Can the Level of CRP in Acute Pulmonary Embolism Determine Early Mortality?

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OBJECTIVE: The purpose of this study was to determine the prognostic role of C-Reactive Protein (CRP) in acute PE.

MATERIAL AND METHODS: Two hundred and twenty patients with acute PE were consecutively enrolled and followed for 30 days after discharge. Serum CRP and NT-proBNP were determined. Right ventricular function was evaluated by transthoracic echocardiography.

RESULTS: There was a significant difference in age, S-PESI, and CRP levels between the early mortality group and without early mortality group. There was statistically no significant difference between the groups with and without early mortality in terms of gender distribution and whether or not they received thrombolytic therapy for DVT. Pulmonary infarct, pleural fluid, or both have no effect on early mortality. There was no correlation between CRP and pro-BNP, right/left ventricular ratio. The serum CRP levels at diagnosis were significantly higher in patients with PE and with pleural effusion and pulmonary infarct than those in PE patients without pleural effusion and pulmonary infarct (4.75±4.91 ng/mL, 9.67±8.02 ng/mL; p<0.0003).

CONCLUSION: High levels of CRP owing to inflammation in pulmonary embolism associated with effusion and infarction reveals why early mortality is significant in this group. CRP may help in the risk stratification of patients with acute PE, especially those with effusion and pulmonary infarction. CRP is an inexpensive and easily applicable biochemical marker, which can be used to predict early mortality.

KEYWORDS: Pulmonary embolism, C-reactive protein, mortality

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INTRODUCTION

Acute pulmonary embolism (PE) is a common and often fatal disease with a mortality rate of approximately 30% without treatment [1]. For this reason, parameters predicting diagnosis and prognosis are important. Many studies have been investigated for the potential benefits of many biomarkers, including high-sensitivity C-reactive protein (Hs-CRP), troponin I and T, type B natriuretic peptide (BNP) in the diagnosis and follow-up of PE [2, 3]. High levels of cardiac troponin I or T or B type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) levels are associated with an increased risk of complications and death in patients with acute PE [4, 5].

C-reactive protein (CRP) is an acute phase reactant and is associated with increased risk of cardiovascular and cerebro-vascular events [6, 7]. CRP is a well-known marker of inflammation and tissue damage. Incubation of highly purified CRP with monocytes of peripheral blood may induce tissue factors that increase pro-coagulant activity significantly. CRP has been shown to increase the tendency to thrombose through the mediation of interleukin (IL) 6 and monocyte chemoattractant protein 1 [8, 9]. Thus, CRP may play a role in the pathophysiology of the vascular wall.

The prognostic value of CRP in acute PE is unknown. The aim of the present study was to determine the prognostic role of CRP (early mortality within 30 days) in acute PE.

MATERIAL AND METHODS

The study was approved by the local ethics committee of İzmir Dr. Suat Seren Chest Diseases and Surgery Training Hospital (6.1.2016 / no: 3). Verbal informed consent was obtained from the patients who participated in this study.

A retrospective study was designed. A total of 300 patients presenting with acute PE between January 2012 and December 2015 in the emergency department of our hospital were included in the study. Of them, 80 were rejected on account of exclusion criteria. The study population included patients in all the categories of PE (massive,
submassive, and low risk). Diseases associated with elevated CRP levels such as active rheumatologic disease, active infection, chronic inflammatory conditions, recent myocardial infarction and cerebrovascular diseases, and a history of decompensated heart failure, diabetes mellitus, and chronic kidney disease were excluded. Demographic data, clinical history, biological markers, and clinical findings of the 220 patients were recorded.

The diagnosis of PE was made by using spiral computed tomography (CT) angiography or by ventilation-perfusion (VQ) scan. VQ scans were performed instead of CT angiography in patients on the basis of their potential risk for developing contrast nephropathy. In addition to clinical, echocardiographic, and radiological data, the diagnosis of PE was further confirmed by a positive D-dimer (upper limit of normal, 0.5 ug/mL), arterial blood gas, and electrocardiographic findings. The patients were divided into two groups as early mortality (<30 days) (n=26) and one month long (n=194). In addition, pleural effusion and pulmonary infarction were recorded according to the chest X-ray or CT findings.

