

## Spontaneous Intramuscular Hematomas in Patients with Severe COVID-19 (Case Report)

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## Спонтанные внутримышечные гематомы у пациентов с тяжелым течением COVID-19 (клиническое наблюдение)

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### Summary

**Aim of the study.** To evaluate the risk factors for the occurrence of intramuscular hematomas in patients with severe coronavirus infection receiving anticoagulant therapy.

**Materials and methods.** Intramuscular hematomas in five patients with severe COVID-19 disease are reported in the paper. The criteria for selecting patients for the study included respiratory distress requiring oxygen, radiographic signs of severe pneumonia, anticoagulant therapy using low molecular weight heparin (LMWH), and spontaneous intramuscular hematoma. Clinical manifestations, blood coagulation results, conservative and surgical management were analyzed.

**Results.** Standard regimen anticoagulation therapy in patients with coronavirus infection requires vigilance because of a risk of development of hemorrhagic complications.

**Conclusion.** When assessing a patient with hematomas, an emphasis should be given to examination of patients and changes in hemoglobin and hematocrit levels. Best strategy of anticoagulant therapy for patients with coronavirus infection and high risk of VTE, as well as optimal laboratory monitoring during LMWH administration are yet to be explored.

**Keywords:** intramuscular hematoma; anticoagulant therapy; coronavirus infection

**Conflict of interest.** The authors declare no conflict of interest.

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### Introduction

Coagulopathy and thrombotic complications are severe complications of coronavirus infection [1]. Disorders of blood coagulation system occurring in SARS-CoV-2 infection result from immune and cellular elements of disease pathogenesis [2]. Vascular manifestations of COVID-19 are associated with thrombus formation both in the microcirculatory system and in large vessels with a variety of clinical manifestations including pulmonary, gastrointestinal, cardiovascular, and neu-

rological ones. Venous and arterial thrombosis, emboli, parenchymal infarcts, erythematous lesions occur in patients [2]. Coagulopathy in COVID-19 associates with a high risk of death. Analysis of autopsy data of patients who died from COVID-19 indicates multiple thromboses of small pulmonary vessels and associated multiple hemorrhages in alveoli, as well as neoangiogenesis, alongside with diffuse alveolar damage [3]. Prolonged bed rest, vascular catheters, severe baseline comorbidities (cardiovascular diseases, obesity, diabetes mellitus), frequent glucocorticoid therapy also con-

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tribute to thrombotic complications. According to the Temporary Guidelines of the Russian Ministry of Health, low molecular weight heparins (LMWH) or unfractionated heparin (UFH), at least in preventive doses, are indicated for all hospitalized patients, unless there are contraindications. LMWH are preferable, UFH is used when they are unavailable or in severe renal failure [3]. Thus, anticoagulation is mandatory in patients with COVID-19. The dosage of heparin could be increased to an intermediate or therapeutic level in patients with high and extremely high D-dimer level or if additional risk factors of venous thromboembolic complications are present, as well as in severe COVID-19 or in patients admitted to ICU. In patients with obesity (body mass index  $> 30 \text{ kg/m}^2$ ), a 50% increase in the prophylactic dose should be considered. The use of anticoagulants in severe COVID-19, especially in progressive elevation of D-dimer level significantly improves patient survival rates [1, 4]. For critically ill patients (i.e., those admitted to intensive care unit) with confirmed or highly probable COVID-19, increased doses of LMWH to prevent VTE are also recommended by international clinical protocols [4].

The use of anticoagulants associates with an increased risk of hemorrhagic complications, primarily gastrointestinal (GI) bleeding. Besides, intramuscular hematomas of various localizations related to anticoagulant administration have been described in COVID-19 patients [5, 6, 7–10]. In some cases patients received anticoagulant therapy in combination with antiaggregant agents [11]. When there are no external signs of hematoma, this complication can present with nonspecific signs and symptoms, such as anemia, low back and anterolateral abdominal discomfort and paresthesia, and hypogastric pain, or, exceptionally, hemodynamic instability with hypovolemic (hemorrhagic) shock [5, 8–13].

