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**ARAŞTIRMA / RESEARCH**

# Relationship between Covid-19-associated pneumonia severity with coagulopathy and mortality

## Covid-19 ile ilişkili pnömoni şiddeti ile koagulopati ve mortalite arasındaki ilişki

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**Abstract**

**Purpose:** In the present study, the possibility of predicting mortality with the change in coagulation parameters depending on the severity of Covid-19-associated pneumonia was investigated.
**Materials and Methods:** A total of 137 patients with Covid-19-associated pneumonia were included in the study. The patients were divided into three groups according to the severity of pneumonia as mild, moderate and severe. According to the severity of pneumonia, the parameters of complete blood count and the levels of biochemical parameters were compared between the groups. By examining blood parameters according to mortality, ROC analysis and regression analysis were performed to determine the net effect of these parameters on mortality.
**Results:** As the severity of pneumonia increased, Prothrombin time (PT), International normalized ratio (INR) and Activated partial thromboplastin time (aPTT) values were also increased, and a statistically significant difference was found between the groups in PT and INR values. PT, INR and aPTT levels were higher in cases with mortality. Mortality can be predicted with 93.5% sensitivity and 97.5% specificity. according to the >45.1 seconds(sec) cut-off value of the coagulation parameter (aPTT+PT.
**Conclusion:** The coagulation parameter (aPTT + PT), whose level increases secondarily to the increase in Covid-19-associated pneumonia severity, provides successful results in predicting mortality, and may be a parameter that we can recommend in clinical use.
**Keywords:**. Covid-19 infection, coagulation, PT, INR, aPTT, mortality.

**Öz**

**Amaç:** Çalışmamızda covid-19 ilişkili pnömoninin şiddetine bağlı olarak koagulasyon parametrelerinde oluşan değişim ile mortalitenin öngörülebilmesi araştırıldı.
**Gereç ve Yöntem:** Çalışmaya toplam 137 covid-19 nedenli pnömonisi bulunan hasta dahil edildi. Pnömoni şiddetine göre hastalar hafif, orta ve şiddetli olarak üç gruba ayrıldı. Pnömoni şiddetine göre tam kan sayımındaki parametreler ile biyokimyasal parametrelerin düzeyleri gruplar arasında karşılaştırıldı. Mortaliteye göre kan parametreleri incelenerek bu parametrelerin mortalite üzerine net etkisini belirlemek için ROC analizleri ve regresyon analizleri yapıldı.
**Bulgular:** Pnömoni şiddeti Protrombin zamanı (PTZ), International normalized ratio (INR) ve Aktive parsiyel tromboplastin zamanı (aPTT) değerlerinde artış kaydedilmiş olup PTZ ve INR değerlerinde gruplar arasında istatistiksel olarak anlamlı farklılık belirlenmiştir. Mortal seyreden olgularda PTZ, INR ve aPTT düzeylerinin daha yüksek olduğu belirlendi. Koagulasyon parametresinin (aPTT+PTZ) >45,1 saniye (sn) cut-off değerine göre 93,5% duyarlılık ve 97,5% özgüllükle belirlendi.
**Sonuç:** Covid-19 ilişkili pnömoni şiddetinin artışına ikincil olarak düzeyi yükselen koagulasyon parametresinin (aPTT+PTZ) mortalitenin öngörülmesinde başarılı sonuçlar sunduğu belirlenmiş olup klinik kullanımda önerebileceğimiz bir parametre olabilir.

**Anahtar kelimeler**: Covid-19 enfeksiyonu, koagulasyon, PTZ, INR, aPTT, mortalite

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## INTRODUCTION

Covid-19 (SARS-CoV-2) infection started in Wuhan, China in December 2019, and as of 30 November 2020, it affected 62.19 million people worldwide and 1.45 million people lost their lives[1]. Although the real-time polymerase chain reaction (PCR) test is the gold standard diagnostic method in the diagnosis of SARS-CoV-2, it is stated that the frequently used nasal swab method can only offer 63% sensitivity[2]. On the other hand, pathological images can be detected in the thorax computed tomography (CT) in up to 96% of patients[3,4]. There is no vaccine or specific antiviral therapy with proven safety and efficacy yet available for clinical use. Despite this, it is important to start symptomatic, antiviral and immunomodulatory treatments at an early stage in order to reduce mortality and morbidity in patients whose clinical condition may deteriorate.