Blood samples were obtained within 3 hours of admission to determine serum CRP (upper limit of normal, 0.5 mg/dL) and NT-proBNP (upper limit of normal, 500 pg/mL) levels. CRP was measured by latex-enhanced nephelometry on a nephelometer.

### Statistical Analysis
The data were analyzed using the Statistical Package for Social Sciences version 18 statistical software (IBM SPSS Corp.; Armonk, NY, USA). Continuous variables were expressed as mean±SD, whereas categorical variables were expressed as ratios. Nonparametric method was preferred for independent group comparisons and compared with Mann–Whitney U test. The class variables were presented as cross tables in frequency and percentages, and their distributions were compared with chi-square test. In all the tests, type 1 error margin was determined as α=0.05 and tested directionally, and when the p value was less than 0.05, the difference between the groups was considered statistically significant. The method of life table analysis was used for the survival analysis. Cumulative survival curves were obtained by the Gehan (generalized Wilcoxon) test. Receiver operating characteristic curve analysis was performed to determine the cutoff levels of CRP to pleural effusion and pleural infarct.

### RESULTS

**Patient Characteristics**
Two hundred and twenty patients with a diagnosis of acute PE were included in the study. The mean age of the patients was 62.7±17.2 years, and 111 of them were male, 109 of them were female patients. Early mortality was observed in 26 (11.8%) cases. There were 54 patients (24.5%) in the intensive care unit (ICU). Thrombolytic therapy was administered to 21 patients (9.5%); 138 patients (62.1%) were diagnosed with angio-CT. Deep vein thrombosis (DVT) was detected in 91 patients (41.4%) (Table 1).

**Relationship among CRP Levels, Infarction, Pleural Fluid, Pro-BNP, and Early Mortality**
Demographic characteristics, ICU admission, thrombolytic therapy, DVT history, D-dimer, s-PESI, CRP, arterial blood gas, and hemogram parameters were compared in 26 patients with PE and early mortality and 194 living patients with PE.

There was a significant difference in age, s-PESI, and CRP levels between the two groups (Table 2), and the median CRP was 5.95 (0.10; 42.0) in the without-early-mortality group (p=0.002; Table 2, Figure 1).

There was statistically no significant difference between the groups with and without early mortality in terms of gender.

### Table 1. Patient characteristics at the time of PE diagnosis

| Characteristics                  | N (%)                  |
|----------------------------------|------------------------|
| Age (years)                      | 65 (min-max, 19-92)    |
| Gender (male/female)             | 111 (50.4 %) / 109 (49.5%) |
| Mortality                        |                        |
| Early mortality (within 30 days) | 26 (11.8%)             |
| Without mortality                | 194 (88.1%)            |
| Thrombolytic therapy             | 21 (9.5%)              |
| Deep venous thrombosis           | 91 (41.5%)             |
| Angio-CT                         | 138 (62.7%)            |
| V/Q scan                         | 92 (37.2%)             |
| Intensive care unit administration| 54 (24.5%)             |
| Infarct                          | 109 (49.7%)            |
| Pleural fluid                    | 51 (24.1%)             |
| Infarct + pleural fluid          | 47 (22.2%)             |
| Biomarkers                       |                        |
| WBC                              | 10100 (3400-22000)     |
| Neutrophil                       | 7000 (600-19300)       |
| Lymphocyte                       | 1700 (300-7000)        |
| D-dimer                          | 4451 (453-15200)       |
| CRP                              | 6.4 (0.1-42)           |
| MPV                              | 8.6 (4.4-14.6)         |
| RDW                              | 14.3 (10.6-33.4)       |

CRP: C-reactive protein; CT: computed tomography; MPV: mean platelet volume; PE: pulmonary embolism; RDW: red-cell distribution width; V/P: ventilation/perfusion; WBC: white blood cell

### MAIN POINTS
- Survival within 30 days was lower in patients with higher levels of CRP.
- High levels of CRP biomarker because of inflammation in PE accompanied by effusion and infarction have shown why early mortality is significant in this group.
- CRP may help in the risk stratification of patients with acute PE especially with effusion and pulmonary infarction.
- CRP is an inexpensive and easily applicable biochemical marker that can be used to predict the early mortality.
distribution, whether or not they received thrombolytic therapy, and DVT (p >0.05). Pulmonary infarct, pleural fluid, or both have no effect on early mortality (p=0.981, 0.976, and 0.948, respectively) (Table 3). There was no correlation between CRP and pro-BNP and right ventricular dysfunction (p=0.201 and 0.787, respectively).

