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The Retrospective Analysis of 54 COVID-19 Patients With Retroperitoneal Bleeding in One Center

Tek Merkezde Retroperitoneal Kanamalı 54 COVID-19 Hastasının Retrospektif Analizi

Yusuf Kasap[1], Muhammed Emin Polat[1], Kazim Ceviz[1], Lutfi Ihsan Boyaci[1], Emre Uzun[1], Samet Senel[1], Esin Olcucuoglu[2]

[1]Department of Urology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey
[2]Department of Radiology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey

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Corresponding Author: Muhammed Emin Polat / University of Health Science, Ankara City Hospital, Department of Urology, Ankara, Turkey / emnplt25@gmail.com / ORCID ID: 0000-0003-0271-0746

Abstract

Objective: We aimed to analyze and report the outcomes of patients with retroperitoneal bleeding (RPB) among our COVID-19 inpatients under anticoagulation therapy.
Materials and Methods: We retrospectively analyzed 54 patients who were anticoagulated with low- molecular-weight heparin (LMWH) and developed RPB during COVID-19 treatment in the hospital, either in intensive care unit or non-intensive care unit services, between March 2020 and March 2021. The patients' demographic and clinical data were analyzed, and we compared the laboratory results at the time of admission and during episodes of RPB. The patients were divided into conservative and interventional treatment groups. We compared the size of retroperitoneal hematoma, anticoagulant doses, erythrocyte suspension transfusion rates, presence of hyperinflammation syndrome between these groups. Also, treatment modalities and mortality status were shown. The hematoma size and erythrocyte suspension transfusion rates were compared between groups, and their correlation with anticoagulant dose and age were analyzed as well.
Results: In the management of RPB that developed, 48 (88.9%) patients were approached conservatively, 4 (7.4%) patients underwent angioembolization, and 2 (3.7%) patients laparotomy. Mortality was observed in 14 (25.9%) patients. Relevant laboratory parameters as lactate dehydrogenase, procalcitonin, interleukin-6 levels and lymphocyte counts were elevated exceedingly, while the hemoglobin values were significantly lower during episodes of RPB ($p=0.007$, $p=0.044$, $p=0.031$, $p=0.018$ and $p<0.001$, respectively). Also, there was a significant correlation between increased LMWH doses and size of the hematomas ($p=0.044$).
Conclusion: Patients experiencing RPB while receiving anticoagulants due to COVID-19 need active treatment depending on the dose of anticoagulants they are using. Considering the patient's clinical need, it may be a logical approach to start treatment with the lowest possible dose of an anticoagulant.

Keywords: heparin, anticoagulant treatment, COVID-19, retroperitoneal hematoma, mortality

Öz

Amaç: Yatarak tedavi gören COVID-19 hastalarımız arasında antikoagülan tedavi gören retroperitoneal kanamalı (RPK) hastaların sonuçlarını analiz ve rapor etmeyi amaçladık.
Gereçler ve Yöntemler: Mart 2020 ile Mart 2021 tarihleri arasında hastanemizde yoğun bakım veya yoğun bakım dışı servislerde COVID-19 tedavisi sırasında düşük molekül ağırlıklı heparin (DMAH) tedavisi ile antikoagülasyon sağlanan ve RPK gelişen 54 hasta retrospektif olarak incelendi. Hastaların demografik ve klinik verileri analiz edildi, başvuru ve RPK anındaki laboratuvar sonuçları karşılaştırıldı. Hastalar konservatif ve girişimsel tedavi gruplarına ayrıldı. Bu gruplar arasında retroperitoneal hematom boyutu, antikoagülan dozları, eritrosit süspansiyon transfüzyon oranları, hiperinflamasyon sendromu varlığı karşılaştırıldı. Ayrıca tedavi modaliteleri ve mortalite durumu da gösterildi. Hematom boyutu ve eritrosit süspansiyonu transfüzyon oranları karşılaştırıldı, antikoagülan dozu ve yaş ile korelasyonları analiz edildi.
Bulgular: Hastalarda gelişen RPK yönetiminde 48 (%88,9) hastaya konservatif olarak yaklaşıldı, 4 (%7,4) hastaya anjiyoembolizasyon, 2 (%3,7) hastaya laparotomi uygulandı. Mortalite 14 (%25,9) hastada gözlendi. Laboratuvar sonuçlarında RPK sırasında laktat dehidrojenaz, prokalsitonin, interlökin-6 düzeyleri ve lenfosit düzeyleri daha yüksek, hemoglobin düzeyi anlamlı olarak daha düşüktü (sırasıyla $p=0,007$, $p=0,044$, $p=0,031$, $p=0,018$ ve $p<0,001$). Ayrıca artmış DMAH dozu ile hematom boyutu arasında anlamlı bir ilişki vardı ($p=0,044$).
Sonuç: COVID-19 nedeniyle antikoagülan alan hastalarda aktif tedavi gerektiren RPK, antikoagülan dozu ile ilişkilidir. Hastanın klinik ihtiyacı göz önüne alındığında mümkün olan en düşük doz antikoagülan ile tedaviye başlamak akılcı bir yaklaşım olabilir.

