Dicle Tıp Dergisi / Dicle Med J (2024) 51 (3) : 369-376

www.diclemedj.org

Original Article / Özgün Araştırma

Evaluation of Coagulation Disorders in Intubated and Non-Intubated Patients with Covid-19 Diagnosis in The Intensive Care unit

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Received: 15.02.2024; Revised: 27.08.2024; Accepted: 02.09.2024

Abstract

Objective: It is known that the need for invasive mechanical ventilation due to severe respiratory failure develops in COVID-19 patients followed in the intensive care unit. It has been reported in the literature that coagulopathy seen during COVID-19 disease is an important cause of mortality and morbidity. Our aim in our study was to evaluate coagulation disorders developing between intubated and non-intubated patients.

Method: The data of 812 patients diagnosed with COVID-19 in the Intensive Care Unit, between March 2020 and September 2021 were retrospectively analyzed. The patients were divided into two groups according to the need for invasive mechanical ventilation. Demographic characteristics, laboratory values at the time of diagnosis, coagulopathy development status and survival of the patients were investigated.

Results: Of the 812 patients included in the study, 459 (56.5%) were male. The mean age was 66,4 ± 15,2. 257 (31.7%) of the patients received invasive mechanical ventilation support. Coagulopathy was detected in 146 (56.8%) of these patients. Distribution of coagulopathy in intubated patients; 26% Disseminated Intravascular Coagulation, 17.9% Acute Coronary Syndrome, 10.5% Hemorrhage (inside or outside the body), 5.4% Pulmonary Embolism, 5% Heparin-Induced Thrombocytopenia, 3.5% Ischemic Stroke, 1.9% Hemorrhagic Stroke and 0.8% found as Deep Vein Thrombosis. We found that 32% of the patients who were not intubated developed coagulopathy, and this difference was statistically significant ($p<0.001$). We found the mortality rate to be 97.7% in intubated patients. Mortality in non-intubated patients was 38.4%.

In our study, coagulopathy development rate was found to be higher in patients with at least one comorbidity ($p=0,006$). Relationship between the laboratory findings at the time of hospitalization and the rate of coagulopathy development were analyzed and a statistically significant differences was found between the hemoglobin, thrombocyte, fibrinogen, d-dimer and INR levels of the patients and development of coagulopathy ($p=0.026$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$). It was seen that 49.8% of the patients who died had at least one coagulopathy condition. This rate was found to be 26.7% in the surviving patients, and this difference was statistically significant ($p<0.001$).

Conclusion: It was determined that approximately one third of the COVID-19 patients hospitalized in the intensive care unit required mechanical ventilation. A coagulation disorder was detected in 56.8% of the patients. A significant correlation was found between intubation and the development of coagulopathy. In addition a significant difference was found between high d-dimer, fibrinogen, INR levels, low hemoglobin and thrombocyte levels and the development of coagulopathy. Comorbidities were also found to be associated with coagulopathy and mortality. It was observed that 97.7% of the intubated patients died.

Keywords: Covid-19, Coagulopathy, Intubation

DOI: 10.5798/dicletip.1552519
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Yoğun Bakım Ünitesinde Covid-19 Tanılı Hastalardan Entübe Olanlarla Olmayanlarda Koagülasyon Bozukluklarının Değerlendirilmesi

Öz

Amaç: Yoğun bakımda takip edilen COVID-19 hastalarında, ağır solunum yetmezliğine bağlı invaziv mekanik ventilasyon ihtiyacı geliştiği bilinmektedir. COVID-19 hastalığının seyrinde görülen koagülopatinin, önemli bir mortalite ve morbidite nedeni olduğu literatürde bildirilmektedir. Çalışmamızda amacımız, entübe olanlar ile olmayanlar arasında gelişen koagülasyon bozukluklarını değerlendirmektir.