Currently, there is no proven biomarker that can clearly determine the prognosis of patients affected by Covid-19 infection. Although the pathophysiological mechanism of Covid-19 infection is still unclear, some studies show a potential relationship between the severity of the disease and the levels of certain elements of immune system such as proinflammatory cytokines, eosinophils, and lymphocyte subgroups[5-9]. Covid-19 infection causes cytokine storms in body fluids, exacerbating the patients' inflammatory response. This may even lead to death in some patients[6-9]. In this type of acute inflammation, there is a mutual interaction between these cytokines and many blood parameters[5-10]. Tissue / organ ischemia and damage may occur as a result of effects such as impairment of perfusion and vascular endothelial damage as a result of acute inflammatory responses[11,12]. Due to the systemic effects caused by inflammation, liver functions are impaired like all organs and causes such as consumption coagulopathy cause the reduction of other coagulation factors, starting with factor VII which has the shortest half-life. This may result in an increase in the levels of coagulation parameters (PT, INR and aPTT)[13,14]. Measuring the levels of cytokine storm that occurs as a result of the severity of pneumonia and alterations in the body (especially in blood parameters) in cases with Covid-19 associated pneumonia can help predict the adverse effects (mortality and morbidity) that may occur. For this purpose, in our study, blood parameters (simple biochemical parameters and hemogram), which cost low and are easy to access in all countries of the world, were examined. It was aimed to determine the severity of the inflammatory response that occurs with the levels of change in various blood parameters depending on the severity of Covid-19 associated pneumonia. In conclusion, the effect of changes in coagulation parameters depending on the severity of Covid-19-associated pneumonia on prognosis and mortality was investigated.

## MATERIALS AND METHODS

This study was conducted as a prospective / retrospective single-center observational study in a tertiary hospital between 15/03/2020 and 30/04/2020. Patients who were admitted to the emergency department of our hospital and diagnosed with Covid-19 according to PCR test positivity and CT imaging were included. Before the study, approval was obtained from our hospital's local and institutional ethics committee (Health Science University, Adana City Research and Training Hospital, Ethics Comittee, 2020 / 55-821). Approval was obtained from the management of our hospital for the use of these study

137 patients diagnosed with Covid-19 were included in the study. Patients' anamnesis, physical examination, PCR test, laboratory results, chest radiography and CT findings (CO-RADS Classification[4]) were evaluated and a diagnosis of covid-19 pneumonia was made by radiologists and clinicians (chest diseases specialist, infectious diseases specialist, internal medicine specialist and emergency medicine specialist). Patients with known coronary artery disease, cardiac arrhythmia, structural heart disease, bundle branch block, signs of myocardial ischemia, acute myocardial infarction, pulmonary embolism, thyroid dysfunction, pregnancy or active malignancy were excluded from the study. Patients who had cardiorespiratory arrest at the admission to the emergency department and died despite cardiopulmonary resuscitation were excluded from the study.

### Procedure

After obtaining patients' detailed medical history, 12-lead electrocardiographic and physical examinations of all patients included in the study were performed in the emergency department of our hospital. Heart rates, blood pressures and basal oxygen saturations

were recorded. Levels of hemogram and biochemical parameters were measured using appropriate commercial kits (Abbott) and an automated chemistry analyzer (Abbott Aeroset, MN, USA).

Determination of patient groups was made according to the extent of CT findings and clinical evaluation. Group-I was defined as patients with mild pneumonia and 45 patients whose CT findings did not exceed 25% of the lung area, whose general condition was good and who did not need oxygen and mechanical ventilation were included in this group. Group-II was defined as patients with moderate pneumonia and 45 patients whose CT findings were larger than 25% of the lung area but did not exceed 50%, whose general condition was medium-good and who did not need mechanical ventilation, rarely offered nasal oxygen support at low flow were included in this group. Group-III was defined as patients with severe pneumonia, and 47 patients whose CT findings exceed 50% of the lung area, whose general condition was moderate-poor and who may need mechanical ventilation (noninvasive / invasive) were included in this group.