This paper reports a series of five clinical cases of hemorrhagic complications of coronavirus infection in patients on anticoagulant therapy.

## Material and Methods

We retrospectively analyzed intramuscular hema-tomas in five of 66 patients with the novel coronavirus infection treated in the Department of Critical Care and Anesthesiology of the A. L. Polenov Russian Research Neurosurgical Institute, a branch of the V. A. Almazov Scientific Research Center. The work was performed in accordance with the requirements of the Declaration of Helsinki of the World Medical Association (2013). The mean age of the patients was  $68 \pm 4.7$  years, of whom 35 were men and 31 were women. The most frequent comorbidities were hypertension (43 patients), coronary heart disease (35 patients), type 2 diabetes mellitus (15 patients), chronic pyelonephritis (11 patients), and 3–4 degree obesity (8 patients). All patients received therapy, including anticoagulants, according to the temporary guidelines on prevention, diagnosis and treatment of the novel coronavirus infection (COVID-19) (Version 9), as well as in accordance with the local protocol of the V. A. Almazov Scientific Research Center. The patients had no GI hemorrhages, but five of them developed intramuscular hematomas of various localizations. Hematomas occurred in the pectoral muscles (2 cases), anterior abdominal wall muscles (two cases), right psoas muscle (1 case).

The criteria for selection of patients for the study included respiratory failure requiring oxygen therapy, radiological signs of severe pneumonia (CT grade 3–4 according to semi-quantitative visual assessment scale), anticoagulant therapy with LMWH, and spontaneous intramuscular hematoma(s).

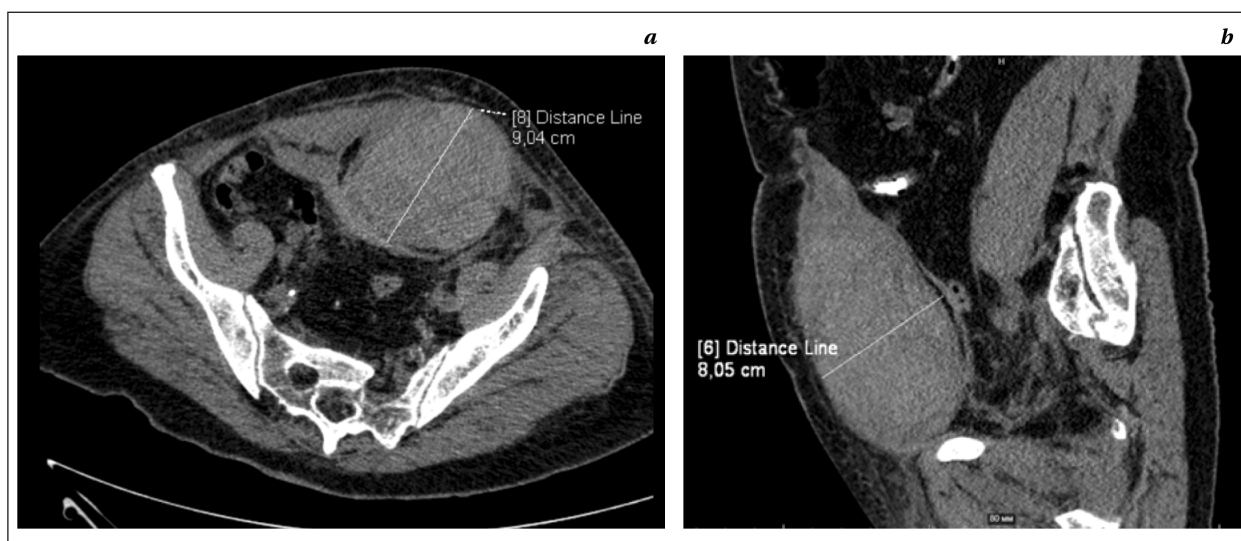


Fig. 1. Anterior abdominal wall hematoma: axial section (a), sagittal section (b). Patient T. (clinical case 1).