Anahtar kelimeler: heparin, antikoagülan tedavi, COVID-19, retroperitoneal hematom, mortalite

ORCID ID:	Y. Kasap	0000-0001-5313-2611	L.I. Boyaci	0000-0002-4373-515X	S. Senel	0000-0003-2280-4192
	K. Ceviz	0000-0001-6343-383X	E. Uzun	0000-0002-3005-2122	E. Olcucuoglu	0000-0002-7883-6524

Introduction

COVID-19 is a widespread and life-threatening viral infection that frequently appears with respiratory symptoms and fever [1]. It can also affect other systems, such as cardiovascular, hepatobiliary, or hematologic systems [2,3]. Retroperitoneal bleeding (RPB) is another life-threatening condition that can manifest due to trauma, vascular lesions, tumors, surgical procedures, anticoagulant treatment, or idiopathic risk factors [2,4]. The hypercoagulable state occurs secondary to the effect of the virus or increased cytokine secretion [5]. Therefore, anticoagulant treatments are recommended widely in COVID-19 patients, and the risk of bleeding concomitantly increases [1,5]. Due to the thromboembolic complications and the bleeding risk of the viral infection, the predictability of bleeding is becoming an important issue requiring safe use of anticoagulants [1]. To predict and prevent this complication, we analyzed the clinical and laboratory results of 54 RPB cases among anticoagulated COVID-19 inpatients. We aimed both to describe incidence, morbidity, and mortality rates related to RPB, also search for factors that affect bleeding to improve clinicians' knowledge.

Materials and Methods

This study was approved by the local institutional review board (University of Health Sciences Ankara City Hospital, approval number- 2021/E2-21-229) and The Turkish Ministry of Health. It was carried out in accordance with the Basic Principles of WMA Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects.

A total of 16.211 inpatients diagnosed as COVID-19 based on the results of polymerase chain reaction (PCR) tests of nasopharyngeal swabs or computed thorax tomographies (CT Thorax) and started to receive anticoagulant treatment (low-molecular-weight heparin-LMWH) in our hospital between 12.03.2020- 12.03.2021 were analyzed. Among them, 3583 patients were treated in the intensive care units (ICUs). Fifty-four patients who developed RPB during follow-up were included in this study. Before hospitalization and treatment, the patients diagnosed with RPB and those already using LMWH due to other indications before the diagnosis of COVID-19 disease was made were excluded.

Data were retrospectively retrieved from the hospital's electronic database. We collected data related to demographic characteristics (age, gender), comorbidities, clinical symptoms (fever, cough, dyspnea, fatigue, myalgia), and results of relevant laboratory parameters [serum creatinine (SCr) (0.67-1.17), lactate dehydrogenase (LDH) (1-247 IU/L), international normalized ratio (INR) (0.8-1.2), activated partial thromboplastin time (aPTT) (9.8-14 second), fibrinogen (1.7-4.2 mg/dL), D-dimer (<550 ng/mL), procalcitonin (0-0.1 ng/mL), ferritin (22-322 µg/L), hemoglobin (13.5-17.2 g/dL), lymphocyte (1.1-4.5 x10^9/L), platelet counts (150-400 x10^9/L), C-reactive protein (CRP) (0-5 mg/L), interleukin-6 (IL-6) (0-50 pg/ml)] at admission and during RPB, radiological imaging (retroperitoneal hematoma size), and treatment protocols of the patients (conservative, angioembolization, laparotomy). Creatinine, LDH, INR, aPTT, fibrinogen, D-dimer, procalcitonin, ferritin, hemoglobin, lymphocyte, platelet, CRP, IL-6 values collected at both admission and during bleeding episodes, were compared.

The anticoagulation dose was determined in consideration of patients' body mass index (BMI) and risk factors for thromboembolism: increased D-dimer, fibrinogen levels, and thrombotic disease history.

Criteria of hyperinflammation syndrome were used to predict severity of COVID-19 infection. We described the hyperinflammation syndrome during the first hospitalization and bleeding episode with two or more of these criteria: LDH >300 IU/L, ferritin >500 mcg/L, D-dimer >1000 ng/mL, lymphocyte count <1000 cell/mm^3 [5].