Yöntemler: Mart 2020 ve Eylül 2021 tarihleri arasında Yoğun Bakım Ünitesinde COVİD-19 tanısı almış 812 hastanın verileri retrospektif olarak incelendi. Hastalar invaziv mekanik ventilasyon ihtiyacına göre iki gruba ayrıldı. Çalışmaya alınan hastaların tanı anındaki demografik özellikleri, laboratuvar değerleri, hastalarda gelişmiş koagülopati durumları ve sağkalımları değerlendirildi.

Bulgular: Çalışmaya dâhil edilen toplam 812 hastanın 459'u (%56,5) erkekti. Ortalama yaş 66,4 ± 15,2 idi. Hastaların 257'si (%31,7), invaziv mekanik ventilasyon desteği almıştı. Bu hastaların 146'sında (%56,8) koagülopati geliştiği saptandı. Entübe hastalarda gelişen koagüolapati dağılımı; %26 Disemine İntravasküler Koagülopati, %17,9 Akut Koroner Sendrom, %10,5 Hemoraji (vücut içi veya dışı), %5,4 Pulmoner Tromboemboli, %5 Heparin İlişkili Trombositopeni, %3,5 İskemik SVO, %1,9 Hemorajik SVO ve %0,8 Derin Ven Trombozu olarak bulundu. Entübe olmayan hastaların ise %32'sinde koagülopati geliştiğini gördük ve bu fark istatistiki olarak anlamlıydı (p<0,001). Entübe olanlarda mortaliteyi %97,7 olarak saptadık. Entübe olmayanlarda mortalite, %38,4 idi.

Çalışmamızda; en az bir komorbiditesi olan hastalarda, diğerlerine göre koagülopati gelişme oranı daha yüksek saptandı (p=0,006). Hastaların yattığı andaki laboratuvar bulguları ile koagülopati gelişme oranı arasındaki ilişkiye bakıldı ve hastaların hemoglobin, trombosit, fibrinojen, d-dimer ve INR düzeyleri ile koagülopati gelişimi arasında istatistiki olarak anlamlı fark bulundu (p=0,026, p<0,001, p<0,001, p<0,001, p<0,001). Ölen hastaların %49,8'inde en az bir koagülopati durumu gelişmiş olduğu görüldü. Yaşayan hastalarda bu oran %26,7 olarak bulundu ve bu fark istatistiki olarak anlamlıydı (p<0,001).

Sonuç: Yoğun bakımda yatan COVID-19 hastalarının yaklaşık üçte birinde mekanik ventilasyon ihtiyacı olduğu saptandı. Bunların %56,8'inde bir koagülosyon bozukluğu tespit edildi. Entübasyon ile koagülopati gelişimi arasında anlamlı ilişki bulunda. Ayrıca yüksek d-dimer, fibrinojen, INR seviyeleri ve düşük hemoglobin, trombosit düzeyleri ile koagülopati gelişimi arasında anlamlı fark bulundu. Komorbiditenin de koagülopati ve mortalite ile ilişkili olduğu gözlendi. Entübe olan hastaların %97,7'sinin öldüğü görüldü.

Anahtar kelimeler: Covid-19, Koagülopati, Entübasyon.

INTRODUCTION

Coronaviruses are important for humans and animals pathogens. At the end of 2019, a new coronavirus was identified in Wuhan in China's Hubei province, as the cause of several of pneumonia. It spread rapidly, causing an epidemic throughout China and then a global pandemic. In February 2020, The World Health Organization identified the disease COVID-19, which means the 2019 coronavirus disease[1].

Coagulation disorder is one of the most important and fatal complications in the course of COVID-19 disease. Thrombosis formation in COVID-19 patients can be explained by the virchow triad[2]. In addition, hypoxia and RAAS (renin - angiotensin - aldosterone system) activation may also contribute to the coagulopathy seen during COVID-19[3,4]. Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, has been reported in 2% to 40% of severely ill patients with COVID-19, particularly in the intensive care unit (ICU) ([5–6]). Arterial thrombotic events, including acute stroke (even in patients younger than 50 years of age without risk factors) and extremity ischemia, have also been reported between 0.8% and 5%[7–8].