## Clinical case 1

Patient T., male, 61 years old, hospitalized on day 12 from the onset of the disease. Patient's weight was 75 kg, height was 168 cm (BMI 26.6). On admission to the hospital, the patient had a positive RT-PCR for SARS-CoV-2 RNA. On chest CT scan the total pulmonary involvement was 76% (CT grade 3 according to the semi-quantitative visual assessment scale), respiratory rate was 24 per minute, SpO<sub>2</sub> was 70% on ambient air. The patient was admitted to the intensive care unit immediately from the emergency department. On day 2 after admission the noninvasive lung ventilation (NILV) was started, which continued for 8 days, and then high-flow oxygen therapy through nasal cannulas was administered for 4 days. To control agitation and prevent SILI (self-inflicted lung injury), the patient received fentanyl by microinfusion at the rate of 0.5–0.6 µg/kg/h in combination with dexmedetomidine 0.3 µg/kg/h during 8 days of NILV. This regimen allowed maintaining a sedation level of -2 to -1 on the RASS scale and 2 to 3 on the Ramsay scale. The patient received anti-inflammatory (glucocorticoids), antihypoxic (cytoflavin), gastroprotective, anticoagulant, fluid therapy, and mucolytics. The patient was in prone position most of the day. On day 23 from the onset (day 11 of hospitalization), the patient complained of severe pain in the left iliac and suprapubic region. The pain worsened with coughing and straining (the patient had constipation, medication therapy and enemas were used). On ultrasonic examination of the abdomen, a nonhomogenous cylindrical mass 160×70 (max) mm with clear, rather straight outlines was revealed in the left iliac region 2–8 mm deep. On chest CT anterior abdominal wall hematoma 350 ml in volume was found (Fig.1, *a* and *b*). A decrease in Hb from 142 to 125 g/l was also noted. After consultation with a surgeon, watchful waiting with conservative management strategy was chosen. Follow-up abdominal CT and soft tissue ultrasound examination 4 and 12 hours after initial investigations showed no change in the size of the mass and no signs of active bleeding.

However, taking into account the persistent pain and the risk of hematoma expansion, surgical intervention was performed on day 3 after hematoma detection which included dissection, revision, hemostasis and drainage. Under general anesthesia a 12 cm long pararectal incision on the left side was made, the skin, subcutaneous fatty tissue, the anterior wall of the sheath of rectus abdominis muscle were dissected. On opening the sheath, the hematoma 300 ml in volume containing clots was revealed. The clots were removed. The rectus abdominis muscle was partially disintegrated with frayed fibers and blood seeping from the muscle. Hemostasis using electrocoagulation and suturing was performed. The wound was sutured in layers. Aseptic dressing was applied. Postoperative drain was removed on day 2 after the surgery. Transfusion of 2 units of packed red blood cells and one unit of fresh frozen plasma (FFP) was done. The patient was transferred to the specialized department. On day 35 of hospitalization the patient was discharged with improvement.