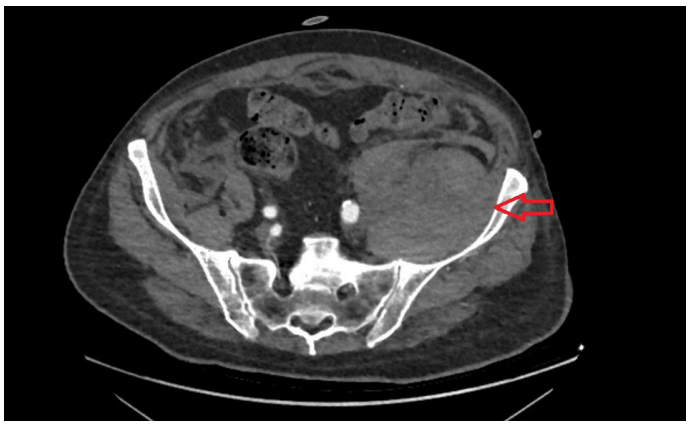

Figure 1. The arterial phase CT imaging of the retroperitoneal bleeding

Retroperitoneal hematoma was detected with CT scanner (Model: General Electrics-Revolution ES CT Scanner) of the abdomen (**Figure 1**). Length, width, and height of the retroperitoneal hematomas were measured. The greatest dimension measured was accepted as hematoma size. We defined the symptomatic period as the time elapsed between hospitalization and detection of the bleeding.

The patients were grouped according to the treatment they received (conservative treatment, angioembolization or surgical intervention: laparotomy) to analyze the factors affecting the requirement for treatment. Conservative treatment options indicated the cessation of anticoagulant treatment or decreasing its dose, follow-up of the immobilized patient and transfusions of blood products like erythrocyte suspension (ES), platelets or coagulation factors. Also, angioembolization of the active bleeding vessels and laparotomy to control bleeding were applied when transfusion rates of the patients increased enormously. Decreased hemoglobin values and the hemodynamic instability which was hardly managed with vasopressor medications were the main indications for intervention. Laparotomy was applied when interventional radiology was not available, and when surgical intervention for hemorrhagic complications is needed. When the interventional radiology was available, angioembolization was applied to these patients. However, the clinical picture did not allow us to use active treatment methods sometimes, for example in some patients we couldn't use any interventional method despite the need for increased rates, and amounts of ES transfusions and hemodynamic instability which didn't respond to the vasopressor treatment.

Table 1. Demographic, clinical, laboratory and treatment characteristics of patients

	Total (n=54)
Demographic data	
Age (year) (Mean ± SD)	70.7±12.8
Gender, female, n (%)	19 (35.2)
Comorbidities	
Hypertension, n (%)	36 (66.7)
Diabetes mellitus, n (%)	13 (24.1)
Asthma/COPD, n (%)	10 (18.5)
CAD, n (%)	20 (37)
CVA, n (%)	10 (18.5)
CKD, n (%)	13 (24.1)
Clinical data	
Fever, n (%)	13 (24.1)
Cough, n (%)	16 (29.6)
Dyspnea, n (%)	18 (33.3)
Fatigue, n (%)	12 (22.2)
Myalgia, n (%)	11 (20.4)
Symptoms duration (day) (mean)(min-max)	13 (1-29)
Hospitalization time (day) (mean)(min-max)	26 (0-95)
Mortality, n (%)	14 (25.9)
Laboratory results during admission and RPB time	
During admission LDH (IU/L) (median)(min-max)	344 (156-1038)
During RPB LDH (IU/L) (median)(min-max)	396.5 (207-16843)
p	**0.007**
During admission INR (median)(min-max)	1.1 (1-2.1)
During RPB INR (median)(min-max)	1.1 (0.8-3)
p	0.574
During admission D-dimer (ng/mL) (median)(min-max)	1515 (300-35200)
During RPB D-dimer (ng/mL) (median)(min-max)	2350 (510-709000)
p	0.253
During admission procalcitonin (ng/mL) (median)(min-max)	0.1 (0-511)
During RPB procalcitonin (ng/mL) (median)(min-max)	0.3 (0-11.7)
p	**0.044**
During admission ferritin (µg/L) (median)(min-max)	517 (31-4600)
During RPB ferritin (µg/L) (median)(min-max)	620.5 (68-111016)
p	0.056
During admission hemoglobin (g/dL) (median)(min-max)	12.2 (6.1-18.3)
During RPB hemoglobin (g/dL) (median)(min-max)	9.2 (4.1-13.6)
p	**<0.001**
During admission lymphocyte (cell/mm3) (median)(min-max)	735 (310-4280)
During RPB lymphocyte (cell/mm3) (median)(min-max)	850 (310-8780)
p	**0.018**

