

Risk Assessment of Death of Tumor-Related PTE by CAR Combined with DD Detection

Xinran Li*, Jiamin Zheng*, Ye Lu, Xiangtao Pan

Department of Hematology and Oncology, Suzhou Medical College of Soochow University, Taicang Hospital Affiliated of Soochow University, Taicang City, Jiangsu Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiangtao Pan, Department of Hematology and Oncology, Suzhou Medical College of Soochow University, Taicang Hospital Affiliated of Soochow University, Taicang City, Jiangsu Province, 215400, People's Republic of China, Tel +86 18915768003, Email panxiangtao@cscs.ac.cn

Objective: To investigate the risk of death in patients with tumor-related PTE (pulmonary thromboembolism) detected by CAR (C-reactive protein/albumin ratio) combined with DD (D-dimer).

Methods: The peripheral hematology and coagulation-related indexes of 109 patients with tumor-related PTE diagnosed by PTCA were retrospectively analyzed, and the differences in relationship indexes between tumor-related PTE patients with good prognosis and poor prognosis were compared and analyzed. The receiver operating characteristic curve (ROC) was used to analyze the risk of death in patients with tumor-related PTE by CAR and DD.

Results: ① The values of CAR and DD in the poor prognosis group were 3.90 ± 2.69 and 21.25 ± 21.20 , respectively, which were significantly higher than those in the good prognosis group (1.66 ± 1.77 , 9.53 ± 3.57) (P all < 0.01). ② WBC, NE and SII in tumor-related PTE patients with poor prognosis were significantly higher than those in patients with good prognosis, while Hb in patients with poor prognosis was significantly lower than that in patients with good prognosis. ③ There was a significant positive correlation between CAR and DD ($P=0.018$). ④ The values of CAR and DD in the death group were 4.07 ± 2.42 and 19.65 ± 20.48 , respectively, which were significantly higher than those in the survival group (1.94 ± 2.12 , 11.52 ± 15.84) (P all < 0.05). ⑤ The results of logistic regression analysis showed that both CAR ($P=0.000$) and DD ($P=0.031$) were independent prognostic factors in patients with tumor-related PTE. ⑥ CAR combined with DD had high sensitivity (77.8%) and specificity (83.5%), and the Youden index was 0.613. ⑦ The area under the receiver operating characteristic curve of CAR combined with DD was the largest (up to 0.806).

Conclusion: CAR and DD were highly expressed in patients with poor prognosis of tumor-related PTE. CAR combined with DD detection is helpful to improve the correct assessment of the risk of death in patients with tumor-related PTE.

Keywords: pulmonary thromboembolism, neutrophil/lymphocyte, C-reactive protein, albumin, C-reactive protein/albumin ratio, plasma D-dimer, risk assessment of death

Introduction

Pulmonary embolism is a group of diseases or clinical syndromes caused by various emboli blocking the pulmonary artery or its branches, including pulmonary thromboembolism (PTE), fat embolism syndrome, amniotic fluid embolism, air embolism and so on. PTE is the most common type of pulmonary embolism, which is caused by thrombus from the venous system or right heart to block the pulmonary artery or its branches, with pulmonary circulatory and respiratory dysfunction as the main clinical and pathophysiological features. The thrombus that causes PTE mainly comes from deep venous thrombosis (DVT). DVT and PTE are essentially the manifestations of a disease process in different parts and stages, both of which are called venous thromboembolism (VTE), and PTE is the most dangerous type of VTE.¹ In the general population, the first incidence of DVT or PTE is estimated at 17 per 100,000 people per year. Cancer increases this risk by more than four times, chemotherapy by 6.5 times, and it is estimated that one in every 200 cancer patients gets sick each year. The incidence of VTE varied greatly in clinical trials and case series involving cancer patients, but generally confirmed an increased risk in this population.² Cancer and its treatment are recognized risk factors for VTE.

