Inflammatory Cytokine Levels in Pulmonary Embolism Severity: A Retrospective Study

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Abstract

Background: Inflammatory cytokines are involved in the development of venous thromboembolism (VTE) and may influence the mortality. But the association between their levels and severity of pulmonary embolism (PE) is unclear. This study aimed to investigate the association of inflammatory cytokines and PE severity.

Methods: We retrospectively analyzed patients who were admitted to Xinhua Hospital with a confirmed diagnosis of PE between Jan 2019 and Apr 2021. Inflammatory cytokines were compared among different severities of PE groups. Spearman rank-order correlation analysis and multivariate Logistic regression analysis were used to analyze the relationship between cytokine level and PE severity. In addition, we estimated the association between comorbidities and PE severity by using multivariate Logistic regression analysis.

Results: A negative correlation between IL-8 level and PE severity was found (r=-0.466, P=0.018). Comorbidities of coronary heart disease [3.76 (1.99-7.10) (P=0.000)], deep venous thrombosis [2.40 (1.15-5.01) (P=0.019)], respiratory failure [2.92 (1.33-6.4) (P=0.007)] were correlated with the severity of PE.

Conclusions: IL-8 level is negative correlated with PE severity. Patients with comorbidities regarding coronary heart disease, deep venous thrombosis, and respiratory failure may have higher risk to surfer a more sever PE.

Introduction

Venous thromboembolism (VTE), clinically presenting as deep vein thrombosis (DVT) or PE, is a common disorder with an estimated incidence of one to three per 1,000 population annually [1]. A rising tendency in VTE incidence rates has been revealed in epidemiological studies [2]. As reported, the incidence of VTE currently is almost 10-30 times higher than that in 20 years ago in China. Pulmonary embolism (PE) as the most frequent acute syndrome in respirology department is a potentially life-threatening disease. Accurate and prompt diagnosis is essential for reducing mortality. Once PE is diagnosed, risk stratification should be performed immediately. PE severity can be classified to low risk, intermediate risk (include intermediate-low risk and intermediate-high risk), and high risk. Treatments and prognosis are different among patients with different severities [3].

Increasing evidence revealed that cytokines are involved in the development of VTE and may influence the mortality [4]. These new insights into the role of cytokines in VTE have aroused Clinicians' attention to anti-inflammatory therapy [5]. A recent review summarized the interplay between cytokines and venous thrombosis. Cytokines including IFNγ, IL-6, IL-17A, IL-9, IL-1β and TGF-β perform pro-thrombotic activity, while other cytokines such as IL-10, TNF-α and IL-8 appear to promote thrombus resolution in late phase of venous thromboembolism [6]. Anomalous cytokines levels and high PE frequency were found in patients with cancer, pneumonia, tuberculous pleural effusion, and other disease [7–9]. Abnormal cytokine levels caused by primary disease may involve in the development of PE. But the relationship

between cytokines and PE severity is unclear. Whether comorbidities would influence PE severity through cytokines is worth studying.

In the present study, we evaluated the relationship between cytokines and PE severity. in addition, we investigated the association of comorbidities and the severity of PE in patients.

Methods

Study design and participants

A retrospective study was conducted to investigate the association between cytokines as well as complications and PE severity. All the patients with confirmed diagnosis of PE in Xinhua hospital affiliated to Shanghai Jiao Tong University School of Medicine between Jan, 2019 and Apr, 2021 were reviewed. Interleukin (IL)-8, IL-6, IL-2R, tumor necrosis factor (TNF-a) and C-reactive protein (CRP), white blood cell (WBC) counts, erythrocyte sedimentation rate (ESR) as well as the rate of comorbidities were compared between different PE severity groups. The association between cytokines, inflammatory makers, comorbidities, and PE severity was analyzed.

This retrospective study only collected the clinical data of patients, did not interfere with the treatment plan of patients, and did not pose any risk to patients' physiology. Due to the retrospective nature of the study, informed consent was waived. All protocols were approved by the Ethics Committee of Xin Hua Hospital, affiliated with Shanghai Jiao Tong University School of Medicine. (NO. XHEC-D-2021-170).

Data Collection

In our hospital, PE severity was stratified as soon as possible according to clinical appearance, systolic blood pressure, imaging for right ventricular dysfunction (CTA or echocardiography) and/or biomarkers (troponin, NT-pro-BNP) as described before [10]. According to the medical record, clinical data includes demographic information (age, gender, previous medical history, comorbidities), PE severity, laboratory tests (CRP, WBC counts, ESR, D-dimer, IL-6, IL-8, TNF-α, and IL-2 receptor) was collected.

