



Research article

Association of major postoperative wound and anastomotic complications in thoracic surgery with COVID-19 infection[☆]

Kajetan Kiełbowski^a, Małgorzata Wojtyś, MD, PhD^{a,*}, Konstantinos Kostopanagiotou, MD, PhD^b, Henryk Janowski, MD, PhD^a, Janusz Wójcik, MD, PhD^a

^a Department of Thoracic Surgery and Transplantation, Pomeranian Medical University, Szczecin, Poland

^b Department of Thoracic Surgery, Attikon University Hospital, Athens, Greece



ARTICLE INFO

Article history:

Received 21 June 2022

Received in revised form 22 September 2022

Accepted 11 October 2022

Available online 07 November 2022

Keywords:

Thoracic surgery

Covid-19

Thoracotomy dehiscence

Anastomosis dehiscence

ABSTRACT

Background: One of the most uncommon manifestations of perioperative Covid-19 infection is impaired wound healing. The aim of this study is to present previously unreported observation of thoracotomy and esophageal anastomosis dehiscence in the course of Covid-19 infection after uncomplicated thoracic surgeries.

Methods: This is a single-center study describing unusual wound and anastomosis complications in COVID-19 patients after uncomplicated thoracic surgeries. Medical data was prospectively collected and retrospectively reviewed. All patients admitted to the hospital were symptom free and tested negative for COVID-19 infection preoperatively. Clinical courses were compared to a non-infected control group from historical data.

Results: The total of 14 patients were included. Study group involved 7 patients with major wound and anastomosis complications concurrent with COVID-19 infection. Control group was composed of 7 patients matched with the type of surgeries and treated before Coronavirus pandemic. Surgeries included lung transplantations, lung cancer surgeries and esophagectomies. The mean age of the study group was 65.7 years. Major wound and anastomosis complications occurred 13.6 days postoperatively while the mean time of Covid-19 detection was 21 days. The course of infection varied from mild to very severe which resulted in 3 deaths due to COVID-19 induced ARDS. The mean time of hospital stay was 40,9 days. There were no differences between both groups in baseline characteristics while hospitalization time was significantly longer in the study group.

Conclusions: COVID-19 infection should be included in differential diagnosis in postoperative patients with major wound or anastomosis complications.

© 2022 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

In late 2019, a Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) originating in China caused an out of proportion global pandemic [1]. It brought new obstacles in surgical departments, as many wards had to close during infection peaks. Elective surgeries have been delayed or canceled, resulting in a significant volume reduction of performed surgeries [2]. Perioperative COVID-19 infection is another challenge and has been associated with increased risk of developing postoperative pneumonia, respiratory failure, and sepsis [3]. COVID-19 infection is considered as endothelial disease and number of autopsies have revealed microthrombi formation in various organs

[4]. Furthermore, SARS-CoV-2 can induce damage to microvasculature and infection might present only as a skin manifestation [5]. The aim of this study is to describe wound and anastomosis dehiscence correlating with SARS-CoV-2 infection and raise awareness on the issue.

Materials and methods

This is a single-center study in which we have reviewed clinical data of COVID-19 patients who postoperatively developed major wound and anastomosis complications between October 2020 and January 2022. Reviewed procedures included thoracotomies, lung transplantations and esophageal surgeries. All patients were symptom free and had a negative RT-PCR swab COVID-19 test on admission. Clinical courses were compared to a non-infected control group from historical data (2018 and 2019). Most of the analyzed measurable variables showed normal distribution ($p > 0.05$ for the Shapiro-Wilk test). Therefore, the parametric t test was used to compare the groups. In other cases, Mann Whitney U test was applied. Nominal variables were presented

[☆] Single-center study with literature review describing perioperative Covid-19 infection at the department of thoracic surgery manifesting as major wound and anastomosis complications.

* Corresponding author at: Department of Thoracic Surgery and Transplantation, Pomeranian Medical University, Alfreda Sokółowskiego 11, 70-891 Szczecin, Poland.

E-mail address: margaretkaw@wp.pl (M. Wojtyś).

as counts, and chi-square test was used to compare their distribution between groups.

Results

The total of 14 patients were included. Both groups were composed of 7 patients each. Study group involved infected patients with sudden and unexplained major wound and anastomosis complications (A, B, C, D, E, F and G). Mean age of those patients was 65.7 years. 6 were males and only 1 female. Preoperatively, there were no indications of potential impaired wound healing as mean BMI, preoperative serum protein and glycemia of those patients were 25.11, 7.08 g/dL and 112.71 mg/dL respectively. Additionally, 2 patients preoperatively were treated with chemotherapy. Patients A and B underwent lung transplantations (LuTx) due to pulmonary artery hypertension and nonspecific interstitial pneumonia, respectively. Patient C and G underwent lung cancer surgery while D, E and F esophagectomies. Major wound and anastomosis complications appeared in all patients ranging from 1 to 34 days postoperatively (mean 13.6). There were no prior signs of potential suppuration. Sternal wires did not completely stabilize sternum in patient B. Total dehiscence of anterior wall of esophagogastric anastomosis developed in patient E. Patient G developed wound complications accompanied by bronchopleural fistula due to persistent air leak from the bronchial stump. Six patients required subsequent explorative rethoracotomy (A, B, C, D, E, G). Patient E underwent repair of anastomosis rupture and Patient G required revision of the bronchial stump. Vacuum assisted closure (VAC) therapy was introduced in patients E and F. Esophageal stent was applied in patient F. All patients with unexplained major wound and anastomosis complications were tested positive for COVID-19 infection with RT-PCR test between 9 to 37 days after initial surgery (mean 21) or 2 to 12 days after dehiscence of thoracotomy or anastomosis (6, 3, 4, 9, 7, 12, 12 days respectively). During this period, radiological examinations (x-ray, CT) revealed pneumothorax (A, C, E, F, G), ground glass opacities (A, B, E, F), atelectasis (B, D, E) or subcutaneous emphysema (A). Two patients (B, D) required admission to the intensive care unit (ICU) for 10 and 5 days, respectively. Patient E did not qualify for the ICU admission. 3 patients died and 4 completed the treatment. They were discharged from the hospital on postoperative days 35, 37, 58 and 73. COVID-19 management differed among patients. Remdesivir therapy was administered in patients A and F. Patients C and E were treated with dexamethasone while patient C also received tocilizumab. Three patients (B, D, F) received oxygen therapy using AirVo machine. Patient G did not require oxygen therapy (Table 1). Control group was composed of 7 patients matched with the type of surgeries and treated before Coronavirus pandemic. Mean age of the control group was 62.42 years, 5 patients were males and 2 females. Mean BMI of the group was 24.98. Preoperative values of serum protein were within normal ranges in all patients (mean 6.93 g/dL). 4 out of 7 patients were active smokers. The only complication in this group was a spleen injury in patient F (Table 2). Mean postoperative hospitalization time was 18 days and it was statistically shorter than COVID-19 patients ($p = 0.02$). There were no differences between both groups in age, BMI, preoperative serum protein, glycemia, and frequencies of active smoking or preoperative chemotherapy. Furthermore, wound complications and COVID-19 infection were associated with increased CRP and leukocytosis in the postoperative period of 30 days compared to patients with uncomplicated surgeries ($p = 0.0003$, $p = 0.02$ respectively, Table 3).

