBC), blood glucose levels, and albumin assessments were carried out at the biochemistry laboratory of our hospital. NLR was obtained by dividing the absolute neutrophil counts to the absolute lymphocytes counts from the same blood sample, PLR was obtained by dividing the absolute platelet counts to the absolute lymphocytes counts from the same blood sample, and MLR was obtained by dividing the absolute monocyte counts to the absolute lymphocytes counts from the same blood samples. All test results were obtained from the same blood sample.
test within 3 days preoperatively.

**Statistical analysis**

Data analysis was performed using Statistical Package for the Social Sciences version 25.0 for Windows (IBM, Chicago, IL, USA). Data of normal distribution were represented as mean ± standard deviation, and the Student t-test was used to compare two groups. The data of abnormal distributions were represented as medians (interquartile range), and Mann-Whitney U test was used to compare two groups. Categorical variables were represented as number or percentages, $c^2$ test or Fisher’s Exact test were performed for categorical variables. Based on the univariate analysis, variables with P value < 0.05 were included in the multivariate logistic regression analysis to confirm the independent risk factors. Forward logistic regression analysis was conducted to estimate the OR and 95%CI for 30-days mortality of NLR, albumin and other parameters after adjusting for potential confounding factors. The receiver operating characteristic (ROC) curve was used to examine the performance of independent risk factors in predicting 30-days mortality. The area under the curve (AUC) was derived from the ROC curve, which ranges from 0.5 to 1.0 - with higher values indicating higher discriminatory ability, and the Youden Index (maximum [sensitivity +specificity] minus 1) was adopted to define the optimal cut-off value. Afterwards, nomogram based on the independent predictors was established, and the calibration curve and decision curve analysis(DCA) were generated to evaluate the nomogram. In addition, the AUC of nomogram were calculated and the differences of AUC between nomogram and independent predictors were compared by pROC package in R software(version 3.6.1). All P values <0.05 were accepted as statistically significant.

**Results**

**Baseline**
During the study period, 125 patients were diagnosed with pulmonary embolism within 90 days after non-cardiac surgery. 24 patients were excluded because they didn’t meet our criteria for hematological disease (2 cases), received blood transfusion within 1 month preoperatively (13 cases), infection (2 cases), received immunosuppressive therapy within 1 month preoperatively (1 case) and missing data (6 cases). Finally, 101 patients with PAPE following non-cardiac surgery met our inclusion criteria and were included in this study, which including 41 males and 60 females, and the mean age was 62.23 years (range: 23-95 years). The demographic data and clinical data of deaths and survivors were listed in Table 1.

**Prognostic factors of PAPE**

24 patients died within 30 days, which corresponding to 30-days mortality of 23.8%. There were no significant differences in term of age, gender, BMI, smoking history, drinking history, surgical type and ASA level (All P value > 0.05). There were no significant differences in term of hypertension, diabetes, respiratory diseases, coronary heart disease, arrhythmia, history of stroke and renal failure (All P value > 0.05). Baseline and comorbidities of patients were shown in Table 1. Preoperative laboratory parameters were presented in Table 2. The value of NLR, neutrophil and creatinine were significantly higher in deaths than in survivors with PAPE (All P value < 0.05), and the value of albumin was significantly lower in deaths than survivors after PAPE (P = 0.008). There were no significant differences in other terms included in our research (Table 2).

To further confirm the independent risk factors of mortality after PAPE, the multivariate logistic analysis was performed. The NLR, MLR, WBC, Neutrophil, Lymphocyte, Creatinine, and Albumin (All P value > 0.05) were included in the multivariate analysis, and the results indicated that both NLR and albumin are independent predictors for 30-days mortality in patients with PAPE. The probability of death increased about 17.1% (OR = 1.171, 95% CI:
1.073–1.277, P=0.000) with one unit of increase of NLR, and the probability of death decreased about 15.4% (OR=0.846, 95% CI: 0.762c–0.939, P=0.002) with one unit of increase of albumin. (Table 3). Besides, the results indicated that Creatinine, MLR, Neutrophil, Lymphocyte and WBC were no longer the independent predictors in multivariate analysis (All P value>0.05).

**Development of a nomogram**

Based on the independent predictors, a nomogram was established to predict the 30 days mortality in PAPE patients(Figure 1). The AUC of nomogram was 0.888(95%CI:0.812-0.964), which was significantly higher than any single predictors(P value<0.05)(Table 4 and Figure 2). Moreover, the calibration curve was shown in Figure 2A, and the results indicated that the prediction by nomogram are highly consistent with the actual observations. In addition, the DCA indicated that if the threshold probability of a patient and a doctor between 5% to 75%, this nomogram to predict 30-days mortality more benefit than the scheme.

