

Hemorrhage and venous thromboembolism in critically ill patients with COVID-19

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Abstract

Objective: The majority of patients with COVID-19 showed mild symptoms. However, approximately 5% of them were critically ill and require intensive care unit admission for advanced life supports. Patients in the intensive care unit were high risk for venous thromboembolism and hemorrhage due to the immobility and anticoagulants used during advanced life supports. The aim of the study was to report the incidence and treatments of the two complications in such patients.

Method: Patients with COVID-19 (Group 1) and patients with community-acquired pneumonia (Group 2) that required intensive care unit admission were enrolled in this retrospective study. Their demographics, laboratory results, ultrasound findings and complications such as venous thromboembolism and hemorrhage were collected and compared.

Results: Thirty-four patients with COVID-19 and 51 patients with community-acquired pneumonia were included. The mean ages were 66 and 63 years in Groups 1 and 2, respectively. Venous thromboembolism was detected in 6 (18%) patients with COVID-19 and 18 (35%) patients with community-acquired pneumonia ($P=0.09$). The major type was distal deep venous thrombosis. Twenty-one bleeding events occurred in 12 (35%) patients with COVID-19 and 5 bleeding events occurred in 5 (10%) patients with community-acquired pneumonia, respectively ($P=0.01$). Gastrointestinal system was the most common source of bleeding. With the exception of one death due to intracranial bleeding, blood transfusion with or without surgical/endoscopic treatments was able to manage the bleeding in the remaining patients. Multivariable logistic regression showed increasing odds of hemorrhage with extracorporeal membrane oxygenation (odds ratio: 13.9, 95% confidence interval: 4.0–48.1) and COVID-19 (odds ratio: 4.7, 95% confidence interval: 1.2–17.9).

Conclusion: Venous thromboembolism and hemorrhage were common in both groups. The predominant type of venous thromboembolism was distal deep venous thrombosis, which presented a low risk of progression. COVID-19 and extracorporeal membrane oxygenation were risk factors for hemorrhage. Blood transfusion with or without surgical/endoscopic treatments was able to manage it in most cases.

Keywords

COVID-19, critically ill, venous thromboembolism, hemorrhage, community-acquired pneumonia

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Introduction

As of 1 October 2020, over 30 million patients have been infected by the coronavirus disease (COVID-19) worldwide.¹ Common clinical manifestations included fever, cough, shortness of breath and ground-glass opacity on chest computed tomography.² In addition to the respiratory system, COVID-19 was also associated with cardiac injury,^{3,4} abnormal coagulation⁵ as well as gastrointestinal symptoms⁶ and might lead to complicated situation if patients were pregnant or immunosuppressed.^{7–9} Although mostly mild,

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approximately 5% of the COVID-positive patients were critically ill and require intensive care unit (ICU) admission,² where they could receive advanced life supports including mechanical ventilation, continuous renal replacement treatment (CRRT), extracorporeal membrane oxygenation (ECMO) and artificial liver support (ALS). ICU patients were high risk for both venous thromboembolism (VTE) and hemorrhage due to a combination of immobility and anticoagulants used during advanced life supports. Both adverse events could be clinically challenging and associated with poor prognosis. Up to now, there is no study comparing the incidence and consequence of hemorrhage and VTE in the ICU between patients with COVID-19 and patients with community-acquired pneumonia (CAP). Therefore, in this study, we report these results and provide prevention and treatments of the two complications.

Methods

Study population

This retrospective study included consecutive patients admitted to the ICU as a result of COVID-19 and CAP. Patients with COVID-19 (Group 1) were enrolled between 10 January 2020 and 26 March 2020 at our hospital, the First Affiliated Hospital, School of Medicine, Zhejiang University. If the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused pneumonia in the community settings, the pneumonia was also diagnosed as CAP. We selected patients with CAP (Group 2) between 1 December 2018 and 1 November 2019 in the same hospital. The duration was before the outbreak of COVID-19, excluding the SARS-CoV-2 as a pathogen. Inclusion criteria for both groups were (a) the patient was critically ill and (b) the patient was either admitted to the ICU directly, or to the general ward at first and then transferred to the ICU due to the deterioration of the pneumonia. The diagnosis of COVID-19 was confirmed by real-time polymerase chain reaction for SARS-CoV-2 RNA. Patients with CAP were diagnosed according to the guideline.¹⁰ If the COVID-19 was suspected by clinical symptoms but not confirmed by positive SARS-CoV-2 RNA, the patient was excluded. The Clinical Research Ethics Committee of our hospital approved this study. Written informed consent was waived due to the urgent need to collect data.