Certain laboratory results are typically altered during COVID-19 infection. Figs. 1, 2, and 3 depict laboratory findings and its changes over time in study and control groups. Inflammatory markers - C-reactive protein (CRP) and white blood cells were elevated in the perioperative period in both groups. However, those values were higher and lasted longer in COVID-19 patients ($p = 0.0003$, $p = 0.02$ respectively). D-dimers, Interleukin-6 (IL-6) and lactate dehydrogenase (LDH) started being examined around the time of positive COVID-19 infection. D-

dimers were elevated in five patients in the study group (A, B, C, D, G), overcoming 5000 $\mu\text{g/L}$ in patient B. Similarly, LDH were increased in patients A, B, C and D. IL-6 was elevated in patient A, B, C, and F. Mean time of complications onset was 13.6 days after surgery. In the COVID-19 group, CRP and leukocytosis values were highly elevated on POD 11–15. On the other hand, values of inflammatory markers in the control group were systematically decreasing after surgery. CRP and leukocytosis values were significantly decreased in the control group compared to the infected patients on POD 11–15 ($p = 0.00001$, $p = 0.004$ respectively).

Discussion

The presented study describes the clinic course for seven patients with unusual wound and anastomotic complications. Dehiscences were sudden and unexplained due to lack of suppuration or tissue necrosis. They involved sutures in cutaneous, subcutaneous and muscle layers. In addition, there were negative post-surgical wound swab cultures. Total postoperative surgical approach dehiscence was strongly correlated with COVID-19 infection. Such complications have not existed prior to the pandemic in the regular postoperative course of patients in our center. At the same time, approximately 5–6% of patients had typical postoperative wound complications with suppuration, necrosis, and infection. Nevertheless, those cases included moderate dehiscence and not complete opening of the surgical approach. In case of esophagectomies, spontaneous bleeding from thoracotomy did not appear in any of the procedure performed before the pandemic. In addition, dehiscence in described patients was almost complete. Typical anastomotic leak is usually minor or moderate.

According to a recent study published by The Cardiothoracic Interdisciplinary Research Network and COVID Surge Collaborative, wound dehiscence occurred in approximately 2% of patients with infection diagnosed preoperatively and in about 4% of positive cases identified postoperatively [6]. Postoperative surgical wound dehiscence was presented in an article by Sharma et al. Out of 793 patients undergoing cancer surgeries, 8 presented unusual and prolonged postoperative course. The total of 5 patients experienced impaired wound healing. Dehiscence occurred in 2 patients on POD 8 and 17 together with break of colostomy in one of those patients on POD 10. Laparotomy scar of one patient broke 3 months postoperatively. All cases with impaired wound healing were tested positive for COVID-19 infection [7]. Ridwan et al. reviewed 579 surgeries performed at the cardiac surgery department. Coronavirus infections occurred in 3 patients on POD 20, 12 and 16. 2 patients required admission to the ICU and subsequently died. Wound dehiscence and mediastinitis occurred in a patient who stayed in the hospital for 52 days [8]. Silveira et al. report a case of coronary artery bypass surgery tested positive for COVID-19 on POD 9. Subsequently, the patient developed sternal dehiscence, similarly to patient B in our study. Debridement and reconstruction of sternal wound with pectoral flap was performed but due to a secondary pulmonary infection, the patient died on POD 40 [9]. Obesity, diabetes, and respiratory failure are some of the factors associated with sternal dehiscence [10]. In the paper published by Inouye et al., the authors presented two patients that underwent uncomplicated segmental mandibulectomies. As in our study, those patients were free from infection preoperatively and were infected in the postoperative period, exhibiting impaired wound healing. The first patient was infected on POD 20 presenting with skin dehiscence and gangrenous changes at the fibula flap donor site. In the second patient, a small dehiscence of neck incision occurred in the early postoperative period. On POD 16, intraoral suture dehiscence was observed. Both patients required debridements and developed infections with prolonged hospital stay (discharged POD 63 and POD 30) [11]. Martínez-Torija et al. compared the outcomes of pressure ulcer surgery in patients with and without COVID-19 infection within 4 weeks preoperatively. The infection was associated with worse wound healing and dehiscence which required reintervention in all

Table 1
Summary of the clinical characteristics of included patients with postoperative wound and anastomosis complications. COPD – chronic obstructive pulmonary disease, GGO – ground-glass opacities, VA ECMO – veno-arterious extracorporeal membrane oxygenation, POD – postoperative day.