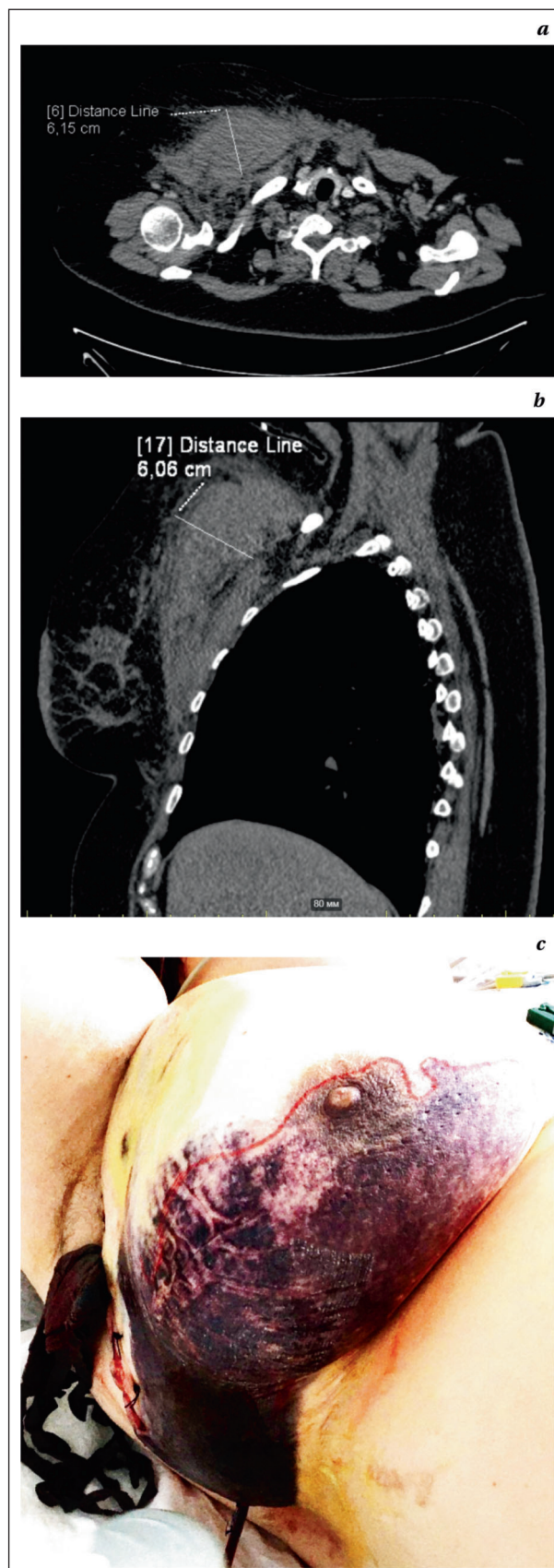


Fig. 2. Subpectoral hematoma: axial section (*a*), sagittal section (*b*) and soft tissue hematoma in the breast area (*c*). Patient M. (clinical case 2).





**Fig. 3. Hematoma of the anterior abdominal wall, axial section. Patient B. (clinical case 3).**

From the first day of admission the patient received anticoagulant therapy with nadroparin calcium 0.6 ml twice a day, on the day of surgery the anticoagulant was discontinued, the next day after surgery the therapy was resumed in a dose of 0.4 ml twice a day, starting from the 4<sup>th</sup> day — 0.6 ml twice a day. This strategy was chosen due to high risk of thrombosis and absent clinical and laboratory signs of hypocoagulation.

### Clinical case 2

Patient M., female, 63 years old, was admitted to hospital with bilateral viral pneumonia. Weight 108 kg, height 157 cm (BMI 43.8). Her comorbidities included 3<sup>rd</sup> degree obesity and chronic kidney disease. Repeated RT-PCR of oropharyngeal swab specimens was negative for SARS-CoV-2. On day 11 from the disease onset, she was admitted to an infectious diseases ward. On admission, chest CT showed 80% lung involvement (CT grade 4 according to the semi-quantitative visual assessment scale). On day 14 (day 3 of admission) she was transferred to the ICU due to progressive respiratory failure. After 7 days of high-flow oxygenation and intensive therapy, the patient stabilized, and the lung involvement decreased down to 60% according to chest CT. Glucocorticoids, antibacterial drugs (for 5 days), combination antihypertensive, anticoagulant (therapeutic dosage) therapy were administered, additionally, the patient received mucolytics.

On day 22 she was transferred to the general ward. On day 28 from the onset of the disease (day 17 from admission to the hospital) persistent hypotension was observed. Laboratory examination revealed reduced hemoglobin and hematocrit (initial Hb 100.0 g/l and Ht 27.9 dropped to Hb 84 g/l, Ht 24). On chest CT, right subpectoral hematoma (6.5×12×15.5 cm) was found (Fig. 2, *a-c*). Surgical intervention was performed urgently and included revision, debridement, and wound packing. Skin and subcutaneous tissue were dissected with a 12 cm incision in the lateral tho-

racic region. The subcutaneous tissue was soaked with blood. The spaces below the mammary gland, between the pectoralis major and minor muscles, and below the small pectoral muscle was separated. 500 ml of liquid blood and clots were evacuated. The wound was drained, diffuse blood oozing from the muscles was noted, and visible sources of bleeding were coagulated. Despite coagulation, sluggish diffuse blood seeping was observed. Packing of all previously separated spaces was performed using 3 45×45 cm surgical sponges. Active Redon drainage was placed under the mammary gland. The wound was loosely sutured. In the early postoperative period, a total of 5 units of FFP and 4 units of packed RBCs were transfused.