**Statistical analysis**

Data were analyzed using SPSS 22.0 (SPSS 22.0 for Windows, Chicago, IL, USA). Data were expressed as mean ± SD for continuous variables and as percentages for categorical variables. Student-t test or ANOVA test was used to compare continuous variables with normal distribution, and Mann-Whitney U-test or Kruskal-Wallis test was used for comparison of samples not showing normal distribution. Chi-square ($\chi 2$) test was used to compare categorical variables. Bonferroni corrected Z test was used for multiple comparisons of group proportions. Logistic regression analysis was performed to determine the relationship between mortality and the independent parameters that differed in patients who deceased due to Covid-19 associated pneumonia. ROC curve analysis was performed to re-evaluate the most important parameters predicting mortality in logistic regression analysis and to determine the cut-off value for these parameters. A p value of $<0.05$ was defined as statistically significant for all analyzes.

## RESULTS

137 patients included in the study were evaluated. 45 patients with mild pneumonia has evaluated as group-I, 45 patients with moderate pneumonia has evaluated as group-II, and 47 patients with severe pneumonia has evaluated as group-III. The demographic, clinical, laboratory data and outcome status of the cases were compared between the groups determined according to the severity of Covid-19 pneumonia. Similar results were obtained between the groups according to the severity of Covid-19-associated pneumonia in gender, WBC, hematocrit, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium and aPTT levels, and it was determined that there was no statistically significant difference between the groups.

On the other hand, it was determined that age, incidence of mortality, glucose, blood urea nitrogen (BUN), creatinine, PT and INR levels increased as the severity of Covid-19-associated pneumonia increasef and provided a statistically significant difference between the groups. Finally, as the severity of Covid-19-associated pneumonia increased, a decrease in hemoglobin level and a decrease and then an increase in the number of platelets were determined, and it was determined that there was a statistically significant difference between the groups (Table 1).

Independent variables were evaluated according to the incidence of mortality. It was determined that the levels of PT, INR, aPTT, BUN, AST and ALT parameters and patients' age were higher in those with mortality and there was a statistically significant difference. It was determined that gender, platelet count, level of creatinine, glucose, sodium and potassium parameters did not make a statistically significant difference according to mortality (Table 2).

Considering that the aPTT level did not show statistical difference according to the severity of pneumonia and showed a difference according to mortality, as well as the fact that PT and INR levels showed statistically significant differences between groups determined according to the severity of covid-19-associated pneumonia and mortality, additional analyzes were performed with these parameters. In this context, regression analysis was performed with independent variables within the scope of the study according to the occurrence of mortality. When the effects of all independent variables were examined, it was determined that no parameter showed a statistically significant difference in determining the mortality risk. ($p>0,05$).