Patient	A	B	C	D	E	F	G
Age (years)	61	57	81	63	61	71	66
Sex	Male	Male	Female	Male	Male	Male	Male
BMI	19.8	28.4	25	32.4	23.7	25.2	21.3
Preoperative serum albumin (g/dl)	3.55	4.21	-	-	-	-	-
Preoperative serum protein (g/dl)	7.31	7.07	6.50	7.09	7.72	6.80	7.10
Active smoker	No	No	No	Yes	Yes	No	No
Previous chemotherapy	No	No	No	Yes	No	Yes	No
Immunosuppressive or steroid therapy	Yes	Yes	Yes	No	Yes	No	No
Comorbidity	Arterial hypertension	Diabetes type 2	Gastro-esophageal reflux Arterial hypertension COPD Cholelithiasis	Arterial hypertension Diabetes type 2	Arterial hypertension	Coronary artery disease Duodenal and gastric reflux Arterial hypertension Diabetes type 2	COPD Duodenal ulcers
Preoperative glycemia (mg/dl)	104	128	111	186	91	74	95
Cause of surgery	Pulmonary Artery Hypertensions, bronchiolitis, COPD	Nonspecific interstitial pneumonia	Lung squamous cell carcinoma – recurrence in mediastinum	Esophagus carcinoma	Esophageal stenosis due to gastric reflux	Esophagus carcinoma	Adenocarcinoma of the right lung
Type of surgery	Lung transplantation with VA Central ECMO support	Lung transplantation with VA Central ECMO support	Resection of the tumor from posterior mediastinum with left diaphragm crus and left pleurectomy	Ivor-Lewis esophagectomy, Pyloromyotomy Explorative thoracotomy due to destructive infiltration of right ribs IV-VIII Thoracotomy	Ivor-Lewis esophagectomy, Heinacke-Mikulicz Pyloromyotomy, Splenectomy Laparotomy Thoracotomy	Subtotal esophagectomy, Ramstedt Pyloromyotomy	Right upper lobectomy
Approach	Clamshell	Clamshell	Thoracotomy	Thoracotomy	Laparotomy Thoracotomy	Laparotomy Thoracotomy Cervicotomy	Thoracotomy
Complication onset	POD 20	POD 34	POD 14	POD 1	POD 10	POD 7	POD 9
Complication	Thoracotomy dehiscence with open pneumothorax	Sternal and right costal dehiscence with open pneumothorax	Thoracotomy dehiscence with open pneumothorax	Bleeding from thoracotomy wound	Dehiscence of anterior wall of esophagogastric anastomosis	Dehiscence of 60% of esophageal anastomosis and 8–9 mm of gastric suture line	Thoracotomy wound swelling, dehiscence, redness Bronchial stump leakage POD 21 Omicron Mild Did not require oxygen therapy
RT-PCR positive test SARS-CoV-2 subtype	POD 26	POD 37	POD 18	POD 9	POD 17	POD 19	POD 21
Covid course	-	-	-	Alpha	Alpha	Alpha	Omicron
Covid management	Moderate Remdesivir	Very severe AirVo Life support with ventilator	Mild Tocilizumab Dexamethasone	Very severe AirVo	Very severe Dexamethasone AirVo	Moderate Remdesivir Oxygen therapy	Mild Did not require oxygen therapy
Radiological imaging (x-ray, CT)	Pneumothorax, GGO, Subcutaneous emphysema	Atelectasis, GGO	Pneumothorax	Atelectasis	Pneumothorax, GGO, Atelectasis	Pneumothorax, GGO	Pneumothorax
Surgical revision	Explorative rethoracotomy	Explorative rethoracotomy	Explorative rethoracotomy	Explorative rethoracotomy	Rethoracotomy with resuture of anastomosis	Esophageal stents	Explorative rethoracotomy
ICU duration	-	10 days	-	5 days	-	-	-
Result	Discharged POD 58	Death POD 47	Discharged POD 37	Death POD 13	Death POD 23	Discharged POD 73	Discharged POD 35

Table 2 Summary of the clinical characteristics of the control group. GERD - Gastroesophageal reflux disease, VA ECMO – veno-arterial extracorporeal membrane oxygenation, POD – postoperative day.

Patient	A	B	C	D	E	F	G
Age (years)	56	60	70	69	55	60	67
Sex	Male	Female	Male	Male	Male	Female	Male
BMI	21.7	21.2	31.6	29.4	24.6	21.2	25.2
Preoperative serum albumin (g/dl)	4.08	4.25	-	-	-	-	-
Preoperative serum protein (g/dl)	7.59	6.76	7.04	6.24	6.73	6.83	7.32
Preoperative glycemia (mg/dl)	92	95	96	120	105	69	102
Active smoker	No	No	Yes	No	Yes	Yes	Yes
Previous chemotherapy	No	No	No	Yes	Yes	Yes	No
Comorbidity	Gastric ulcers, Arterial hypertension, nodular goiter, nephrolithiasis	Cholelithiasis, osteoporosis	Arterial hypertension, Diabetes type 2	Gastric ulcers, GERD, esophageal hernia	None	Arterial hypertension, COPD, nodular goiter	Arterial hypertension
Cause of surgery	Interstitial lung disease	Hypersensitive alveolitis	Lung squamous cell carcinoma	Esophageal cancer	Esophageal cancer	Esophagus carcinoma	Adenocarcinoma of the right lung
Type of surgery	Lung transplantation with VA Central ECMO support	Lung transplantation with VA Central ECMO support	Tumor resection	Hybrid subtotal esophagectomy	Ivor-Lewis esophagectomy, Heineke-Mikulicz pyloromyotomy, resection of pulmonary tumor from upper right lung	Subtotal esophagectomy, Pyloromyotomy	Right upper lobectomy
Approach	Clamshell	Clamshell	Thoracotomy	Laparotomy Thoracoscopy Cervicotomy	Laparotomy Thoracotomy	Laparotomy Thoracoscopy Cervicotomy Spleen injury	Thoracotomy
Complications	None	None	None	None	None	None	None
Outcome	Discharged POD 24	Discharged POD 29	Discharged POD 6	Discharged POD 35	Discharged POD 11	Discharged POD 17	Discharged POD 4