Later the patient was transferred to the surgical department, the wound was drained with a VAC system on day 17 after surgery, the patient was discharged on day 30 after surgery (day 47 from admission).

### Clinical case 3

Patient B., female, 58 years old, was hospitalized on day 9 from the onset of the disease in the infectious disease unit. On admission, the chest CT showed 54% lung involvement. SARS-CoV-2 RT-PCR was positive. The patient's weight was 55 kg, height was 168 cm (BMI 19.49). Comorbidities included varicose veins of the lower extremities. Anti-inflammatory (steroid) and anticoagulant (therapeutic dosage) therapy was started. Due to severe systemic inflammatory response and evidence of «cytokine storm», olokizumab was prescribed with a positive effect.

On day 4 of hospitalization, the patient felt sharp pain in the left iliac region. Examination of the hypogastrium revealed a hematoma about 9×5 cm in size. Laboratory tests showed Hb decrease from 140 to 105 g/l. On chest CT, a hematoma 54×29×104 mm of the anterior abdominal wall in the left rectus abdominis muscle region was found (Fig. 3). Emergency surgical intervention was performed which consisted of dissection, debridement, and drainage of the



**Fig. 4. Subpectoral hematoma. Patient T. (clinical case 4).**

hematoma of the anterior abdominal wall. The hematoma of the left rectus abdominis muscle 20×15 cm in size was opened along the linea alba below the umbilicus. About 400–500 ml of liquid blood was released. The rectus abdominis muscle was soaked with blood. In the middle third of the muscle, a vessel of less than 1 mm was identified amid the muscle, which was the source of active bleeding. The vessel was sutured. Hemostasis was achieved. Aponeurosis and skin were sutured. Intraoperative transfusion of 1 unit of packed RBCs and 2 units of FFP was performed. In the early postoperative period, 600 ml of hemorrhagic discharge was drained. Subsequently, repeated surgical interventions were performed three times (6 hours after the first surgical intervention, on day 6 and 8) for surgical revision of hematoma, stopping the bleeding, and packing the rectus abdominis muscles. Anticoagulant therapy was adjusted: LMWH was withheld for the first two days after the bleeding, and then, due to the high risk of thrombotic complications, it was restarted in a prophylactic regimen. The total volume of transfusions during the treatment was 7 units of FFP, 7 units of packed red blood cells. The patient's condition was stable thereafter, treatment continued in the specialized ward. The wound healed by secondary intention. On day 36 the patient was discharged.