During admission IL-6 (pg/mL) (median)(min-max)	32.5 (2.8-992)
During RPB IL-6 (pg/mL) (median)(min-max)	36.8 (3-16241)
p	**0.031**
Medical treatment	
Anticoagulant dose (mL), n (%)	0.8 (0.4-1.2)
RPB treatment	
Conservative, n (%)	48 (88.9)
Angioembolization, n (%)	4 (7.4)
Laparotomy, n (%)	2 (3.7)

COVID-19: coronavirus disease-19; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; CKD: chronic kidney disease; ES: erythrocyte suspension; LDH: lactate dehydrogenase; INR: international normalized ratio; IL-6: interleukin-6; RPB: retroperitoneal bleeding

Table 2. Comparison of clinical data of patients

Retroperitoneal bleeding administration	**Conservative (n=48, 88.9%)**	**Angioembolization/Laparotomy (n=6, 11.1%)**	**p**
Retroperitoneal hematoma size (cm) (median)(min-max)	10.5 (2-32)	20 (6-25)	0.116
Anticoagulant dose (mL) (median)(min-max)	0.8 (0.4-1.2)	1.2 (0.8-1.2)	**0.016**
ES transfusion rates (Unit) (median)(min-max)	5 (0-24)	9 (6-15)	**0.01**
Hyperinflammation syndrome during admission, n (%)	38 (79.2)	5 (83.3)	0.646
Hyperinflammation syndrome during RPB, n (%)	40 (83.3)	5 (83.3)	0.685

COVID-19: coronavirus disease-19; ES: erythrocyte suspension

Table 3. Correlation of retroperitoneal hematoma size, anticoagulant dose, erythrocyte suspension transfusion rate and age

	Retroperitoneal hematoma size		**ES transfusion rate**	
	r	**p**	**r**	**p**
Retroperitoneal hematoma size			0.186	0.178
Anticoagulant dose	0.263	**0.044**	0.09	0.52
ES transfusion rate	0.186	0.178		
Age	0.162	0.242	0.005	0.971

aPTT: activated partial thromboplastin time; COVID-19: coronavirus disease-19**;** ES: erythrocyte suspension; RPB: retroperitoneal bleeding

Also, two treatment groups were compared according to the size of retroperitoneal hematomas, anticoagulant dose, ES transfusion rate**,** hyperinflammation syndrome present at both admission and during bleeding episodes.

The hematoma size and ES transfusion rates were compared between groups. Their correlation with anticoagulant dose and age was analyzed as well.

Statistical Analysis

SPSS 22 software (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA) package program was used for the statistical analysis. This SPSS program is a frequently used up-to-date program that yields accurate results. The conformity of the variables to the normal distribution was examined using the Shapiro-Wilk tests. Variables were expressed as mean ± standard deviation or median (minimum-maximum) values. Mann-Whitney U test was used to compare groups in terms of non-categorical parameters. Categorical variables were expressed as percentages. Fisher's exact tests were used to compare categorical variables. Wilcoxon test was used to evaluate the significance of the differences between both groups. Correlation between parameters was evaluated with the Spearman test. Cases with a p-value below 0.05 were considered statistically significant.

Results

The RPB was seen in a total of 54 patients including 38 patients hospitalized in ICU, and 16 in non-ICU services.

The mean age of the patients was 70.7±12.8 years, and the study population consisted of 19 (35.2%) female cases. All patients received anticoagulant therapy (LMWH) as part of their COVID-19 treatment. In addition to LMWH treatment, 21 patients who had coronary artery disease (CAD) and/or cerebrovascular accident (CVA) were using their routine acetylsalicylic acid containing drugs before bleeding. In the management of RPB, 48 (88.9%) patients were approached conservatively, 4 (7.4%) patients underwent angioembolization, and 2 (3.7%) patients laparotomy. Fourteen (25.9%) patients exited. Only one patient (16.6%) died after laparotomy among the interventionally treated patients. Furthermore, 13 patients (39.5%) died in the conservatively treated group.

We compared the laboratory data at the time of admission and during RPB. Accordingly, at the time of RPB, LDH, procalcitonin, IL-6 levels and lymphocyte levels were higher, while the hemoglobin values were statistically significantly lower ($p=0.007$, $p=0.044$, $p=0.031$, $p=0.018$ and $p<0.001$, respectively).