7 patients. Wound complications also consisted of necrotic areas and postsurgical hematomas [12]. San Norberto et al. reviewed outcomes of vascular surgeries performed in COVID-19 positive patients. Among 75 patients in the study group, postoperative wound dehiscence occurred in 6 (8%) [13]. In the paper by Marenco-Hillebrand et al., the authors describe clinical courses of 11 neurosurgical patients infected with COVID-19. One developed wound dehiscence together with pneumonia, deep vein thrombosis and hemothorax, and subsequently required hospitalization in the ICU for 13 days [14]. Impaired wound healing could be also associated with post COVID syndrome – long-lasting multi organ impairment. Vrba et al. report a case of oncological patient who was infected with COVID-19 14 weeks prior to esophagectomy. On POD 6 CRP elevation and leukocytosis was detected. CT scan revealed dehiscence of cervical esophageal anastomosis. Dehiscence required surgical revision and drainage. The patient stayed 56 days in the hospital [15]. In this study, patient D developed massive postoperative bleeding from thoracotomy wound. On POD 9, coronavirus infection was detected. Clinical course was very severe, resulting in death on POD 13. According to Chiariello et al., perioperative COVID-19 infection increases the risk of bleeding complications from 2% in virus-free patients to 48% (p = 0.0001). Consequently, risks of surgical exploration due to bleeding are increased (25% vs 2%, p = 0.0001) [16]. Patient G underwent right upper lobectomy for adenocarcinoma. Postoperatively, the patient developed wound dehiscence and bronchopleural fistula. In similar case published by Testori et al., the patient underwent pneumonectomy due to lung adenocarcinoma and was readmitted to the hospital 14 days postoperatively with fever, subcutaneous emphysema, bronchopleural fistula, and COVID-19 infection. Laboratory findings included elevation of LDH and D-Dimers. The patient was treated with remdesivir, steroids and meropenem. Death occurred 28 days later [17]. Bronchopleural fistula complicating COVID-19 pneumonia in non-surgical patients has also been described [18–19]. Patients A and B underwent lung transplantations, and the onset of wound complications was observed on POD 20 and 34 respectively. Dehiscence of all layers of thoracotomy wound developed in patient A, who subsequently was treated with remdesivir, and oxygen therapy set to 1 to 2 L/min. On the contrary, patient B developed dehiscence of sternal and right-sided costal sutures with open pneumothorax, and further required oxygen therapy with AirVo machine and admission to the ICU, where he spent 10 days and died. According to Messika et al., who reviewed 35 lung recipients with a COVID-19 infection, course of infection was mostly severe. 31 patients (88.6%) were hospitalized, while 13 recipients required admission to the ICU and 5 died [20]. In this study, mean hospitalization time was 40.9 days and death occurred in 3 out of 7 patients in the study group. In the control group, mean hospitalization time was 18 days and none of the patients died. According to Gomes et al., postoperative COVID-19 infection is responsible for prolonged hospitalization and increased mortality compared to patients with the infection detected preoperatively [21].

Our hypothesis is that wound dehiscence may be a result of inflammation and thrombosis in microvasculature of the wound. Vascular abnormalities in lungs have been already identified in the early stage of pandemic. Those included thrombosis and microangiopathy [22]. Nevertheless, the virus may infect endothelial cells in blood vessels of other organs as well (e.g., heart, skin, kidney) due to their expression of angiotensin converting enzyme 2 (ACE2) which is its entry receptor [23]. Using nailfold videocapillaroscopy, Sulli et al. have observed that COVID-19 survivors have less capillaries compared to patients with Raynaud's phenomenon [24]. Reduction of vascular density in infected patients has also been demonstrated [25]. ACE2 converts Angiotensin II to Angiotensin 1–7. Binding of the virus to the ACE 2 is associated with its downregulation which causes augmentation of renin-aldosterone-angiotensin system (RAAS). Consequently, the level of angiotensin II is increased, which has prothrombotic effect [26]. According to Senchenkova et al., prothrombotic effects of Angiotensin II can occur in large arteries, as well as in microvasculature [27]. Proinflammatory

Table 3
Comparison between study and control groups.

	COVID-19 (+) (n = 7)	COVID-19 (-) (n = 7)	P = value
Age (years, mean)	65.71	62.42	0.4
Male	6	5	0.5
Female	1	2	
BMI (mean)	25.11	24.98	0.95
Active smoking	2	4	0.28
No active smoking	5	3	
Previous chemotherapy (yes)	2	3	0.58
Previous chemotherapy (no)	5	4	
Preoperative serum protein (g/dl, mean)	7.08	6.93	0.49
Preoperative glycemia (mg/dl, mean)	112.71	97	0.31
Postoperative hospitalization time (mean days)	40.85	18	0.02
Mean CRP value in the first 30 days	16.19	6.91	0.0003
Mean leukocytes count in the first 30 days	12.19	9.97	0.02

environment may block fibrinolysis and further activate prothrombotic conditions by stimulating endothelium and innate immunity cells to secrete factors such tissue factor, neutrophil extracellular traps (NET) and von Willebrand Factor [28].

NETs are large extracellular structures composed of proteins connected with chromatin from nucleus and mitochondria. Their role is to eliminate pathogens and to prevent from bacterial dissemination [29]. However, NETs can be also responsible for healthy tissue damage. Neutrophil traps are associated with the state of immunothrombosis by dysregulating hemostasis and damaging the endothelium (Fig. 4) [30]. NETs are also responsible for triggering coagulation cascade via intrinsic pathway [31]. The activity of NETs is associated with impaired wound healing processes as proteins attached to nucleic scaffold of the traps can degrade essential proteins in wounds such as collagen and proteoglycans. NETs dysregulate endothelial cell functions while cytotoxic histones induce death of those cells [32]. Elevated levels of NETs have been