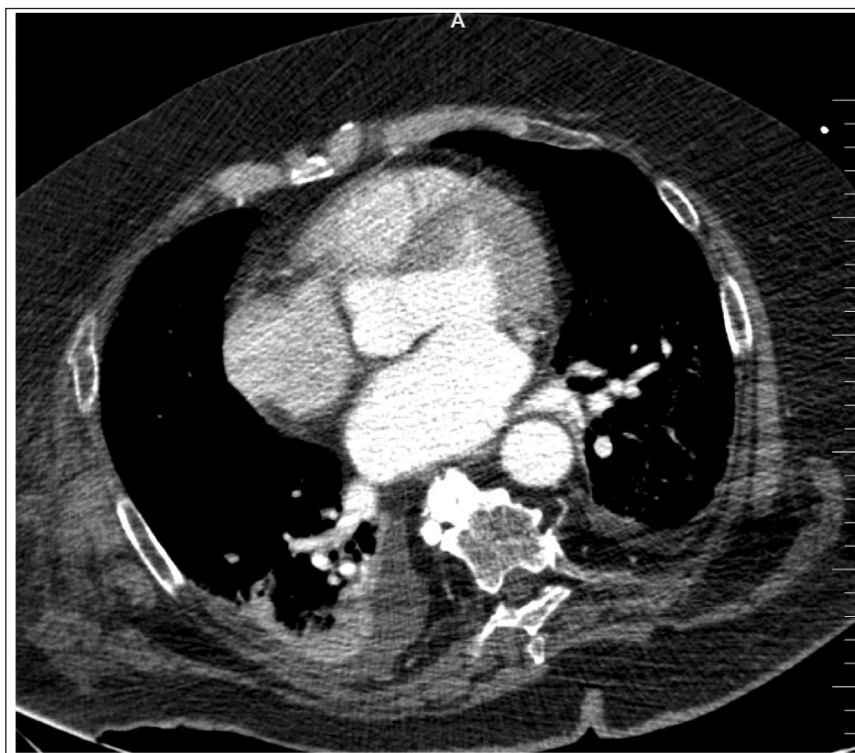
#### Clinical case 4

Patient T., female, 73 years old, was admitted to the infectious disease department on day 10 from the onset of disease. Chest CT revealed 70% of lung involvement (CT grade 3 according to the semi-quantitative visual assessment scale). RT-PCR for SARS-CoV-2 was

positive. The patient's weight was 60.0 kg, height was 154 cm (BMI 25.3). The patient received anti-inflammatory (glucocorticoids), gastroprotective, anticoagulant therapy (in therapeutic regimen), and mucolytics. On day 21, follow-up chest CT scan revealed a fluid-containing abnormal mass located under the right pectoralis major and extending into the retro-mammary space 103×47×139 mm in size (Fig. 4). On the following day the subcutaneous hematoma increased to 128×81×156 mm. On palpation the mass was hard and protruding from under the lateral edge of the pectoralis major muscle. Patient's hemoglobin dropped from 123 to 87 g/L. Surgery was performed and included dissection, debridement, stopping the bleeding, and drainage. The skin and subcutaneous fatty tissue were dissected along the right anterior axillary line. The hematoma was dissected, 450 ml of lysed blood with clots was evacuated. The source of active bleeding was not identified. The surrounding tissues were markedly soaked with blood, scattered areas of active bleeding were spotted and coagulated. Two units of packed red blood cells were transfused. The postoperative period was uneventful. Anticoagulant therapy was withheld on the first day after surgery, then it was resumed in prophylactic regimen. The drainage was removed on the 2<sup>nd</sup> day. On day 29, the patient was discharged.

#### Clinical case 5

Patient T., male, 74 years old, was admitted to the intensive care unit on day 10 from the onset of the disease. RT-PCR for SARS-CoV-2 was positive. The chest CT showed that lung involvement was 80% (CT IV according to the semi-quantitative visual assessment system). Pa-



**Fig. 5. Soft tissues of the lumbar area soaked with blood and hematoma in the psoas major muscle. Patient T. (clinical case 5).**

tient's weight was 120 kg, height was 173 cm (BMI 40.09). Hypertension, chronic heart failure, rapid atrial fibrillation, 3<sup>rd</sup> degree obesity, and linea alba abdominal hernia were among comorbidities.

Before admission, the patient had been taking warfarin 5 mg continuously for a long time. The following coagulation test results were obtained on admission: APTT 47.8 s, prothrombin time 38.4 s, prothrombin (according to Quick) 18.00%, INR 3.40. Warfarin was discontinued due to the prescription of LMWH in a therapeutic dosage. On days 3 and 4 of hospitalization, due to progressive consumption coagulopathy (evidenced by further decrease in fibrinogen, increase in INR, and prolongation of prothrombin time) the dosage of LMWH was adjusted and transfusion of FFP was performed. Intensive therapy included anti-inflammatory (glucocorticoids), anticoagulant, antihypoxant, antihypertensive, antibacterial medications (both for bacterial superinfection of lungs and urinary tract infection). Propofol sedation was administered to relieve psychomotor agitation and discontinued after selection of neuroleptic drug. The patient received high-flow oxygen therapy for 16 days. Considering obesity and large umbilical hernia, the prone position was not easy to maintain, the patient was mostly in the lateral and supine position.