Demographic, clinical, laboratory data and treatment modalities of the patients are shown in **Table 1**. The anticoagulant dose and ES transfusion rates of the patients who required active treatment (angioembolization or laparotomy) due to RPB were higher than the patients who were approached conservatively ($p=0.016$ and $p=0.01$, respectively). There was no significant difference between these two groups regarding retroperitoneal hematoma size and the presence of hyperinflammation syndrome at the time of admission and RPB (**Table 2**). In the subsequent analysis, a positive correlation was found between the anticoagulant dose given to the patients and the size of the developing retroperitoneal hematoma ($r=0.263$, $p=0.044$) (**Table 3**).

Discussion

This study aimed to analyze the RPB complication in the COVID-19 patients who had undergone anticoagulant treatment due to a high risk of thrombosis [6]. The increasing rate of this condition causes unpredictable clinical deterioration and needs to be identified at an early stage [5]. Before this study, only case series were trying to identify and describe this condition [5,7]. To our knowledge, this is the first study that evaluates a large series of patients with RPB.

The most important cause of death in COVID-19 patients is thromboembolism due to the cytokine storm and altered coagulation profiles of the patients [1,8,9]. To avoid this complication, the authors have recommended anticoagulation treatment [10,11]. However, there is no standard dose that can provide a totally safe environment for patients because the clinic of each patient is unique, and the predisposition to this complication may vary [5,10]. In our study, the hematoma size increased with the increasing dose of the anticoagulant. The anticoagulant doses and the ES transfusion rates of the interventional treatment group were higher than the conservative group. So that, if we decrease the use of unnecessarily administered high-dose anticoagulants, we may treat RPB with only conservative treatment.

In a case series, incidence rate of RPB was declared as 7.6 per 1000 hospitalizations among patients infected with COVID-19 [5]. The rate of retroperitoneal bleeding was 0.10% among patients admitted to our hospital, especially to ICUs. Also, in all patients who underwent anticoagulant treatment, the rate of bleeding was 0.003%. It seems that the need for ICU may increase the rates of retroperitoneal bleeding. In ICUs, the increased cytokine storm of the patients and increased susceptibility to the DIC may make bleeding easier with anticoagulation.

For the treatment of RPB, there are different recommendations. Still, the first step must include conservative approaches like stopping the anticoagulant drugs, initiation of intravenous fluid resuscitation, balanced transfusion of ES and coagulation products in case of need, and monitorization of the immobilized patient to avoid additional trauma [1,5]. These first-step treatments are vital because if we control the bleeding, we can decrease the number of healthcare workers who will make therapeutic interventions [1]. However, if the patient needs an intervention for his/her survival, we need to choose the proper treatment modality according to the patient's clinical condition [5]. In our hospital, we applied laparotomy in 3.7% and angioembolization in 7.4% of the patients.

The other risk factors for RPB have been indicated as age, presence of comorbidities including hypertension (HT), chronic kidney disease (CKD) and diabetes mellitus (DM) [5]. Also, increased aPTT levels, and disseminated intravascular coagulation (DIC) increase the risk and worsen the prognosis of this condition [2,5,12]. In our results, the mean age of the patients was 70.7 years, and all of them were using LMWH. The patients had HT (6.7%), CAD (37%), and DM (24%). We did not find a significant difference between aPTT values of the patients during the bleeding episodes, but LDH, procalcitonin, lymphocyte and IL-6 values were significantly higher in these patients during the bleeding period compared to their baseline values. We think that proinflammatory cytokines like IL-6, indicators of hyperinflammation syndrome like LDH-lymphocyte count and procalcitonin levels which indicate increased level of infection may provide information about propensity for the retroperitoneal hemorrhage parallel to the severity of infection.

Our study also has limitations. First of all, our study was designed retrospectively. In addition, the small number of patients is one of the limitations. Due to the restriction of the data, we could not analyze the non-RPB control group. However, we think that our study will be an essential source for the RPB clinic, as this study was performed during COVID-19 epidemic with the highest number of patients reported in the literature.

Conclusion

Patients experiencing RPB while receiving anticoagulants due to COVID-19 need active treatment depending on the dose of anticoagulants they are using Considering the patient's clinical need, it may be a logical approach to start treatment with the lowest possible dose of an anticoagulant. Nevertheless, we need more studies to identify a safe dose of LMWH treatment. Also, the clinicians must be aware of this complication and its risk factors. They must not hesitate to make interventions to decrease the mortality rates due to RPB in case of need.

Ethics Committee Approval: This study was approved by University of Health Sciences Ankara City Hospital Review Board (approval date and number 07.04.2021/E2-21-229) and Turkish Ministry of Health.
Informed Consent: An informed consent was obtained from all the patients or relatives.
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Peer-review: Externally and internally peer-reviewed.
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