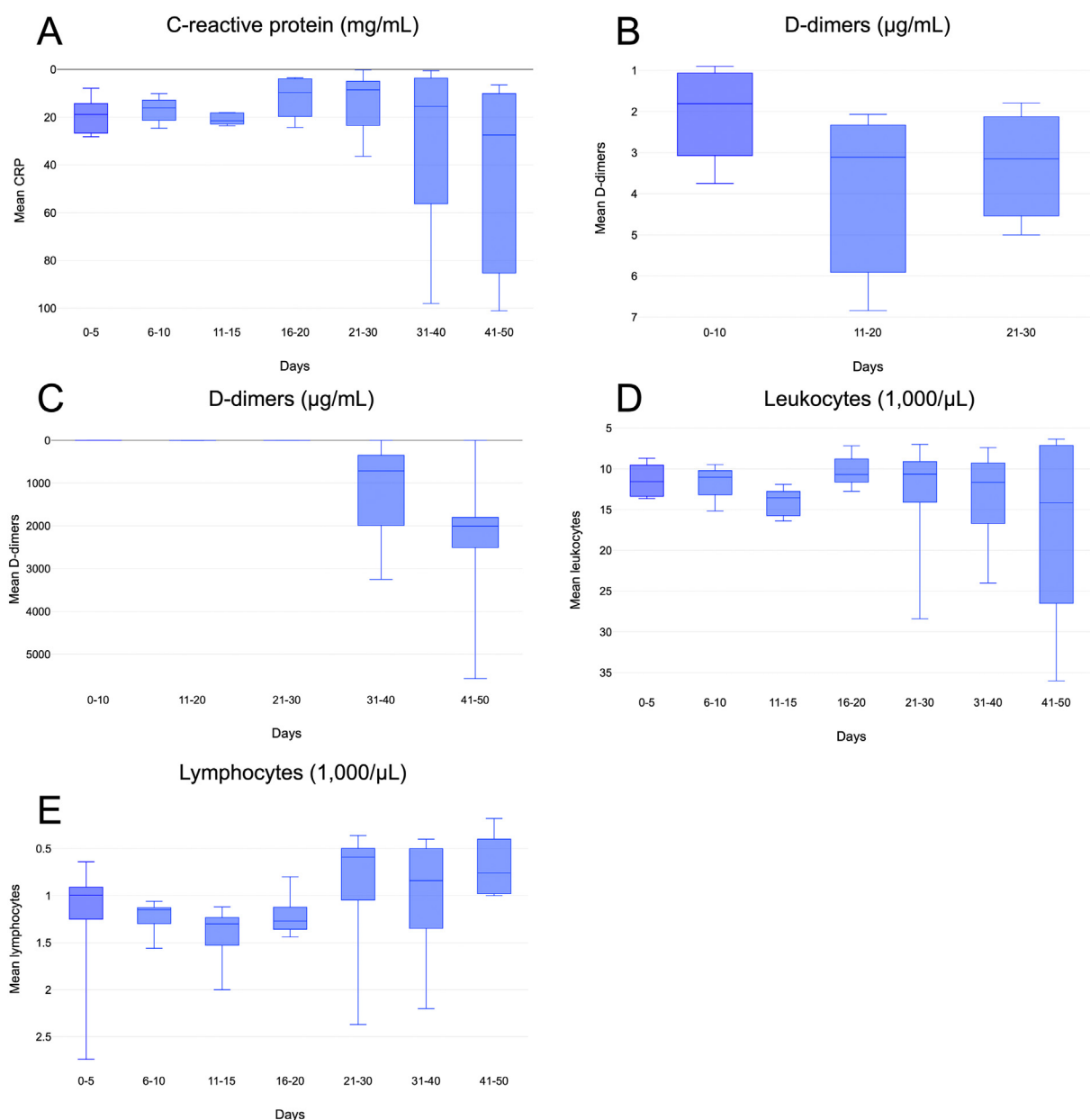


Fig. 1. Box-plot graphics showing laboratory findings and their changes over time in patients from the study group. Day 0 indicates surgery. A – C-reactive protein mg/ml; B – D-dimers µg/ml including a postoperative period of 30 days; C – D-dimers including a postoperative period of 50 days; D – leukocytes thousand/µl; E – lymphocytes thousand/µl.

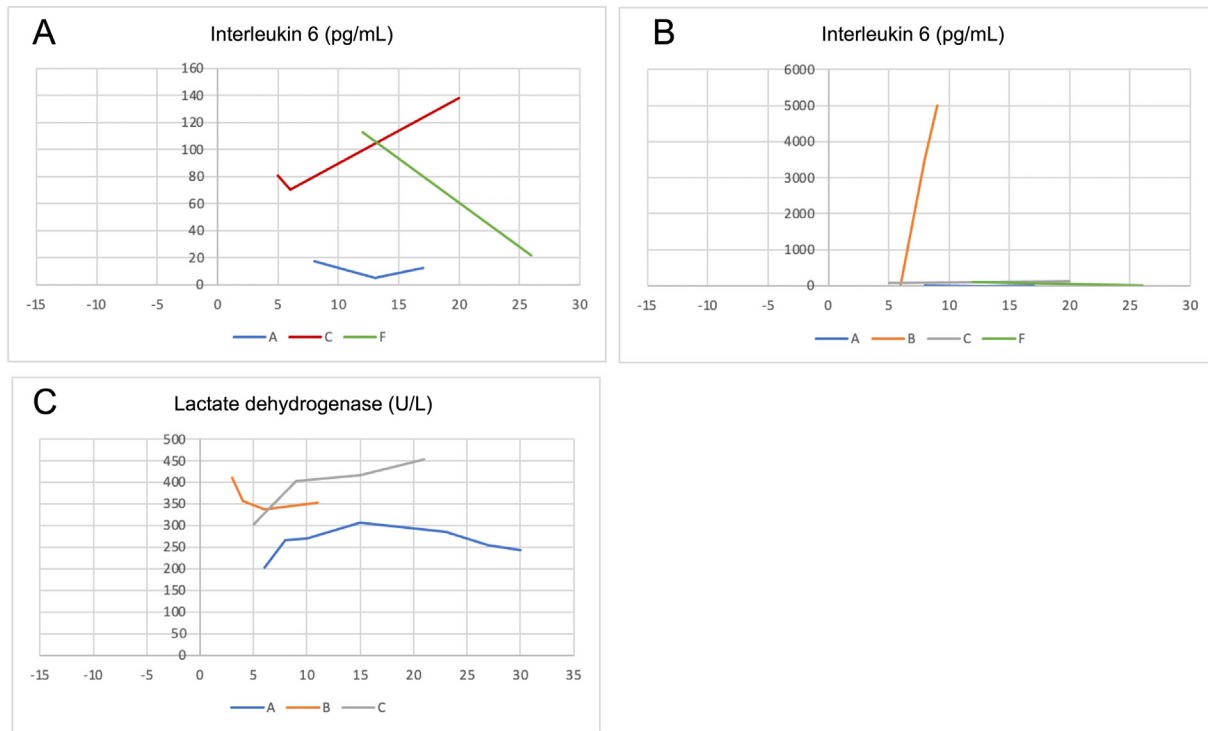


Fig. 2. Laboratory findings and its changes over time in patients from the study group. Day 0 indicates wound or anastomosis complications. A – Interleukin-6 values from 3 patients; B – Interleukin-6 values including patient B with values reaching 5000 pg/ml; C – lactate dehydrogenase.