CRP Levels with Regard to Pleural Effusion and Pulmonary Infarction

The serum CRP levels at diagnosis were significantly higher in patients with PE and with pleural effusion and pulmonary infarct than those in patients with PE without pleural effusion and pulmonary infarct (4.75±4.91 ng/mL, 9.67±8.02 ng/mL; p <0.0003) (Figure 2. a-c).

Receiver operating characteristic curve (ROC) analysis (Figure 3) demonstrated that serum CRP levels for PE with or without pleural effusion and infarct about sensitivity and specificity. The area under the curve for CRP level was 0.64 (95% CI, 0.57-0.70, p=0.0035). The analysis of serum CRP values show an association with effusion and infarct of patients with PE. Thus, in our study, the cutoff CRP level is >8.25 in patients with PE and with effusion and infarct and the sensitivity and specificity was 63.8% and 67.6%, respectively. In addition, if CRP levels were over 8.25, the chances of a pulmonary infarct and pleural fluid increased two-fold (positive likelihood ratio: 1.98).

The Effect of Pulmonary Infarct and Pleural Fluid on Survival

The overall survival (OS) rate in patients with infarct and fluid was 50.43±5.3 months (95% CI, 39.97-60.88), without infarct and fluid was 44.37 ± 2.6 (95% CI, 39.20-49.55). There was no difference in survival rates between patients with infarct and fluid and those without. (p=0.684) (Figure 4a). OS in patients with pleural fluid or pulmonary infarct was 48.6 months (95% CI, 38.5-5.6) and 49.8 months (95% CI, 42.62-57.00), respectively, (p=0.954, 0.312) (Figure 4. b, c).

DISCUSSION

The risk stratification in acute PE has been explained recently. Echocardiography and other radiological methods, such as
CT angiography, are not always available to determine the prognosis in acute PE. The use of biochemical biomarkers has been suggested in risk stratification and determination of prognosis in acute PE. Cardiac troponin T and NT-proBNP have been recently studied for risk stratification in acute PE. A combination of elevated biomarkers and echocardiographic RV dysfunction seems to be a better predictor of mortality [4, 5, 10]. Despite these strategies for the risk stratification of PE, there is still a need for a simple and easily applicable method to determine prognosis. In this study, we investigated the prognostic role of CRP biomarker (early mortality within 30 days) in acute PE and found that the CRP level was higher in patients with early mortality.

The number of studies on the association between CRP and VTE is limited, and the results are conflicting. In contrast to our study, serum levels of Hs-CRP were not associated with future development of VTE [11]. A recent review found poor evidence for the causal role of CRP in the etiology of VTE [12]. Of the eight biomarkers analyzed for six months in patients with sub-massive PE, CRP was not found to be significantly associated with PE [13]. Ohigashi et al. [14] stated that serum CRP levels had no predictable value for the outcome of PE.

Some studies have found a positive relationship between CRP and VTE. Abul et al. explored the prognostic value of CRP in patients with acute PE and found that RV dysfunction was more frequent among the patients with elevated CRP levels when the patients were divided into groups according to CRP levels of less than 10 mg/L, (10-100 mg/L) and greater than 100 mg/L [3]. Also, most of the studies explored the association between elevated plasma CRP levels (mostly defined as >10 mg/L) and VTE but not PE [15-18].

A recent study investigated the value of BNP, cTnI, CRP, and D-dimer blood concentrations at the time of hospital admission in predicting 30-day PE caused death in patients with spontaneous versus provoked PE. The authors found that

| Table 3. Relationship among infarction, pleural fluid, and early mortality |
|---------------------------------------------------------------|
| Early mortality                                             |
| Present (n=23) | Absent (n=188) | p       |
| Infarct (present) | 12 | 52% | 93 | 49% | 0.981     |
| Effusion (present) | 5 | 22% | 46 | 24% | 0.976     |
| Infarct and effusion (present) | 5 | 22% | 42 | 22% | 0.948     |