The COVID-19 pandemic, which was first detected in December 2019 and has been responsible for the death of millions of people so far, still continues, and vaccines and drugs studies for the disease continue. COVID-19 disease, which generally progresses with mild symptoms, has a severe course in some patients (especially in advanced age and comorbid diseases), and these patients require invasive mechanical ventilation support. Microvascular and macrovascular thrombosis and other coagulopathies that may be observed during COVID-19; increases mortality and morbidity.

Our aim in this study; to evaluate coagulation disorders in intubated and non-intubated COVID-19 positive patients hospitalized in the

Intensive Care Unit between March 2020 and September 2021.

METHODS

Our study has been approved by Ethics Committee at 15.12.2021 with file number 523. In our study, the information available in the patient registry system of 812 patients older than 18 years of age, who were hospitalized for more than 1 day and whose diagnosis of COVID-19 was confirmed in the Intensive Care Unit between March 2020 and September 2021, was retrospectively analyzed.

Demographic characteristics of the patients, existing comorbid diseases, length of stay in the intensive care unit, vital signs and laboratory parameters at the time of first admission were recorded. Patients DIC scores were calculated using the ISTH DIC Scoring system. Platelet counts, INR, fibrinogen, and d-dimer levels of patients were examined from the moment of admission. Then daily scoring was done. Patients with a score of 5 and above (excluding those with additional diseases that could affect the scoring system such as liver disease) were recorded. Patients who developed thrombocytopenia after anticoagulant therapy were scored using the 4 T scoring system. LMWH treatments were stopped for patients who scored 'high probability of HIT' as a result of the scoring. Platelet values were evaluated after initiating non-heparin anticoagulant agent treatments. Patients who responded to the treatment were evaluated as HIT and recorded. Patients diagnosed with ACS (cardiac enzyme, ECG and clinical evaluation) were recorded. Patients diagnosed with 'Pulmonary Thromboembolism' by imaging methods and laboratory and clinical evaluation recorded. In addition, patients with venous thrombosis confirmed by imaging findings were recorded. Patients diagnosed with 'CVD (Cerebrovascular Disease)' (Ischemic Stroke, Hemorrhagic Stroke) with cranial imaging were recorded. Patients with internal or external bleeding (Gastrointestinal bleeding, Hematuria, Alveolar bleeding, etc.) were recorded.

In our study, we divided the patients into provincial groups. We grouped patients who received invasive mechanical ventilation support for at least 24 hours as 'Intubated' and other patients as 'Non-Intubated'.

Statistical Analysis

Data analysis was performed using SPSS 26 (Statistical Package Social Science) statistical program. Categorical data were evaluated using the Chi-square. Normally distributed data were analyzed with the Student's T-test and expressed as mean±standard deviation. Variables that did not fit the normal distribution were expressed as median and minimum-maximum values. Difference between the patient and control group that did not fit the normal distribution were analyzed with the Mann Whitney U test. P values below 0.05 were considered statistically significant in all tests.

RESULTS

Of the 812 patients included in the study, 459 (56.5%) were males and 353 (43.5%) were females. The mean age was 66.4±15.2 years and the median age was 69 (youngest – largest;18 – 109) was found. Of these patients, 257 (31.7%) were intubated and 555 (68.3%) to be non-intubated. At least one comorbid disease was detected in 552 (68%) patients, and hypertension was the most common comorbid disease. While 464 (57.1%) of 812 patients who died, 348 (42.9%) were transferred to clinics or discharged. The mortality rate was 97.7% (251) in intubated patients and 38.4% (213) in non-intubated patients.