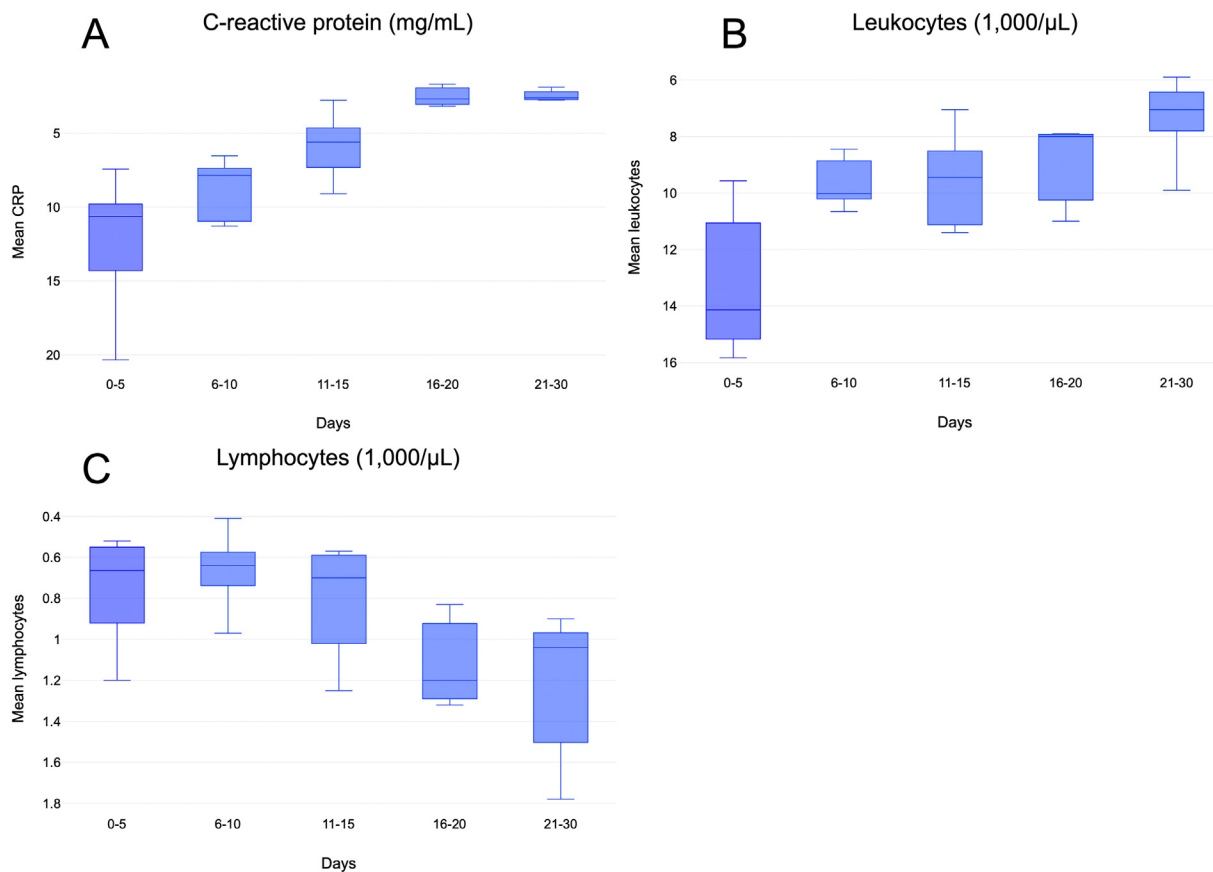


Fig. 3. Box-plot graphics showing laboratory findings and their changes over time in patients from the control group. Day 0 indicates surgery. A – C-reactive protein mg/ml; B – leukocytes thousand/ μ l; C – lymphocytes thousand/ μ l.

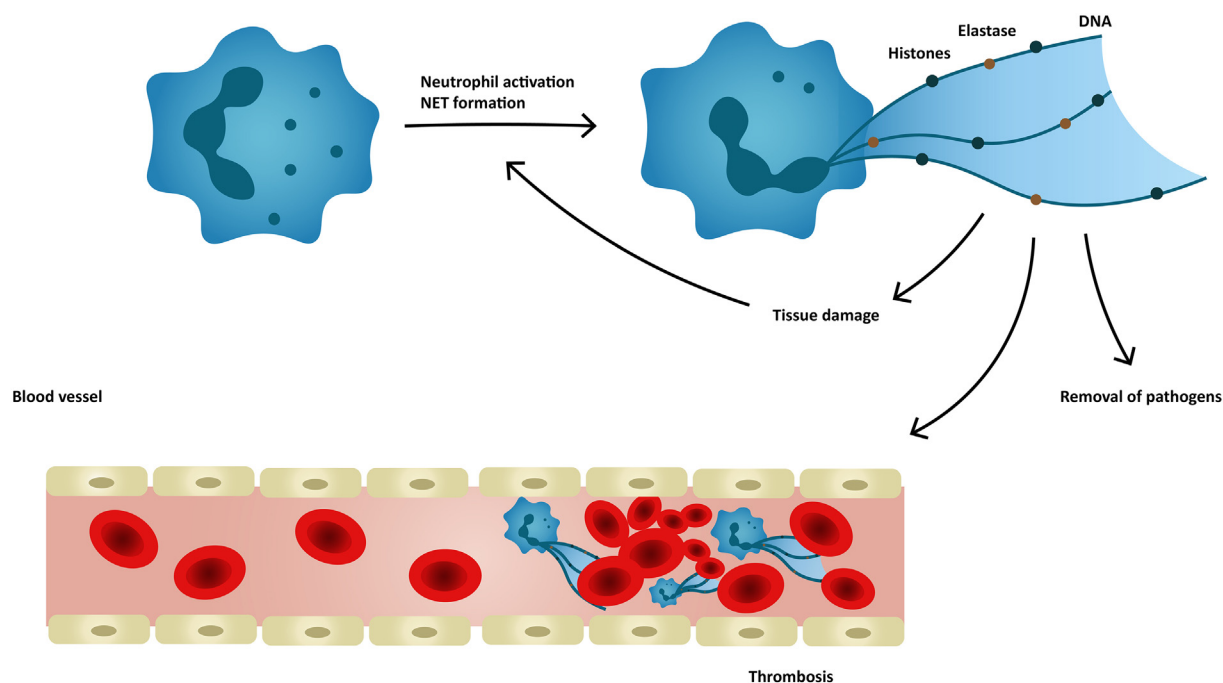


Fig. 4. Scheme of neutrophil extracellular trap and its prothrombotic activity.

detected in patients infected with COVID-19 and may serve as inflammatory biomarkers of severe course of infection [33].