**Discussion**

PAPE is one of the most dangerous complications following operations, and it is necessary to early predict the prognosis of patients. To the best our knowledge, it is the first study to investigate the predictors and establish the nomogram of 30-days mortality among patients with PAPE following non-cardiac surgery. The primary finding of our study was the level of NLR is significantly higher in non-survivor patients than survivors and plasma albumin was significantly lower in deaths than survivors, and both NLR and albumin were independent predictors for 30-days mortality among patients with PAPE following non-cardiac surgery. Moreover, the nomogram based on the NLR and albumin showed good performance in predicting the 30 days mortality of patient with PAPE.

NLR is the comprehensive presentation of systemic inflammation and the balance between
neutrophils and lymphocytes in CBC. Previous studies have showed that the elevated NLR is associated with increased rate of hospital mortality among patients with acute pulmonary embolism\[13\], AECOPD\[18\], and acute type A aortic dissection\[19\], 30-mortality among patients with acute pulmonary embolism\[20\], acute kidney injury\[21\], ST-elevation myocardial infarction\[22\], and intracerebral emorrhage\[23, 24\] and long-term mortality among patients with ST-Elevation Myocardial Infarction\[25\], breast cancer\[26\] and epithelial ovarian cancer\[27\].

The link between inflammation and pulmonary embolism has been well investigated, although the underlying mechanism was not completely understood. The relationship between them may be linked by cytokines, proinflammatory cytokines, such as CRP, IL-8, and tumor necrosis factor which promote procoagulant state and play an important role in the progress of VTE by inducing the expression of tissue factor. In addition, it has recently been reported that the inflammatory mediators, such as polyphosphates and bradykinin, which can directly activate contact systems and initiate external coagulation pathways\[28–30\]. In our research, we found that NLR is an independent predictor for 30-days mortality in patients with PAPE, and the area under the curve of NLE was 0.823. Therefore, we concluded that the NLR value is a simple and effective prognostic predictor for patients with PAPE.

We also found that albumin is significantly lower in deaths than survivors. To our knowledge, it was the first study to indicate the relationship between albumin and mortality in patients with PAPE. Albumin is an indicator of the nutritional status of patients and can regulate the anticoagulation system to some extent. Hypoproteinemia has been confirmed to be associated with mortality in patients with acute pulmonary embolism in previous studies\[16\]. In the previous study, the mechanism of the association between albumin and mortality was partly explained. Plasma albumin can interact with NO to some
extent and generate S-nitrosoproteins, and then promote vasomotor and inhibit platelet aggregation. When albumin levels drop, the effect will be weakened[31, 32]. In addition, plasma albumin was an important antioxidant, anti-inflammatory and drug carrier effects in human physiological functions[33]. Therefore, lower plasma albumin concentration will inevitably lead to a decrease or loss of these effects.

There were also some limitations in our research. Firstly, as a single-center research, only 101 patients meet the criteria and were included in our study, which was a small sample size. The small sample size makes it impossible to classify and discuss patients with PAPE for specific operations, such as arthroplasty and gastrointestinal cancer resection.

Secondly, although the nomogram showed good performance in AUC, calibration curve and DCA, the independent validation is needed. Finally, as a retrospective study, our research had its own limitations. We hoped that the multicenter and prospective research can be performed to confirm our conclusion in the future.

Conclusions

Both NLR and albumin were independent predictors for 30-days mortality among patients with acute pulmonary embolism following non-cardiac surgery, and NLR and albumin were better predictors together than separately. It enables assessing the severity of PAPE, and could guide the clinical management of PAPE.

Abbreviations

PAPE: postoperative acute pulmonary embolism; NLR: neutrophil–lymphocyte ratio; LMR: lymphocyte to monocyte ratio; RDW: red blood cell distribution width; CRP: C-reactive protein; CBC: Complete blood count; ROC: receiver operating characteristic curve; AUC: area under the curve; DCA: decision curve analysis

Declarations
Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Affiliated Hospital of Chengde Medical University. Written informed consent was obtained from all patients. No children (under 16 years old) were included in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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We received no external funding for this study.

Authors' Contributions

C L, CL Z, C H, LH Z, and ZH H made substantial contributions to the design of this study, acquisition of data; C L, C MY Z, YX S, and YX T analyzed the data; C L, ZY F and GY M wrote the manuscript; All authors read and approved the final manuscript.