Table I: Relationship between variables and intubation

		Intubated (n, 257)	*Non-Intubated (n, 555)*	*p*
Age		69 ± 13.8	65.5 ± 15.5	**0.002**
Gender	Male	141 (%54.9)	318 (%57.3)	0.515
	Female	116 (%45.1)	232 (%42.7)	
Hemoglobin (g/dL)		11.94 ± 2.46	11.88 ± 2.38	0.753
Platelets (10^3/uL)		226 ± 105	234 ± 119	0.355
CRP (mg/dL)		12 (0.2 - 54)	8.65 (<0.1 – 41.9)	**<0.001**
Ferritin (ng/ml)		795 (6.6 – 9956)	573 (9.6 – 9452)	**0.006**
Fibrinogen (mg/dL)		513 ± 212	499 ± 200	0.381
D-dimer (mg/L)		2.09 (0.3 – 100)	1.3 (0.1 – 100)	**<0.001**
INR		1.14 (0.9 – 5.5)	1.1 (0.72 – 13.9)	**<0.001**
Comorbid Disease	+	184 (%71.6)	368 (%66.3)	0.133
	-	73 (%28.4)	187 (%33.7)	
Coagulopathy Development	+	146 (56.8)	178 (%32)	**<0.001**
	-	111 (%43.2)	377 (%68)	

It was found that at least one coagulopathy developed in 324 (39.9%) of the patients included in the study. Coagulopathy was detected in 146 (56.8%) intubated patients. Distribution of coagulopathy in intubated patients; 26% Dissemine Intravascular Coagulation, 17.9% Acute Coronary Syndrome, 10.5% Hemorrhage (inside or outside the body), 5.4% Pulmonary Embolism, 5% Heparin Induced Thrombocytopenia, 3.5% Ischemic Stroke, 1.9% Hemorrhagic Stroke, and 0.8% found as Deep Vein Thrombosis.

Table II: Distribution of Coagulopathy, Number of Patients and Rates

	Number and Rate of Patients Developing Coagulopathy	
	General (324/812)	**Intubated (146/257)**
Dissemine Intravascular Coagulation	110 (%13.5)	67 (%26)
Acute Coronary Syndrome	83 (%10.2)	46 (%17.9)
Hemorrhage	76 (%9.4)	27 (%10.5)
Ischemic Stroke	36 (%4.4)	9 (%3.5)
Pulmonary Embolism	36 (%4,4)	14 (%5.4)
Heparin Induced Thrombocytopenia	21 (%2.6)	13 (%5)
Hemorrhagic Stroke	10 (%1.2)	5 (%1.9)
Deep Vein Thrombosis	7 (%0.9)	2 (%0.8)

The mean age of patients with coagulopathy was 67.1 ± 14.9, and those without coagulopathy were 66 ± 15.4 years. There was no statistically significant relationship between age and the development of coagulopathy (p=0.373). Of the 324 patients who developed coagulopathy, 189 (58.3%) were male. In patients who did not develop coagulopathy, the male ratio was 55.3%. There was no statistically significant difference between gender and the development of coagulopathy (p=0.398). Development of coagulopathy; statistically significant correlation was found between hemoglobin level, platelet count, fibrinogen level, d-dimer level and INR level (p=0.026, p<0.001, p<0.001, p<0.001, p<0.001). No significant correlation was found between CRP and ferritin levels and the development of coagulopathy (p=0.807, p=0.305). It was determined that 73.4% of the patients who developed coagulopathy had at least one comorbid disease. In those who did not develop coagulopathy, this rate was found to be 64.3%. There was a statistically significant difference between the development of coagulopathy and the presence of comorbidity. (p=0.006). The differences between the variables and coagulopathy is summarized in Table 3.