One of the most common disruption due to COVID-19 infection is coagulopathy and it can be detected with elevated D-dimer levels in plasma when thrombus in the organism is dissolved by fibrinolysis [34]. In our series, D-dimer levels were elevated in five patients (A, B, C, D, G). C-reactive protein is a marker of disease severity, and its level is usually increased in the early period of inflammation, before morphological changes seen in CT [35]. LDH is present in various tissues, including liver, heart, brain, and erythrocytes, among others. After cell death, elevation of LDH is observed and it is common in such diseases like heart infarction or hemolysis. According to a systematic review performed by Szarpak et al., LDH level can be used as a survival predictor in patients infected with SARS-CoV-2 [36].

This study cannot be considered without certain limitations, such as small sample size, or heterogenous study group composed of patients undergoing different types of surgical procedures and with various baseline characteristics. Postoperative deep wound and anastomosis dehiscence are potential surgical complications. Nevertheless, presented complications differed from typical wound dehiscences encountered in routine surgical practice. Furthermore, all included patients with wound and anastomosis complications were operated during peaks of COVID-19 infections in Poland and all were subsequently tested positive for the infection which brought our attention. Dehiscence might develop due to other reasons such as low nutritional status, diabetes, smoking, preoperative chemotherapy, or prolonged steroid administration [37]. However, BMI and serum protein were within normal ranges in all included patients and there were no differences compared to the control group. In addition, differences between both groups in frequencies of active smoking and preoperative chemotherapy were not statistically significant. Furthermore, 15 lung transplantations are performed in our center each year. Steroid and immunosuppressive therapy is introduced to lung recipients and similar wound complications requiring additional interventions have not happened previously. All presented patients were considered to have a low risk for major wound complications. We have not identified any similar complications in patients not infected with coronavirus. These were also the only cases with significant wound and anastomosis complications among infected patients. Number of infected patients in

postoperative period is hard to estimate as there was no routine COVID-19 testing in case of asymptomatic patients.

Conclusions

This study raises awareness that Coronavirus infection in the perioperative period may masquerade as surgical complications and significantly prolong hospitalization time. It is also associated with elevated inflammatory markers in the postoperative period compared to the healthy controls. Dehiscence might be a result of inflammatory and thrombotic changes in the microvasculature of the operating area. Therefore, COVID-19 infection should be included in the differential diagnosis in postoperative patients with major wound or anastomosis complications. Further studies should focus on impact of the virus on wound healing process. In addition, COVID-19 infection in postoperative period is responsible for increased mortality and prolonged hospital stay.

Funding sources

This study received no external funding.

Ethics approval

This study was reviewed by the Pomeranian Medical University Institutional Review Board (IRB) and was granted exempt status (KB.006.77.2022/Z-5738).

CRedit authorship contribution statement

Kajetan Kielbowski: Methodology, Investigation, Resources, Data curation, Writing, Visualization; **Małgorzata Wojtyś:** Methodology, Investigation, Resources, Data curation, Supervision; **Konstantinos Kostopanagiotou:** Supervision, Writing; **Henryk Janowski:** Resources, Writing; **Janusz Wójcik:** Resources, Supervision, Writing.

Declaration of competing interest

The authors report no conflict of interest.