Figure 2. a-c. Relationship among infarction, pleural fluid, and CRP biomarker
BNP has the strongest predictive value for both spontaneous and provoked PE, and cTnI and CRP have very good predictive value for spontaneous PE but are less valuable in provoked PE [19]. Abul et al. [3] demonstrated that high levels of NT-proBNP and CRP in acute PE might predict adverse outcomes during the 36 months of follow-up. High levels of CRP and NT-proBNP were associated with RV dysfunction and lower survival rates. Patients with acute PE and with low CRP values also had a better 36-month survival rate than those with high CRP levels. The cumulative proportion surviving at the end of 36 months was lower in patients with CRP levels higher than 10 mg/L compared with those with CRP levels less than 10 mg/L (cumulative survival ratio, 0.64±0.09 vs 0.86±0.13). Also, the hazard rate of the patients with CRP levels less than 10 mg/L within the 36 months was lower than the hazard rate of the patients with CRP levels higher than 10 mg/L (0.05±0.05 vs 0.11±0.04). Although the association with RV dysfunction was statistically significant for both NT-proBNP and CRP, the association with mortality was significant only for NT-proBNP. In our study, patients were followed up only for 30 days, and the level of CRP in the early mortality group was higher than that

Figure 3. ROC analysis demonstrating that serum CRP levels for PE with or without pleural effusion and infarct about sensitivity and specificity. The area under the curve for CRP level was 0.64 (95% CI, 0.57-0.70, p=0.0035).

Figure 4. a-c. Survival in pulmonary infarct and pleural fluid

![ROC Analysis](image-url)
in the living group. We did not find a correlation between CRP and pro-BNP, right/left ventricular ratio. We think that the small sample size in the early mortality group (n = 26) might be a reason for the statistical insignificance for correlation CRP and pro-BNP.

In the present study, higher CRP levels were seen in patients with PE and with effusion and pulmonary infarct and also in the early mortality group, CRP levels were higher than in patients with PE but without early mortality. Hemorrhagic necrosis of infarction exacerbates inflammatory reactions, causing pleural effusion or worsening; therefore, we believe that CRP levels are elevated because of this inflammation. In another study [19], patients with PE and with pleural effusion were found to be more common than patients with PE and without pleural effusion, and there was no predictor of pleural effusion related to PE, in-hospital mortality associated with PE, adverse outcomes, and the length of hospital stay. Pulmonary infarction and CRP levels were independent risk factors for the development of pleural effusion because of PE [20]. In our study, the cutoff value of CRP was >8.25 in patients with PE and with effusion and infarct and the sensitivity and specificity was 63.8% and 67.6%, respectively. Although there was a high level of CRP owing to infarct and fluid, there was statistically no significant difference in survival compared with those without infarct and fluid. Two studies both evaluating the diagnostic value of a standard CRP test at a cutoff level of 5 mg/L excluding pulmonary embolism demonstrated a relatively modest sensitivity of 84% not allowing a safe exclusion of PE and a sensitivity of 95.7%, potentially useful for excluding PE, respectively [21, 22]. In another study [23], CRP testing further reduced the number of clinically relevant alternative diagnoses in patients where the general practitioner excluded PE, which combines a possible Wells decision rule and a negative D-dimer test.

There were a few limitations to our study. The main limitation was the small sample size in the early mortality group and this study was retrospective. In addition, we did not study other inflammatory cytokines in parallel with CRP levels. We only included CRP and NT-proBNP levels, hematological parameters determined at the time of admission, and we did not look at the changes in CRP levels during the treatment. Furthermore, missing laboratory data such as NT-proBNP levels and pulmonary arterial pressure influenced our results. Another limitation was echocardiography. It was done with portable echocardiography so right ventricular dysfunction may not be calculated very accurately.

Survival within 30 days was lower in patients with higher levels of CRP. Also, high levels of CRP biomarker because of inflammation in PE accompanied by effusion and infarction have shown why early mortality is significant in this group. Thus, CRP may help in the risk stratification of patients with acute PE especially with effusion and pulmonary infarction. CRP is an inexpensive and easily applicable biochemical marker that can be used to predict the early mortality. In order to determine early mortality in PE, larger patient groups and prospective studies with inflammation markers such as CRP are needed.

**Ethics Committee Approval:** Ethics Committee approval for the study was obtained from the local ethic committee of Izmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital.

**Informed Consent:** Written informed consent was obtained from the patient.

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**Conflict of Interest:** The authors have no conflicts of interest to declare.

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