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Tables
|                                | Total(n=101) | Deaths(n=24) | Survivors(n=77) | P  |
|--------------------------------|--------------|--------------|-----------------|----|
| **Age, yr**                    | 64.00(57.50-71.00) | 67.00(59.00-75.75) | 63.00(57.00-70.00) | 0.200 |
| **Sex (Female)**               | 60           | 12           | 29              | 0.283 |
| **BMI, kg/ (mean±SD)**         | 25.85±3.68   | 24.54±4.10   | 26.31±3.59      | 0.050 |
| **Smoking history**            | 23           | 6            | 17              | 0.766 |
| **Drinking history**           | 19           | 4            | 15              | 0.758 |
| **Surgical type**              |              |              |                 | 0.861 |
| Musculoskeletal                | 45           | 12           | 33              |     |
| Abdominal                      | 28           | 7            | 21              |     |
| Respiratory                    | 10           | 2            | 8               |     |
| Gynecologic                    | 8            | 2            | 6               |     |
| Neurosurgery                   | 5            | 1            | 4               |     |
| Vascular                       | 5            | 0            | 5               |     |
| **ASA**                        |              |              |                 | 0.787 |
| II                             | 65           | 16           | 49              |     |
| III                            | 36           | 8            | 28              |     |
| **Comorbidities**              |              |              |                 |     |
| Hypertension                   | 38           | 9            | 29              | 0.989 |
| Diabetes                       | 15           | 2            | 13              | 0.484 |
| Coronary heart disease         | 19           | 4            | 15              | 0.993 |
| Respiratory diseases           | 9            | 1            | 8               | 0.600 |
| Arrhythmia                     | 4            | 1            | 3               | 1.000* |
| History of stroke              | 7            | 2            | 5               | 1.000 |
| Renal failure                  | 1            | 1            | 0               | 0.238* |

* Fisher’s Exact test
Table 2 Comparison of admission laboratory data between deaths and survivors

|                      | Deaths (n=24) | Survivors (n=77) | P      |
|----------------------|--------------|------------------|--------|
| NLR                  | 14.13(7.67-23.04) | 5.93(2.60-8.70)  | 0.000  |
| PLR                  | 230.00(102.25-396.24) | 157.29(103.99-243.52) | 0.193  |
| MLR                  | 0.80(0.44-1.27) | 0.44(0.31-0.77)  | 0.004  |
| WBC, ×10^9/L         | 13.84(8.80-17.47) | 9.74(6.62-12.71)  | 0.001  |
| Neutrophil, ×10^9/L  | 12.21(8.04-15.85) | 6.20(3.98-9.91)   | 0.000  |
| Lymphocyte, ×10^9/L  | 0.82(0.51-1.59) | 1.21(0.90-1.82)  | 0.017  |
| PLT, ×10^9/L         | 163.50(131.25-215.25) | 199.00(141.00-247.00) | 0.273  |
| MPV, fl              | 10.15(9.30-10.78) | 10.10(9.40-10.88) | 0.631  |
| PDW                  | 12.75(11.28-15.80) | 13.25(10.73-16.08) | 0.990  |
| Hb, g/L              | 121.00(108.25-141.50) | 108.00(90.00-119.00) | 0.795  |
| RDW                  | 13.15(12.73-15.33) | 13.20(12.45-14.35) | 0.369  |
| Creatinine, μmol/L   | 84.40(71.72-106.50) | 72.00(59.75-87.00) | 0.023  |
| GLU, mmol/L          | 8.19(6.95-13.83) | 7.60(5.56-9.92)   | 0.054  |
| Albumin, g/L         | 32.33(27.37-35.69) | 38.20(32.49-45.80) | 0.008  |

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet to lymphocyte ratio; WBC: white blood cell; MLR: monocyte-to-lymphocyte ratio; PLT: platelet; MPV: mean platelet volume; PDW: platelet distribution width; Hb: hemoglobin; RDW: red cell distribution width; GLU: glucose

Table 3 Multivariate regression results of 30-days mortality

|         | B     | SE    | Wald  | OR     | 95% CI          | P       |
|---------|-------|-------|-------|--------|-----------------|---------|
| Albumin | -0.167| 0.053 | 9.881 | 0.846  | 0.762-0.939     | 0.002   |
| NLR     | 0.158 | 0.044 | 12.644| 1.171  | 1.073-1.277     | 0.000   |

NLR: neutrophil-to-lymphocyte ratio

Table 4 Values of predictors in predicting 30-days mortality

| Predicators | AUC | 95% CI for AUC | P  | Cut-off | Sensitivity | Specificity |
|-------------|-----|----------------|----|---------|-------------|-------------|
| NLR         | 0.823 | 0.729-0.917   | 0.000 | 12.00 | 0.625 | 0.909 |
| Albumin     | 0.768 | 0.668-0.868   | 0.000 | 36.66 | 0.571 | 0.875 |

AUC: area under the curve

NLR: neutrophil-to-lymphocyte ratio

Figures
Figure 1

ROC curves of NLR for predicting 30-days mortality

Figure 2

ROC curves of albumin for predicting 30-days mortality
Figure 3

[Legend not available with this version.]