Statistical analysis

SPSS version 22.0 (IBM Corporation, New York) was used for the statistical analysis. Data were presented as median with interquartile range. Categorical data were presented as frequencies or percentages. Comparison of median among groups was performed by using Kruskal-Wallis test. Comparison of rates among groups was performed by Chi-square test. The association between cytokines and the severities of PE was analyzed by using Spearman rank-order correlation analysis. The association between commodities and the severities of PE was analyzed by using ordinal multinomial Logistic regression analysis. Statistical significance was set at $P < 0.05$.

Results

The demographics and clinical characteristics of patients.

There were 256 patients in all. 51 patients who without complete clinical information were excluded. 205 patients were enrolled in this study, among whom 95 patients were low risk, 56 patients were intermediate-low risk, 30 patients were intermediate-high risk, 24 patients were high risk. The median age was 68 (interquartile range, (IQR):23-92) years old. The number of male and female patients were 87(42.4%) and 118 (57.6%) respectively. pleural effusion, pulmonary infection, coronary heart disease, hypertension, deep venous thrombosis, cardiac arrhythmia, carcinoma, respiratory failure, renal dysfunction, diabetes, chronic obstructive pulmonary disease (COPD) were reported in 38 (18.5%), 108(52.7%), 57(27.8%), 79(38.5%), 33(16.1%), 27(13.2%), 24(11.7%),27(13.2%),13(6.3%), 16 (7.8%), 14 (6.8%) patients respectively (Table 1).

Table 1
The Demographics and clinical characteristics of 205 patients.

	Total (n=205)	Low-risk (n=95)	Intermediate-low risk (n=56)	Intermediate-high risk (n=30)	High risk (n=24)	P value
Gender(male%)	87 (42.4%)	43(45.3%)	26 (46.4%)	10 (33.3%)	8 (33.3%)	0.474
Age (years)	68(23-92)	64(23-91)	71(40-90)	67.5(37-92)	70.5(47-88)	0.001
DD	1.32(0.02-20.54)	0.87(0.02-8.38)	1.80(0.03-20.54)	2.62(0.55-11.62)	2.83(0.1-10.64)	0.000
TNF-α	10.9(4-322)	12.3(4-322)	9.83(4-115)	10.5(5.2-38.5)	9.33(4-57.8)	0.174
IL-2R	487(122-2779)	458(181-2779)	517(122-1946)	503(266-963)	518.5(154-1346)	0.046
IL-6	8.59(2-212)	8.2(2-208)	7.9(2-212)	8.86(2-53.5)	9.70(2.26-49.9)	0.962
IL-8	18.8(5-1213)	22.8(6.8-1213)	18.8(5-980)	16(5-180)	14.9(5.65-132)	0.046
CRP	8(1-200)	8(1-160)	8(1-200)	11(1-168)	7(1-160)	0.357
WBC	6.8(1.8-17.7)	6.4(3.1-17.7)	6.41(1.8-14.2)	5.9(3.8-11.1)	6.11(1.8-13.5)	0.987
ESR	27(2-120)	28(2-120)	31.5(2-120)	26(2-97)	24(2-87)	0.530
Pleural effusion	38(18.5)	27(28.4)	6(10.7)	4(13.3)	1(4.2)	0.007
Pulmonary infection	108(52.7)	53(55.8)	33(58.9)	11(36.7)	11(45.8)	0.188
Coronary heart disease	57(27.8)	11(11.6)	17(30.4)	19(63.3)	10(41.7)	0.000
Hypertension	79(38.5)	32(33.7)	24(42.9)	13(43.3)	10(41.7)	0.620
DVT	33(16.1)	11(11.6)	9(16.1)	5(16.7)	8(33.3)	0.081
Cardiac arrhythmia	27(13.2)	10(10.5)	9(16.1)	6(20)	2(8.3)	0.439
Carcinoma	24(11.7)	12(12. 6)	10(17.9)	1(3.3)	1(4.2)	0.140

Note: D-dimer (DD); c-reaction protein (CRP); white blood cell (WBC); erythrocyte sedimentation rate (ESR); deep venous thrombosis (DVT); chronic obstructive pulmonary disease (COPD)