There is evidence that the absolute risk of VTE in cancer patients depends on the type of tumor, the stage or degree of cancer, and the treatment of antineoplastic drugs. The most common types of cancer in patients with thrombosis are breast cancer, colorectal cancer and lung cancer, reflecting the prevalence of these malignant tumors in the general population. If the potential prevalence rate is taken into account, pancreatic, ovarian and brain cancer are most closely related to thrombotic complications.³ Exploring and summarizing the suspicious risk factors is helpful to determine the existence or non-existence of tumor-related PTE.¹

Recently, studies have shown that the C-reactive protein(CRP)/albumin ratio (CAR) is of great significance in judging the prognosis of malignant tumors.⁴⁻⁷ The CAR is a new marker, which is calculated by the ratio of these acute phase reactants.⁸ However, there are few reports on the prognosis of thrombotic diseases with CAR and plasma D-dimer (DD).⁹ Therefore, this study retrospectively analyzed the characteristics of peripheral hematology and blood coagulation indexes in 109 patients with tumor-related PTE, so as to explore the clinical value of CAR combined with DD in predicting the prognosis and risk assessment of death in patients with tumor-related PTE.

Materials and Methods

Materials

From January 1, 2015, to December 31, 2019, 270,983 patients were discharged from the hospital, including 433 patients with PTE diagnosed by CTPA, etc., and 109 patients with tumor-related PTE with complete data and clear prognosis records. There were 63 males and 46 females, aged 28–91 years, with an average age of 69 years. Amniotic fluid embolism, fat embolism, and other cases of non-venous thromboembolism were excluded. The medical record number, name, gender, age, inpatient department, primary disease, inducing factors, location, preventive measures, relevant inspection results, treatment methods and prognosis of all cases were collected.

This research was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Taicang Hospital Affiliated to Soochow University, and informed consent was signed with relevant personnel. We confirm that the data were anonymous or confidential.

Research Methods

According to the data of VTE cases hospitalized from January 1, 2015, to December 31, 2019, provided by the VTE network of our hospital, all relevant medical records were reviewed by the hospital's medical record center, referring to ultrasound or CTPA, DD, C-reactive protein (CRP), prothrombin time (PT), thrombin time (TT), antithrombin III (AT-III, AT for short), fibrinogen (FB), international standardized ratio (INR), as well as hemoglobin (Hb), white blood cells (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), and platelets (PLT) count and other test data results.

Grouping Methods

According to the prognosis of the patients, the patients were divided into good prognosis group (including cure and improvement, a total of 78 cases, accounting for 71.56%) and poor prognosis group (including 18 cases deteriorated to death and 13 cases were not cured, a total of 31 cases, accounting for 28.44%). The death group (18 deaths, accounting for 16.51%) and the survival group (all surviving cases except death, 91 cases, accounting for 83.49%). To make a comparative analysis.

Statistical Analysis

SPSS 23.0 software was used for statistical analysis. The measurement data between the two groups was compared by *t*-test and *u*-test, and the count data was compared by Pearson correlation analysis. Binary logistic regression was used to analyze whether and to what extent the elevation of CAR and DD in tumor-related PTE patients resulted in death. The diagnostic value of CAR and DD for the risk of death in patients with tumor-related PTE was analyzed by receiver operating characteristic curve (ROC), with *P*<0.05 being considered statistically significant.

Results

The Test results of CAR and Other Indicators in the Two Groups with Good Prognosis and Poor Prognosis

From Table 1, it can be seen that the specific hematological indexes, inflammatory indexes and coagulation indexes of 109 cases of tumor-related PTE patients with good prognosis group and poor group were compared and analyzed. The WBC, NE, neutrophil/lymphocyte (neutrophil to lymphocyte ratio, NLR), systemic immune inflammatory index (SII), DD, CRP and CAR values in the group were significantly lower than those in the poor prognosis group. Other indicators including LY, MO, lymphocyte/monocyte ratio (LMR), PLT and platelet/lymphocyte ratio (PLR) were not statistically significant.

Results of Correlation Analysis

Considering that there is statistical significance between WBC, NE, NLR, SII, DD, CRP and CRP/ALB values between the two groups of tumor-related PTE patients with good and poor prognosis, while CRP and albumin (ALB) constitute a new index (CRP/ALB, CAR), the correlation between CAR and DD, NLR, gender and age is analyzed. The specific results are shown in Table 2.