**Table 1. The clinic, demographic, and biochemical findings according to study groups**

| Variable | Mild (Group 1) n=45 | Moderate (Group 2) n=45 | Severe (Group 3) n=47 | p | Post hoc p |
|---|---|---|---|---|---|
| | Mean±SD | Mean±SD | Mean±SD | | |
| Age (year) | 49.08±15.64 | 51.84±15.16 | 60.12±14.54 | 0.002 | 3-1; p=0.002 3-2; p=0.029 |
| Sex (male/female) | 25/20 | 28/17 | 22/25 | 0.329 | |
| Result (Discharge/Exitus) | 44/1 | 42/3 | 35/12 | 0.001 | 3-1; p=0.001 3-2; p=0.011 |
| Glucose (mg/dL) | 110.46±31.54 | 127.15±54.16 | 151.59±75.99 | 0.003 | 3-1; p=0.002 |
| Blood urea nitrogen (mg/dL) | 32.86±20.13 | 38.08±26.17 | 50.97±31.88 | 0.004 | 3-1; p=0.004 |
| Creatinine (mg/dL) | 0.76±0.27 | 0.88±0.41 | 0.98±0.49 | 0.040 | 3-1; p=0.034 |
| Sodium (mmol/L) | 138.24±2.64 | 138.26±3.68 | 138.0±3.30 | 0.908 | |
| Potassium (mmol/L) | 4.35±0.36 | 4.42±0.50 | 4.43±0.50 | 0.694 | |
| Aspartate aminotransferase (AST) (U/L) | 32.13±10.16 | 36.71±36.10 | 40.91±22.14 | 0.397 | |
| Alanine aminotransferase (ALT) (U/L) | 29.77±12.51 | 28.97±22.71 | 34.04±20.78 | 0.249 | |
| Hemoglobin (g/dL) | 13.52±1.76 | 13.01±2.11 | 12.51±1.63 | 0.034 | 1-3; p=0.029 |
| White blood cell (10^3/μl) | 8246.7±3056.7 | 10191.1±4717.2 | 8995.7±3893.8 | 0.066 | k |
| Platelet count (10^3/μl) | 259991.1±60506.1 | 212733.3±107405.2 | 262297.8±107783.9 | 0.022 | 3-2; p=0.040 |
| Hematocrite (%) | 39.25±4.72 | 37.85±5.33 | 36.92±4.22 | 0.067 | |
| PT* (sn) | 12.59±1.22 | 13.72±4.77 | 16.05±3.38 | 0.000 | 3-1; p=0.000 3-2; p=0.005 |
| INR** | 1.03±0.10 | 1.10±0.25 | 1.37±0.31 | 0.000 | 3-1; p=0.000 3-2; p=0.000 |
| aPTT*** (sn) | 25.13±3.66 | 25.28±4.32 | 26.58±5.62 | 0.257 | |

The values were shown as mean ± standard deviation or n (%)
Group I= COVID-19 patients mild pneumonia
Group II= COVID-19 patients with moderate pneumonia
Group III = COVID-19 patients with severe pneumonia
α = the significant association between the Group I and Group III ($p<0.05$)
¥ = the significant association between the Group I and Group II ($p<0.05$)
β = the significant association between the Group II and Group III $p<0.05$)
*PT= Prothrombin time
**INR= International normalized ratio
***aPTT: Activated partial thromboplastin time

**Table 2. The clinic, demographic, biochemical and hemogram findings related to mortality**

| Variable | Mortality (+) n=16 | Mortality (-) n=121 | p |
|---|---|---|---|
| Age (year) | 64.25±14.48 | 52.39±15.42 | 0.005 |
| Sex (male/female) | 7/9 | 68/53 | 0.351* |
| Glucose (mg/dL) | 156.81±76.31 | 126.52±56.09 | 0.073 |
| Blood urea nitrogen (mg/dL) | 56.25±34.26 | 38.75±25.95 | 0.044 |
| Creatinine (mg/dL) | 1.09±0.62 | 0.85±0.37 | 0.321 |
| Sodium (mmol/L) | 137.62±3.24 | 138.23±3.22 | 0.216 |
| Potassium (mmol/L) | 4.36±0.60 | 4.41±0.44 | 0.637 |
| ALT** (u/L) | 57.75±31.46 | 27.43±13.63 | 0.000 |
| AST*** (u/L) | 61.31±30.54 | 33.38±22.58 | 0.000 |
| PT**** (sn) | 20.40±6.99 | 13.32±1.91 | 0.000 |
| INR***** | 1.68±0.39 | 1.10±0.17 | 0.000 |
| aPTT****** (sn) | 34.00±7.04 | 24.57±2.77 | 0.000 |
| Platelet count (10^3/µl) | 282187.50±154649.37 | 240347.10± 86143.74 | 0.408 |

Mann-Whitney U test. The values were shown as mean ± standard deviation or n (%)
*Chi-Square Test; ** ALT= Alanine aminotransferase; *** AST= Aspartate aminotransferase; **** PT= Prothrombin time; ***** INR= International normalized ratio; ****** aPTT= Activated partial thromboplastin time

ROC analyzes were performed in terms of predicting mortality with PT, INR and aPTT parameters, which differ between groups according to mortality and pneumonia severity. As a result of the analyzes, cut-off values were determined, which provided the highest sensitivity with PT and the highest specificity with aPTT. Positive results were obtained with the "Coagulation" parameter, which was created by adding the PT value to aPTT in analyzes performed with different combinations of study parameters. In terms of predicting mortality with the "Coagulation" parameter, it was determined that when the cut-off value was taken as> 45.1 sec, it provided the most successful results with 93.5% specificity and 97.5% sensitivity [AUROC Curve: 0.943, 95% CI: 0.846-1.000, p = 0.000] (Table 3).