	Total (n=205)	Low-risk (n=95)	Intermediate-low risk (n=56)	Intermediate-high risk (n=30)	High risk (n=24)	P value
Respiratory failure	27(13.2)	5(5.3)	8(14.3)	9(30)	5(20.8)	0.003
Renal dysfunction	13(6.3)	4(4.2)	4(7.1)	2(6.7)	3(12.5)	0.508
Diabetes	16(7.8)	4(4.2)	8(14.3)	1(3.3)	3(12.5)	0.088
COPD	14(6.8)	7(7.4)	4(7.1)	2(6.7)	1(4.2)	0.956

Note: D-dimer (DD); c-reaction protein (CRP); white blood cell (WBC); erythrocyte sedimentation rate (ESR); deep venous thrombosis (DVT); chronic obstructive pulmonary disease (COPD)

The comparison of clinical characteristics among different PE severity groups.

Medians of age (P=0.001), D-dimer (P=0.000), IL-2R (P=0.046) and IL-8 (P=0.046) were found statistically different among different PE severity groups. A raising tendency of D-dimer levels and a decreasing tendency of IL-8 levels were detected as PE severities increase. No significant differences were found in other biomarkers such as TNF-α, IL-6, CRP, WBC, and ESR among groups. With respect to commodities, rates of pleural effusion (P=0.007), coronary heart disease (P=0.000) and respiratory failure (P=0.003) were found statistically different among groups (Table 1).

Correlation between biomarkers and PE severity.

A spearman rank correlation analysis showed a negative correlation between IL-8 levels and PE severity (r= -0.466, P=0.018). A week negative correlation between TNF-α and PE severity was also found (r=-0.14, P=0.046). There was a positive correlation between Age and PE severities (r=0.280, P=0.000) and between D-dimer and PE severities (r=0.527, P=0.000) respectively. No significant correlation was found between other biomarkers (IL-2R, IL-6, CRP, WBC, ESR) and PE severity (Table 2).

Table 2
Correlation between PE severity and cytokine levels. (Spearman rank correlation analysis).

PE severity	Variables	Correlation coefficient	P value
	Age	0.280	0.000
	DD	0.527	0.000
	TNF-α	-0.14	.046
	IL-2R	0.072	0.308
	IL-6	0.11	0.118
	IL-8	-0.466	0.018
	CRP	0.019	0.784
	WBC	-0.042	0.547
	ESR	0.064	0.36
Note: D-dimer (DD); c-reaction protein (CRP); white blood cell (WBC); erythrocyte sedimentation rate (ESR);			

Association between commodities and PE severity.

An ordinal multinomial Logistic regression revealed that with comorbidities of pleural effusion [0.433 (0.196-0.957) (P=0.039)], coronary heart disease [3.76 (1.99-7.10) (P=0.000)], deep venous thrombosis [2.40 (1.15-5.01) (P=0.019)] respiratory failure [2.92 (1.33-6.4) (P=0.007)] were correlated with the severity of PE. While no significant correlation was found between PE severity and commodities regarding pulmonary infection, hypertension, cardiac arrhythmia, carcinoma, renal dysfunction, diabetes, and COPD in current study (Table 3).

Table 3
The correlation between comorbidities and PE severity. (Ordinal multinomial Logistic regression analysis)

Comorbidities(without=1)	Odds ratio	95%CI	P value
Pleural effusion	0.433	0.196-0.957	0.039
Coronary heart disease	3.761	1.992-7.102	0.000
DVT	2.404	1.152-5.014	0.019
Respiratory failure	2.921	1.333-6.402	0.007
Pulmonary infection	1.152	0.631-2.101	0.645
Hypertension	0.957	0.538-1.703	0.881
Cardiac arrhythmia	1.279	0.579-2.823	0.543
Carcinoma	1.084	0.441-2.665	0.860
Renal dysfunction	1.233	0.414-3.676	0.707
Diabetes	1.923	0.704-5.25	0.202
COPD	0.872	0.290-2.624	0.808
Note: deep venous thrombosis (DVT); chronic obstructive pulmonary disease (COPD)			

Discussion

In the present study, we investigated the relationship between plasma cytokines as well as comorbidities and PE severity. To the best of our knowledge, this is the first study to investigate the association between cytokines and PE severity in the literature. According to our study, a negative correlation between IL-8 levels and PE severity was found. A weak negative correlation between TNF-α and PE severity was also found. We didn't observe any significant correlation between cytokines like IL-6, IL2R, CRP, WBC, ESR, and PE severity. In addition, we found that patients with comorbidities regarding coronary heart disease, deep venous thrombosis, and respiratory failure may have higher risk to surfer a more sever PE.