Table III: Difference between variables and coagulopathy

		Developed Coagulopathy (+) (n, 324)	Coagulopathy Undeveloped (-) (n, 488)	p
Age		67.1 ± 14.9	66 ± 15.4	0.373
Gender	Male	189 (%58.3)	270 (%55.3)	0.398
	Female	135 (%41.7)	218 (%44.7)	
Hemoglobin (g/dL)		11.6 ± 2.6	12 ± 2.2	**0.026**
Platelets (10^3/uL)		214 ± 119	244 ± 111	**<0.001**
CRP (mg/dL)		11.6 (0.1 - 54)	10.7 (<0.1 – 39)	0.807
Ferritin (ng/ml)		1092 (6.6 – 9956)	945 (13 – 9452)	0.305
Fibrinogen (mg/dL)		460 ± 207	531 ± 196	**<0.001**
D-dimer (mg/L)		1.9 (0.12 – 100)	1.3 (0.1 – 100)	**<0.001**
INR		1.14 (0.9 – 5.1)	1.1 (0.72 – 13.9)	**<0.001**
Comorbid Disease	+	238 (%73.4)	314 (%64.3)	**0.006**
	-	86 (%26.6)	174 (%35.7)	

Coagulopathy was detected in 49.8% of the patients who died. In survivors, this rate was found to be 26.7%. This difference was statistically significant (p<0.001). The differences between the variables we evaluated and survival is summarized in Table 4.

Table IV: Relationship between variables and survival

		Dead (n, 464)	Survived (n, 348)	p
Developing Coagulopathy	Yes	231(%49.8)	93(%26.7)	**<0.001**
	No	233(%50.2)	255(%73.3)	

DISCUSSION

In our study, we evaluated the coagulation disorders between intubated and non-intubated patients treated in the intensive care unit due to COVID-19.

In our study, the mean age was 69 ± 13.8 in intubated patients and 65.5 ± 15.5 in non-intubated patients. The mean age was 69.4 ± 13 years in patients who died, and 62.9 ± 16.8 years in patients who survived. A statistically significant correlation was found between increasing age and both intubation and mortality. In the study of Bayrak et al. with 86 patients diagnosed with COVID-19 and followed up in the intensive care unit; the mean age of the patients was 71.1 ± 14.1 and the proportion of males was 70.9%[9]. Similarly, in the study conducted by Dursun et al. with patients hospitalized in intensive care due to COVID-19, increasing age and the presence of comorbidities were found to increase mortality[10]. In our study, there was no significant relationship between gender and intubation and mortality. We found that 68% of the patients included in the study had at least one comorbid disease, and 35.1% had two or more comorbid diseases. In our study, we found that the presence of comorbidities caused a slight increase in the rate of intubation, but this difference was not statistically significant. Mortality was increased in patients with comorbid diseases, and this difference was statistically significant. Our findings were similar to the literature. In the study by Azoulay et al. with 85 intensive care patients diagnosed with COVID-19, a significant relationship was found between the presence of comorbidities and mortality, but there was no significant relationship between the presence of comorbidities and the need for invasive mechanical ventilation[11].

In our study, we found that the hemoglobin levels of the patients were below the normal range. The platelet counts and INR levels of the patients were within the normal range. CRP, ferritin, fibrinogen and d-dimer levels were above the normal range. When we evaluated the relationship between laboratory parameters of patients with intubation and mortality; we did not find a statistically significant relationship

between hemoglobin levels and mortality and intubation. We did not find a significant relationship between platelet counts and intubation, but we found a statistically significant relationship between the decrease in platelet count and mortality. We found a statistically significant relationship between CRP, ferritin, d-dimer and INR levels of the patients and intubation and mortality. In our study, the fibrinogen level of the patients was above the normal range. Despite this height, we did not find a statistically significant relationship between fibrinogen levels and intubation and mortality. Our findings in our study were consistent with the literature. In a study conducted by Elhadi et al. in April 2021 with 465 patients diagnosed with COVID-19, the CRP, ferritin and fibrinogen levels of the patients were found to be above the normal range. There was no statistically significant relationship between fibrinogen level and mortality, but there was a significant relationship between ferritin increase and mortality. In addition, decreased platelet count and increased CRP levels were associated with mortality[12]. In the study by Ayaz et al. in November 2020 with 66 patients diagnosed with COVID-19 and hospitalized in intensive care, there was no significant relationship between the hemoglobin levels of the patients and mortality. A significant correlation was found between the increase in INR and mortality in the patients[13].