Table 1 Comparison of CAR and Other Indicators Between the Two Groups with Good Prognosis and Poor Prognosis in Tumor-Related PTE Patients

	Good Prognosis Group (n=78)	Poor Prognosis Group (n=31)	t/U
WBC ($\times 10^9/L$)	8.71 $\pm$ 6.46	11.41 $\pm$ 6.22	2.2379*
NE ($\times 10^9/L$)	6.91 $\pm$ 5.21	9.45 $\pm$ 5.70	2.2345*
LY ($\times 10^9/L$)	1.06 $\pm$ 0.62	1.27 $\pm$ 1.20	1.1952
MO($\times 10^9/L$)	0.62 $\pm$ 0.61	0.75 $\pm$ 0.85	0.8826
NLR	8.56 $\pm$ 8.15	11.38 $\pm$ 9.33	U=2.0251
LMR	2.61 $\pm$ 3.37	2.72 $\pm$ 3.10	U=0.7758
Hb (g/L)	121.44 $\pm$ 22.31	98.61 $\pm$ 25.11	4.6503**
PLT ($\times 10^9/L$)	192.36 $\pm$ 88.36	192.84 $\pm$ 125.16	0.0226
PLR	231.63 $\pm$ 170.37	283.94 $\pm$ 347.95	U=0.8852
SII ($\times 10^9/L$)	1618.95 $\pm$ 1600.68	2295.39 $\pm$ 2441.52	1.9963*
DD ($\mu g/L$)	9.53 $\pm$ 3.57	21.25 $\pm$ 21.20	3.4322**
CRP (mg/L)	54.96 $\pm$ 56.17	117.63 $\pm$ 74.60	4.7688**
ALB (g/L)	35.32 $\pm$ 4.84	31.45 $\pm$ 5.11	3.7051**
CAR	1.66 $\pm$ 1.77	3.90 $\pm$ 2.69	5.0898**

Notes: ①* $P < 0.05$, ** $P < 0.01$, the rest are $P > 0.05$. ②Non-normal distribution data, using rank sum test (U).

Abbreviations: NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; PLR, platelet/lymphocyte ratio; CAR, C-reactive protein/albumin ratio.

Table 2 Results of Correlation Analysis

Compare Items	r	P
CAR/DD	0.226	0.018
CAR/NLR	0.226	0.018
CAR/Age	-0.120	0.214
CAR/Gender	-0.021	0.830

Table 3 Results of Logistic Regression Analysis

Variable	β	SE	Wals	P	OR (95% CI)
NLR	0.949	0.670	2.006	0.157	2.583 (0.695–9.605)
DD	2.269	1.052	4.655	0.031	9.672 (1.231–76.009)
CAR	2.875	0.633	20.606	0.000	17.733 (5.124–61.373)
Gender	−0.601	0.520	1.336	0.248	0.548 (0.198–1.519)
Age	0.849	1.078	0.620	0.431	2.337 (0.283–19.338)

It can be seen from [Table 3](#) that there is a significant correlation between CAR and DD and NLR (P all <0.05), and $r=0.226$ ($r<0.3$) indicates that the degree of correlation is weak. The correlation coefficient between CAR and age and gender was not statistically significant (P all >0.05).

Detection of CAR, DD and NLR in Survival Group and Death Group of Patients with Tumor-Related PTE

The detection results of various indexes in survival group and death group of 109 patients with tumor-related PTE are shown in [Table 4](#).

Logistic Analysis of CAR, DD and Other Indicators in 109 Patients with Tumor-Related PTE

Taking CAR, DD, NLR, age and gender as covariates, and taking the death of tumor-related PTE patients as the dependent variable. The specific results are shown in [Table 3](#).

[Table 3](#) shows that CAR ($P=0.000$) and DD ($P=0.031$) are independent prognostic factors in patients with tumor-related PTE.

Combination or Separate Detection of CAR and DD for Risk Assessment of Death in Patients with Tumor-Related PTE

The receiver operating curve (ROC) was used to analyze and calculate the AUC. The specific results are shown in [Table 5](#) and [Figure 1](#).