IL-8, the most important C-X-C chemokine, is produced by both inflammatory cells and structural cells including monocytes, neutrophils, endothelial cells, and epithelial cells. It was the most powerful chemoattractant of neutrophils [11]. As previous study, elevated IL-8 level was found in PE patients compared to control [12]. According to our study, once regarding to PE severity, elevated IL-8 may be a protect factor. This result was consistent with Henke's study. Used rats VTE model, Henke and colleagues found that extrinsic IL-8 treatment enhances thrombus resolution through neovascularization and neutrophil recruitment. Invaded neutrophils modulate collagen and fibrin degradation through the secretion of matrix metalloproteinases (MMP) in the thrombus. In addition, neovascularization is part of thrombus remodeling and involves the vascular endothelial growth factor (VEGF) that contributes to vein

recanalization [13]. Whether the decreased level of IL-8 contributes to the severity of pulmonary embolism by affecting thrombus absorption needs further research. Nosaka and colleagues found that TNFα may have a beneficial role during thrombus resolution by promoting fibrinolysis, collagenolysis and neovascularization [14]. In our study, the negative correlation between TNFα and PE severity is week. Whether a strong correlation could occur when increase the sample size is need to further research. Elevated IL-6 circulating levels were found in VTE patients compared to healthy controls which indicated an important role of IL-6 in VTE even the underlying mechanism is unclear [15, 16]. But in our study, there was no significant difference of IL-6 among groups and no significant correlation between IL-6 and PE severity.

Further, we investigated whether the presence of comorbidity at the time of diagnosis of PE could influence PE severity. As our data shown, PE patients with coronary heart disease, DVT, and respiratory failure had increased risk of 3.76-fold, 2.4-fold, 2.92-fold to suffer more sever PE respectively. As a previous study revealed, patients with coronary heart disease have a higher prevalence of PE than those without cardiovascular disease which indicated similar risk factors of coronary heart disease and PE [17]. In addition, patients with coronary heart disease usually have lower cardiac reserve function. When occurred with PE, hemodynamics instability and elevated biomarkers such as TNI and NT-proBNP may increase the PE severity. As another type of VTE, DVT usually coexist with PE. The diagnosis of concomitant DVT has been identified as an independently risk factor of death within the first 3 months after acute PE which indicated a more sever PE [18]. The underlying mechanism of respiratory failure caused by PE is the sever mismatch of ventilation and perfusion which results in a decreased diffusing capacity of the lungs. Furthermore, respiratory failure contributes to myocardial hypoxia injury and increase the expression of cardiac troponin which would increase the PE severity. Unfortunately, we didn't found association between comorbidities and cytokines levels (data not shown), which indicated that comorbidities do not affect PE severity through cytokine levels.

There are several limitations to our study that must be addressed. First, the small number of high-risk PE patients must be emphasized, bearing the risk of sample size error. Second, the retrospective design of the study limited the richness of the research. We didn't observe the dynamic changes of cytokines in the course of disease. A prospective, ideally designed study with physicians randomly blinded to routinely collected data would be required to solve the above problems.

Conclusion

IL-8 is negative correlated with PE severity. Patients with comorbidities regarding coronary heart disease, deep venous thrombosis, and respiratory failure may have higher risk to surfer a more sever PE.

Abbreviations

CRP, C-reactive protein; CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; ESR, erythrocyte sedimentation rate; IL, interleukin; IFN-γ, Interferon γ; NT-pro-BNP , N-terminal pro-

natriuretic peptide; PE, pulmonary embolism; TGF-β, transforming growth factor-β; TPE, tuberculous pleural effusion; WBC, white blood cell.

Declarations

Ethics approval and consent to participate

This study complied with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (NO. XHEC-D-2021-170).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from

Xiaoming Li (email: lixiaoming13734@126.com) on reasonable request.

Competing interests

The authors declared no competing interests.

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Authors' contributions

XML conceived the study and participated in its design and performance, statistical analysis, and drafting and revising the manuscript. YKL conceived the study and participated in its design and performance, statistical analysis, and drafting and revising the manuscript. WJY and XC conceived the study and participated in its design and performance. XJG conceived the study, participated in its design and coordination, and revised the manuscript. WG conceived the study, participated in its design and coordination, and revised the manuscript. All authors reviewed the manuscript.

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