**Table 3. ROC curve analysis for predicting mortality**

| Variable | AUROC Curve | p | Cut-off | Sensitivity | Specificity |
|---|---|---|---|---|---|
| Age (year) | 0.718 (0.591-0.844) | 0.005 | > 53.5 | 81.3% | 54.5% |
| aPTT* (sn) | 0.877 (0.732-1.000) | 0.000 | > 28.75 | 87.5% | 94.2% |
| PT** (sn) | 0.931 (0.871-0.990) | 0.000 | > 15.15 | 93.8% | 85.1% |
| INR*** | 0.929 (0.867-0.992) | 0.000 | > 1.315 | 87.5% | 88.4% |
| aPTT+PT (sn) | 0.943 (0.846-1.000) | 0.000 | > 45.1 | 93.5% | 97.5% |

* aPTT= Activated partial thromboplastin time; ** PT= Prothrombin time; *** INR= International normalized ratio

Regression analysis of Coagulation (aPTT + PT) parameter and other independent variables were performed according to the incidence of mortality. As a result, it was determined that there was a statistically significant difference only in the Coagulation parameter and the mortality risk increased by 2.625 times (OR: 2.625, 95% CI: 1.126-6.116, p = 0.025) for each unit increase of the Coagulation parameter (Table 4).

**Table 4. Independent parameters for occurrence of mortality**

| | Odds Ratio | 95% Confidence Interval | p |
|---|---|---|---|
| Age (each year) | 0.958 | 0.824 - 1.114 | 0.578 |
| Sex (female) | 3.515 | 0.122 - 101.140 | 0.463 |
| WBC (10^3/µl) | 1.000 | 0.999 - 1.000 | 0.523 |
| Platelet (10^3/µl) | 1.000 | 1.000 - 1.000 | 0.317 |
| Hematocrite (%) | 0.602 | 0.293 - 1.238 | 0.168 |
| Hemoglobin (g/dL) | 1.000 | 0.980 - 1.021 | 0.982 |
| Blood urea nitrogen (mg/dL) | 1.091 | 0.973 - 1.224 | 0.135 |
| Creatinine (mg/dL) | 0.006 | 0.000 - 37.234 | 0.249 |
| Sodium (mmol/L) | 0.883 | 0.555 - 1.403 | 0.598 |
| Potassium (mmol/L) | 0.113 | 0.002 - 5.340 | 0.268 |
| ALT (U/L) | 1.126 | 0.979 - 1294 | 0.095 |
| AST (U/L) | 1.021 | 0.951 - 1097 | 0.565 |
| Glucose (mg/dL) | 0.999 | 0.973 - 1.025 | 0.937 |
| aPTT+PT (sn) | 2.625 | 1.126 – 6.116 | 0.025 |

The reference value for mortality was determined at discharge. The variables entered on this analysis: Sex (female), Age, Glucose, Urea, Creatinine, Sodium, Potassium, ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), WBC (White Blood Cell), Hemoglobin, Hematocrite, Platelets, Koagulasyon (aPTT+PTZ).

## DISCUSSION

As of November 30, 2020, the Covid-19 pandemic affected more than 62 million people worldwide and caused the deaths of approximately 1.5 million people[1]. As a result of cytokine storm caused by Covid-19 infection, systemic inflammatory response and pneumonia (ARDS) cause respiratory distress and mortality[8]. In some studies, it is stated that cytokine storm and pneumonia secondary to Covid-19 infection cause widespread inflammation in the lungs and ARDS[6,8]. As a result of this cytokine storm, a systemic inflammatory response occurs and the functions of many tissues and organs are affected. Cytokines can cause changes in many blood parameters by causing organ damage due to tissue hypoperfusion[6,8]. Measuring the cytokine response in patients is difficult and costly and it is not possible to be performed in all health centers worldwide.