As can be seen from [Table 5](#), DD alone had the highest sensitivity (94.4%) but lower specificity (36.3%) in assessing the risk of death in patients. CAR combined with DD assessment had high specificity (83.5%), while having high sensitivity (77.8%). The area under the receiver operating characteristic curve of CAR combined with DD was the largest (up to 0.806).

Table 4 Results of NLR, DD and CAR in Two Groups of Patients

	Survival Group (n=91)	Death Group (n=18)	t	p
NLR	8.73±8.19	12.55±9.99	1.7410	>0.05
DD (μg/L)	11.52±15.84	19.65±20.48	U=2.379*	0.017
CAR	1.94±2.12	4.07±2.42	U=3.689*	0.000

Note: *The data are non-normal distribution and rank sum test (U) is applied.

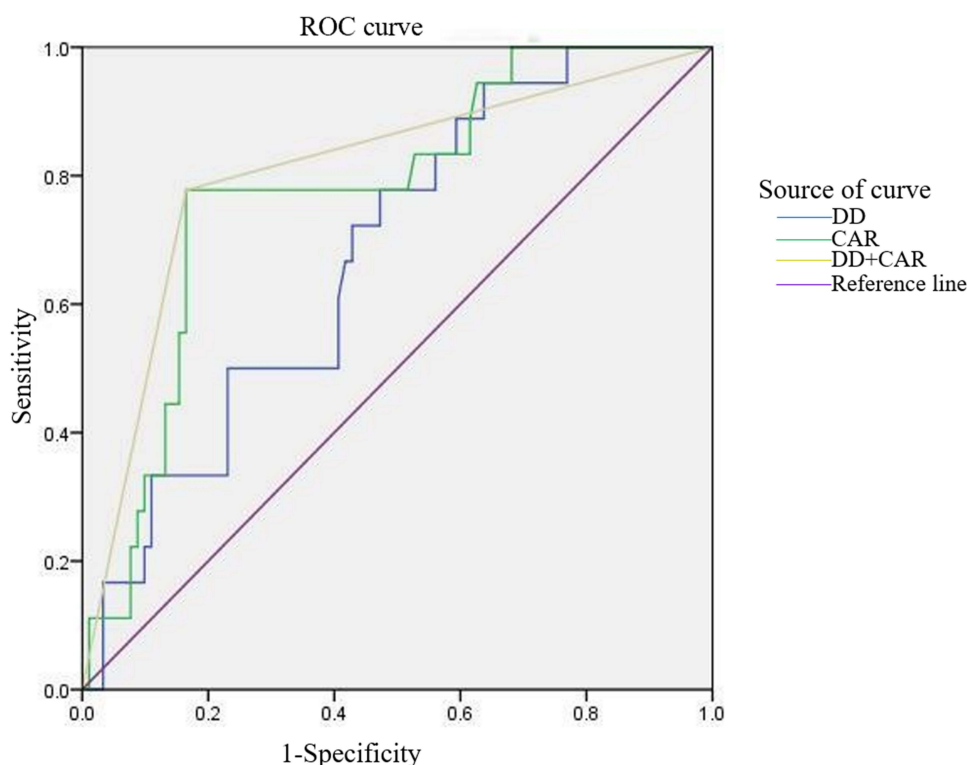
Table 5 Assessment of the Risk of Death in PTE Patients by Detecting DD and CAR Alone and in Combination

Project	AUC (95% CI)	Youden	Sensitivity (%)	Specificity (%)	Cut-off
DD	0.678 (0.557–0.799)	0.307	94.4%	36.3%	3.800
CAR	0.776 (0.663–0.889)	0.613	77.8%	83.5%	2.880
DD+CAR	0.806 (0.686–0.927)	0.613	77.8%	83.5%	0.267

Discussion

VTE is a common complication in patients with malignant diseases. Since Armand Trousseau first reported this observation in 1865, epidemiological and scientific data have supported a strong biological link between cancer and thrombosis. Recognizing that VTE in cancer patients has a different natural history from that in non-cancer patients, more studies have focused on the prevention and treatment of VTE in cancer patients.³ In spite of the advances in medical therapies, acute PTE is still a major cause of morbidity and mortality worldwide.¹⁰ The mortality rate of untreated PTE is 30%, and the short-term mortality rate with treatment can be reduced to 2% to 8%.¹¹ Because there are many complications in tumor patients, there are many factors affecting the prognosis. Accurate and rapid diagnosis of PTE is essential to avoid significant morbidity and mortality in high-risk groups such as cancer patients.^{12,13}