References

- [1] Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. *Viruses*. 2020; 12(2):135.
- [2] Prasad NK, Englum BR, Turner DJ, Lake R, Siddiqui T, Mayorga-Carlin M, et al. A nation-wide review of elective surgery and COVID-surge capacity. *J Surg Res*. 2021;267:211–6.
- [3] Deng JZ, Chan JS, Potter AL, Chen YW, Sandhu HS, Panda N, et al. the risk of postoperative complications after major elective surgery in active or resolved COVID-19 in the United States. *Ann Surg*. 2022;275(2):242–6.
- [4] Otifi HM, Adiga BK. Endothelial dysfunction in Covid-19 infection. *Am J Med Sci*. 2022;363(4):281–7.
- [5] Gawaz A, Guenova E. Microvascular skin manifestations caused by COVID-19. *Hamostaseologie*. 2021;41(5):387–96.
- [6] Cardiothoracic Interdisciplinary Research Network and COVIDSurg Collaborative. Early outcomes and complications following cardiac surgery in patients testing positive for coronavirus disease 2019: An international cohort study. *J Thorac Cardiovasc Surg*. 2021;162(2):355–72.
- [7] Sharma R, Chaudhary D, Goel P, Khandelwal S, Singh V, Kapoor R. COVID-19 masquerading as postoperative surgical complications after cancer surgery. *Indian J Surg Oncol*. 2021:1–4.
- [8] Ridwan K, DeVarennes B, Tchervenkov C, Shum-Tim D, Cecere R, Lachapelle K. Post-operative nosocomial COVID-19 infection in cardiac surgery: an uncommon event with high mortality rate. *CJC Open*. 2021;3(10):1217–20.
- [9] Silveira LMVD, Guerreiro GP, Lisboa LAF, Mejia OAV, Dallan LRP, Dallan LAO, et al. Coronary artery bypass graft during the COVID-19 pandemic. *Braz J Cardiovasc Surg*. 2020;35(6):1003–6.
- [10] Fu RH, Weinstein AL, Chang MM, Argenziano M, Ascherman JA, Rohde CH. Risk factors of infected sternal wounds versus sterile wound dehiscence. *J Surg Res*. 2016; 200(1):400–7.
- [11] Inouye D, Zhou S, Clark B, Swanson M, Chambers T. Two cases of impaired wound healing among patients with major head and neck free-flap reconstruction in the setting of COVID-19 infection. *Cureus*. 2021;13(12):e20088.
- [12] Martínez-Torija M, Esteban PF, Espino-Rodríguez FJ, Paniagua-Torija B, Molina-Holgado E, Ceruelo S, et al. Post-COVID complications after pressure ulcer surgery in patients with spinal cord injury associate with creatine kinase upregulation in adipose tissue. *Cells*. 2022;11(8):1282.
- [13] San Norberto EM, De Haro J, Peña R, Riera L, Fernández-Caballero D, Sesma A, et al. COVID-VAS Investigators from the Vascular Investigation Network (RIV) of the Spanish Society of Angiology and Vascular Surgery (SEACV). outcomes after vascular surgery procedures in patients with COVID-19 infection: A National Multicenter Cohort Study (COVID-VAS). *Ann Vasc Surg*. 2021;73:86–96.
- [14] Marenco-Hillebrand L, Erben Y, Suarez-Meade P, Franco-Mesa C, Sherman W, Eidelman BH, et al. Outcomes and surgical considerations for neurosurgical patients hospitalized with COVID-19-A multicenter case series. *World Neurosurg*. 2021;154: e118–29.
- [15] Vrba R, Lubuska L, Spicka P. Hybrid transthoracic oesophagectomy due to carcinoma with complications after COVID-19 pneumonia - a case report. *Int J Surg Case Rep*. 2022;90:106749.
- [16] Chiariello GA, Bruno P, Pavone N, Calabrese M, D'Avino S, Ferraro F, et al. Bleeding complications in patients with perioperative COVID-19 infection undergoing cardiac surgery: a single-center matched case-control study. *J Cardiothorac Vasc Anesth*. 2021;S1053-0770(21):00976–9.
- [17] Testori A, Giudici VM, Alloisio M, Cioffi U. Case report: COVID-19 pneumonia following left pneumonectomy for lung cancer complicated by empyema and bronchopleural fistula. *Front Surg*. 2021;8:679757.
- [18] Donatelli P, Trentacosti F, Pellegrino MR, Tonelli R, Bruzzi G, Andreani A, et al. Endobronchial valve positioning for alveolar–pleural fistula following ICU management complicating COVID-19 pneumonia. *BMC Pulm Med*. 2022;22(1):50.
- [19] Shah S, Mandal P, Chamlagain R, Yadav R, Pande Y, Sah SK, et al. Bronchopleural fistula and bilateral pneumothorax in a patient with COVID-19. *Clin Case Rep*. 2021;9 (11):05149.
- [20] Messika J, Eloy P, Roux A, Hirschi S, Nieves A, Le Pavec J, et al. French group of lung transplantation. COVID-19 in lung transplant recipients. *Transplantation*. 2021;105 (1):177–86.
- [21] Gomes WJ, Rocco I, Pimentel WS, Pinheiro AHB, Souza PMS, Costa LAA, et al. COVID-19 in the perioperative period of cardiovascular surgery: the Brazilian experience. *Braz J Cardiovasc Surg*. 2021;36(6):725–35.
- [22] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383(2):120–8.
- [23] Østergaard L. SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: consequences of capillary transit-time changes, tissue hypoxia and inflammation. *Physiol Rep*. 2021;9(3):14726.
- [24] Sulli A, Gotelli E, Bica PF, Schiavetti I, Pizzorni C, Aloè T, et al. Detailed videocapillaroscopic microvascular changes detectable in adult COVID-19 survivors. *Microvasc Res*. 2022;142:104361.
- [25] Rovas A, Osiaevi I, Buscher K, Sackardm J, Tepaspe PR, Fobker M, et al. Microvascular dysfunction in COVID-19: the MYSTIC study. *Angiogenesis*. 2021;24(1):145–57.
- [26] Ali MAM, Spinler SA. COVID-19 and thrombosis: from bench to bedside. *Trends Cardiovasc Med*. 2021;31(3):143–60.
- [27] Senchenkova EY, Russell J, Almeida-Paula LD, Harding JW, Granger DN. Angiotensin II-mediated microvascular thrombosis. *Hypertension*. 2010;56(6):1089–95.
- [28] Katneni UK, Alexaki A, Hunt RC, Schiller T, DiCuccio M, Buehler PW, et al. Coagulopathy and thrombosis as a result of severe COVID-19 infection: a microvascular focus. *Thromb Haemost*. 2020;120(12):1668–79.
- [29] Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol*. 2018;18(2):134–47.
- [30] Ng H, Havervall S, Rosell A, Aguilera K, Parv K, von Meijenfildt FA, et al. Circulating markers of neutrophil extracellular traps are of prognostic value in patients with COVID-19. *Arterioscler Thromb Vasc Biol*. 2021;41(2):988–94.
- [31] Gould TJ, Vu TT, Swystun LL, Dwivedi DJ, Mai SH, Weitz JI, et al. Neutrophil extracellular traps promote thrombin generation through platelet-dependent and platelet-independent mechanisms. *Arterioscler Thromb Vasc Biol*. 2014;34(9):1977–84.
- [32] Zhu S, Yu Y, Ren Y, Xu L, Wang H, Ling X, et al. The emerging roles of neutrophil extracellular traps in wound healing. *Cell Death Dis*. 2021;12(11):984.
- [33] Zuo Y, Zuo M, Yalavarthi S, Gockman K, Madison JA, Shi H, et al. Neutrophil extracellular traps and thrombosis in COVID-19. *J Thromb Thrombolysis*. 2021;51(2): 446–53.
- [34] Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. *Int J Hematol*. 2021;113(1):45–57.
- [35] Luan YY, Yin CH, Yao YM. Update advances on C-reactive protein in COVID-19 and other viral infections. *Front Immunol*. 2021;12:720363.
- [36] Szarpak L, Ruetzler K, Safiejko K, Hampel M, Pruc M, Kanczuga-Koda L, et al. Lactate dehydrogenase level as a COVID-19 severity marker. *Am J Emerg Med*. 2021;45: 638–9.
- [37] Anderson K, Hamm RL. Factors that impair wound healing. *J Am Coll Clin Wound Spec*. 2014;4(4):84–91.