On the other hand, it is thought that the secondary response to Covid-19 can be determined by monitoring the changes in blood parameters (cellular etc.) caused by the cytokine response. It is thought that the severity of Covid-19 infection and the mortality that may develop secondary to Covid-19 infection can be predicted by evaluating both the numerical and proportional changes of the cells in the hemogram parameters and the quantitative or proportional changes in the biochemical parameters.

The most common pattern of coagulopathy observed in patients hospitalized with COVID-19 is reported to be elevations in fibrinogen and D-dimer levels and mild prolongation of PT / aPTT, which parallels the increase in inflammation markers (eg CRP). Endothelial damage and thromboses may occur in the following period[14]. In the studies conducted, it has been stated that in patients with COVID-19, changes in coagulation parameters, disseminated intravascular coagulation (DIC), consumption coagulopathy and susceptibility to thrombosis can be observed[15]. In this context, our study aimed to determine the prognosis by examining the changes in coagulation and other blood parameters during the first admission of cases with Covid-19- associated pneumonia. Patients' hemogram parameters, liver function tests, kidney function tests, glucose levels, electrolytes and especially coagulation parameters (PT, INR and aPTT) were examined.

Recent studies have reported that patients hospitalized with covid-19 associated pneumonia have an increase in coagulation parameters such as d-dimer and PT and aPTT. It has been reported that

PT prolongation, high d-dimer levels, increased thromboembolic events and DIC occur especially in patients treated in intensive care. Many studies indicate that d-dimer is associated with disease severity and mortality. Current studies suggest that some blood parameters that may increase with the severity of the covid-19 infection may be associated with mortality[16,17]. In our study, it was determined that the most successful results were achieved with coagulation parameters to predict mortality among parameters at varying levels according to the severity of Covid-19 associated pneumonia. It was determined that as the severity of pneumonia increased, the levels of coagulation parameters (PT, INR and aPTT) increased. Coagulation parameters were found to be higher in patients who died. These results are consistent with the results of existing studies. Analyzes were performed to determine the effects of coagulation parameters, which differ significantly according to the severity of pneumonia associated with Covid-19 and mortality. In the prediction of mortality, it was determined that the cut-off value of> 15.15 sec for PT provided the highest sensitivity at 93.8%, and the cut-off value of> 28.75 sec for aPTT provided the highest specificity with 94.2%. The cut-off value of the "Coagulation (PT + aPTT)" parameter, which was created by the sum of both parameters, was determined as> 45.1 sec. In predicting mortality, it was determined that the coagulation parameter provided the most successful results with 93.5% sensitivity and 97.5% specificity.

In the regression analysis performed with other independent variables to determine the effect of the coagulation (PT + aPTT) parameter in terms of predicting mortality, it was determined that the cogulation parameter was the only parameter that gave statistically significant results (OR: 2.625, 95% CI: 1.126-6.116, p = 0.025). As a result, it is thought that the coagulation parameter can provide successful results in predicting mortality.

The retrospective design of the study is an important limitation of our study. Further research with prospective design and higher number of patients can provide more information about this subject.

In conclusion, coagulation (aPTT + PT) parameters, which increases in correlation with the increase in Covid-19-associated pneumonia severity, can predict mortality with a cut-off value of> 45.1 seconds and with a sensitivity of 93.5% and a specificity of 97.5%, and, each unit increase in the Coagulation parameter increases the mortality risk 2,625 fold. In conclusion, the "coagulation" parameter can be a successful parameter that we can recommend for predicting mortality and determining its risk.

**Yazar Katkıları:** Çalışma konsepti/Tasarımı: TT, HES, BŞA; Veri toplama: HÇ, NÜ; Veri analizi ve yorumlama: BŞA, TT, HES, AK; Yazı taslağı: BŞA, TT, HES, Fİ, HY; İçeriğin eleştirel incelenmesi: TT; Son onay ve sorumluluk: BŞA, AK, HES, FGUİ, HY, NÜ, ÖY, HÇ, TT; Teknik ve malzeme desteği: -; Süpervizyon: BŞA, ÖY, HES; Fon sağlama (mevcut ise): yok.
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