This study found that CAR, DD and CRP in patients with poor prognosis of tumor-related PTE were significantly higher than those in patients with good prognosis (NLR had no statistical significance because of its abnormal distribution, but it was also meaningful to change to rank sum test), suggesting that inflammatory reaction did exist in patients with tumor-related PTE. Previous studies have shown that changes in Hb are not the cause of PTE.¹⁴ Although the NLR of the group with good prognosis was significantly lower than that of the group with poor prognosis, and there was a positive correlation between NLR and CAR. However, further analysis showed that there was no statistical

**Figure 1** Risk assessment of death in patients with tumor-related PTE by single and combined detection of CAR and DD.

significance in NLR between the death group and the survival group, and logistic regression analysis showed that NLR, age and gender were not independent prognostic factors in patients with tumor-related PTE. Therefore, we do not combine NLR with CAR and DD for further study.

Many studies have shown the correlation between DD and tumor-related PTE. Qdaisat et al reviewed the records of patients who visited a large general cancer center during the study because they suspected PTE to determine whether cancer patients with normal DD levels could develop PTE. One thousand one hundred and fifty-six patients had PTE, of which only 35 (3.0%) had normal DD levels. There were 26 cases of acute PTE and 9 cases of subacute or chronic PTE. There were only 926 patients with normal DD and 4% (35 cases) of patients with normal DD developed PTE. After the activation of coagulation cascade, thrombus and DD were formed at the same time.¹⁵ This makes DD, the main biomarker of blood clot, an effective biomarker for the exclusion of VTE because of its high sensitivity.¹⁶ Cui et al determined the independent risk factors of PTE by stepwise logistic regression analysis. The results showed that high DD, chemotherapy, DVT, III–IV stage and adenocarcinoma were independent risk factors for PTE ($P < 0.05$).¹ The ROC curve results of this study showed that DD alone had the highest sensitivity (94.4%) in assessing the risk of death in patients, but the specificity was low (36.3%), and the Youden index was also low (0.307), so new indicators or integrated indicators need to be found. Combined detection to improve the diagnostic specificity of tumor-related PTE.

The level of Hb in the poor prognosis group of tumor-related PTE patients is lower than that in the good prognosis group, which is consistent with the results of our previous studies.¹⁷ Inflammation can lead to the high expression of hepcidin, which can lead to the inability of the body to use iron and lead to anemia.⁹ The values of WBC, NE and SII in the good prognosis group were significantly lower than those in the poor prognosis group, suggesting that the inflammatory response and immune function were abnormal in tumor-related PTE patients. This may explain why the NLR and CAR in the good prognosis group of tumor-related PTE patients were significantly lower than those in the poor prognosis group, which is consistent with the results reported in the literature.^{9,18–20}

DD has the highest sensitivity (94.4%), but poor specificity (only 36.3%). The Youden index is only 0.307, indicating that it cannot correctly assess the risk of death in tumor-related PTE patients. The specificity of CAR was significantly higher than that of DD (83.5%), and the sensitivity was 77.8%. The Youden index is also up to 0.613, suggesting that it is of significance to evaluate the risk of death in patients with tumor-related PTE. After combining CAR and DD, although the sensitivity, specificity and Youden index were not significantly improved compared with CAR alone, the AUC increased to 0.806. It shows that CAR alone is helpful to evaluate the death risk of tumor-related PTE patients, and CAR combined with DD can further improve the value of evaluating the death risk of tumor-related PTE patients.

This study is a retrospective analysis, which is a single-center study, and does not fully include PTE underlying diseases and primary diseases as the research scope. The results may have limitations and biases. Therefore, we will combine multi-center expansion of the number of cases, unified diagnostic criteria and Parameter indicators, strict patient inclusion and exclusion criteria, and further research to clarify the significance of CAR combined with DD in tumor-related PTE death risk assessment.

Disclosure

The authors declare that they have no competing interests in this work.

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