On day 21 of hospitalization, examination revealed a hematoma in the right lumbar region (Fig. 5). There were no complaints. Chest CT scan demonstrated hematoma in the right psoas muscle 110×50×45 in size. There was no evidence of extravasation. Consulting surgeon recommended conservative management. Follow-up CT (on days 17 and 26 from the hematoma formation) showed hematoma without worsening, its size was

115×56×52 mm. The right kidney and ureter were displaced laterally due to expansion of the right psoas muscle. Renal excretory function was intact. Serial CT and ultrasound examinations indicated stable size of hematoma with signs of lysis. The size of subcutaneous hematoma increased, but there was no damage to the skin integrity. Transient hematuria was noted. Anticoagulation was adjusted according to the results of coagulation tests and withheld for a short period of time if needed. On day 57 of hospitalization the patient was discharged.

## Results

We analyzed possible risk factors for intramuscular hematomas. In all five clinical cases described, hematomas occurred with underlying anticoagulant therapy with LMWH administered in therapeutic doses due the high risk of thromboembolic complications. In patient from case 1 we initially considered possible link of hematoma with the technique of LMWH injection (into the anterior abdominal wall), but this hypothesis was rejected due to the deep localization of hematoma.

The data presented in Table show that intramuscular hematomas occurred with normal values of the routine coagulation tests, only in patient 5 a prolonged APTT was revealed. We should note that the measurement of individual coagulation factors was not performed due to technical reasons. The



**Coagulation test results and platelet counts in patients at the moment of diagnosis of hematoma.**

Test values	Values				
Patient	1	2	3	4	5
Prothrombin time, s	12.8	12.1	11.2	10.2	14.2
Prothrombin, %	84	93	106	129	86
INR	1.1	1.04	0.96	0.87	1.09
APTT, s	27.7	36.9	24.5	19.5	45.8
Fibrinogen, g/l	3.57	2.20	2.15	3.55	3.15
D-dimer, ng/ml	1798	511	1840	887	1730
Platelet count, $\times 10^9/l$	223	253	315	199	114

direct anticoagulants enoxaparin and nadroparin are known to block the Xa and IIa factors. The use of anti-Xa activity to monitor the therapeutic effect of LMWH in patients with COVID-19 seems more reasonable, as it reduces the risks of hemorrhagic complications [2, 4]. However, this test is performed in a limited number of laboratories and is relatively expensive compared to routine coagulation tests. Platelet count was also in normal range in all patients. Notably, patients with novel coronavirus infection are generally characterized by a decreased platelet count, which does not manifest clinically in most cases.

Apparently, the localization of hematomas was to some extent due to positional factors coupled with muscle strain in particular area. The subpectoral hematomas may have been precipitated by turning laterally. Interestingly, subpectoral hematomas were found only in women which is consistent with the other observations found in the literature [14]. The loss of blood vessel elasticity and lack of muscle elasticity, which are more commonly observed in the elderly, have also been reported in the literature as risk factors for hematoma development [14].

All patients had no other hemorrhagic complications, only the patient from case 5 had transient macrohematuria. In all cases the development of hematomas was clinically significant and accompanied by hypotension and severe anemia requiring blood transfusion. Surgical treatment of hematomas was indicated in 4 cases, moreover, repeated surgical interventions were required in 2

cases. All surgeries were performed under general anesthesia, with tracheal intubation and mechanical ventilation. Fentanyl or ketamine as well as propofol were used at the induction and anesthesia maintenance stage; rocuronium was used as a muscle relaxant. Despite severe viral lung injury there was no need in prolonged lung ventilation in postoperative period, all patients were extubated at the end of surgery, blood acid-base status remained stable, respiratory failure did not progress, and the oxygen therapy through nasal cannulas was continued in the postoperative period. Active drains were left in the wound in the postoperative period, otherwise wound packing was used, followed by stepwise removal of internal dressing.

## Conclusion

Intramuscular and subcutaneous hematomas are uncommon but severe complications of coronavirus infection in patients receiving LMWH at therapeutic doses. High index of suspicion should be maintained in patients with COVID-19 regarding the risks of hemorrhagic complications. Physical examination and serial assessment of hemoglobin and hematocrit changes are crucial for the timely diagnosis of hematomas. Best strategies for anticoagulation in patients with coronavirus infection and high risk of VTE, as well as laboratory monitoring of LMWH use are yet to be explored.

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