We found that at least one coagulopathy developed in 324 (39.9%) of the 812 patients in our study. The distribution of coagulopathy in intubated patients; 26% Disseminated Intravascular Coagulation, 17.9% Acute Coronary Syndrome, 10.5% Hemorrhage (inside or outside the body), 5.4% Pulmonary Embolism, 5% Heparin-Induced Thrombocytopenia, 3.5% Ischemic Stroke, 1.9% Hemorrhagic Stroke and 0.8% Deep Vein Thrombosis. When we compared the findings of our study with the data in the literature, our findings and the literature were mostly similar. In the study published by Jenner et al., which examined the relationship between thrombosis and COVID-19, 2929 patients were diagnosed with COVID-19; a thrombotic event was found to occur in 34% of the patients. Pulmonary embolism was observed in 12.6% of these patients, Acute Coronary Syndrome in 8%, and cerebrovascular accident in 3%[14]. In the study conducted by Lodigiani et al. with 388 patients diagnosed with COVID-19 and treated in intensive care; Pulmonary Embolism was detected in 7.7% of the patients, ischemic stroke in 2.5%, Acute Coronary Syndrome in 1.1% and Disseminated Intravascular Coagulation in 2.2% of the patients[15].

In our study, we found that 56.8% of intubated patients developed coagulopathy, whereas 32% of non-intubated patients developed coagulopathy. This difference was statistically significant. Of the 464 patients who died, 49.8% developed at least one coagulopathy condition. Of the surviving patients, 26.7% had at least one coagulopathy condition. This difference was statistically significant. When we compared gender and the development of coagulopathy; the relationship between gender and the development of coagulopathy was not statistically significant. We also found a statistically significant relationship between comorbidity and the development of coagulopathy. In our study, we found a statistically significant relationship between low hemoglobin levels and platelet count and the development of coagulopathy. In addition, the relationship between high ferritin, fibrinogen, d-dimer, and INR levels and the development of coagulopathy was statistically significant. Although we found that the CRP and ferritin levels of the patients were higher in those with coagulopathy, this difference was not statistically significant. In literature reviews, studies investigating the relationship between

the development of coagulopathy and intubation in patients diagnosed with COVID-19 are limited. However, we found a significant relationship between the development of coagulopathy and mortality, with or without COVID-19, and the findings were consistent with the literature. In the study conducted by Daughety et al. with 192 patients; it was determined that thrombosis occurred in 12% of patients diagnosed with COVID-19 and a hemorrhagic event occurred in 6.3% of patients treated in intensive care and a significant relationship was found between intubation and the development of coagulopathy. There was no significant relationship between the gender of the patients and the development of coagulopathy. A significant correlation was found between D-dimer elevation and the development of coagulopathy[16]. In the study conducted by Long et al. with 108 intensive care patients diagnosed with COVID-19; a significant correlation was found between high CRP, ferritin, INR and d-dimer levels and the development of coagulopathy[17]. In the study by Iba et al., a relationship was found between high fibrinogen levels, high d-dimer levels, low platelet counts, and coagulopathy seen during COVID-19[18]. In a meta-analysis of 11 cohort studies investigating the relationship between thrombosis and COVID-19 published by Chi et al.; a significant correlation was found between high D-dimer and low hemoglobin levels with thrombosis and mortality[19].

CONCLUSION

It is understood that coagulopathy, as well as respiratory failure, has a high impact on mortality in the course of COVID-19 disease. Considering these data, coagulopathy development and mortality rates can be reduced in patients diagnosed with COVID-19 by identifying comorbidities, closely monitoring clinical and laboratory parameters and taking necessary precautions in a timely manner.

Ethics Committee Approval: Our study has been approved by Ethics Committee at 15.12.2021 with file number 523.

Conflict of Interest: The authors declared noconflicts of interest.

Financial Disclosure: The authors declared thatthis study has received no financial support.

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