Treatment strategies

For Group 1, members of the multidisciplinary team would discuss the optimal treatment plan for each patient, which contains individualized antiviral, anti-shock and anti-hypoxia treatments and advanced life supports.¹¹ For Group 2, the treatments were according to the latest guidelines.^{10,12} Advanced life supports included intubation and mechanical ventilation, ALS, ECMO and CRRT. The ALS, which could

clear cytokines and toxic molecules and supplement albumin and coagulation factors, was indicated if there was a high level of inflammatory cytokines or rapid deterioration.¹³ ECMO was indicated if mechanical ventilation failed to provide sufficient oxygenation or the patient was not suitable for long-term ventilation. CRRT was employed for severe kidney injury. Complete blood count, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen and D-dimer were measured at least once a day. Intermittent pneumatic compression with or without prophylactic anticoagulation (low-molecular-weight heparin, 100 U/Kg once a day) was used in all patients for thromboprophylaxis. If VTE was suspected due to the elevation of D-dimer or the swollen extremities, ultrasonography and/or computed tomography pulmonary angiography would be used to detect the thrombosis with anticoagulants used according to the guideline.^{14,15} If the bleeding was suspected, conservative treatments such as blood transfusion and suspension of anticoagulation were employed, combined with surgical/endoscopic treatments used in selected cases. The transfusion threshold was 7-g/dL hemoglobin. Endoscopic treatments included fiberoptic bronchoscope intervention and gastroenterological endoscope intervention. Surgical treatments included open surgery and embolization of the artery under digital subtraction angioplasty.

Data collection

We reviewed medical records to extract demographic information, laboratory results, computed tomography and ultrasound finds, treatment strategies and adverse events of each patient. The data we collected were documented in standardized data collection forms. For original data, please contact the corresponding author.

Statistical analysis

Categorical data were compared using the chi-square test or Fisher's exact test. Normal and non-normal distributed continuous data were analyzed using Student's t test and Mann-Whitney U test, respectively. Results were given as mean, median (interquartile range (IQR)) or number (percentage) wherever appropriate. To explore risk factors associated with hemorrhage, multivariable logistic regression model was used. Considering the total number of patients (n = 85) in our study and to avoid overfitting in the model, five variables were chosen for multivariable analysis, namely age, COVID-19, CRRT, ECMO and ALS. The choice was based on theoretical connection between the variable and hemorrhage. Anticoagulation was frequently used in CRRT, ECMO and ALS. Age was related to morbidity.^{16,17} COVID-19 might also contribute to abnormal coagulation.^{5,18} Statistical analysis was performed via SPSS 22.0 for Windows (SPSS Inc.,

Table 1. Characteristics of patients with COVID-19 and patients with CAP.

	Group 1: Patients with COVID-19	Group 2: Patients with CAP	P value
sample size	34	51	–
Male (%)	24 (71)	34 (65)	0.64
Mean age (range), years	66 (37–91)	63 (36–89)	0.80
Comorbidities (%)			
Any	27 (79)	43 (82)	0.78
Hypertension	24 (71)	25 (49)	0.07
Diabetes	7 (21)	11 (22)	1.00
COPD	1 (2.9)	10 (18)	0.05
Any heart disease	5 (15)	15 (29)	0.19
Cancer	0 (0)	5 (10)	0.08
Chronic renal insufficiency	6 (18)	15 (29)	0.31
Immunodeficiency	1 (2.9)	4 (7.8)	0.64
Smoking (%)	6 (18)	23 (45)	0.01

CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease.
Data are given as number (%) unless otherwise stated.

Table 2. Coagulation tests.

Item		Group 1: Patients with COVID-19 (n=34)	Group 2: Patients with CAP (n=51)	P value	Reference range
On admission to the hospital	HBG	128	109	<0.01	131–172 g/L
	PLT	173	196	0.58	83–303 × 10 ⁹ /L
	INR	1.02	1.29	<0.01	0.85–1.15
	PT	12.17	15.20	<0.01	10.00–13.5 s
	APPT	33.76	35.01	0.66	23.9–33.5 s
	FBG	4.93	4.94	0.45	2.0–4.0 g/L
	D-dimer*	604 (median, IQR 340–1048)	3630 (median, IQR 1653–8522)	<0.01	0–700 μg/L
On admission to the ICU	APACHE II score	8.4	13.9	0.36	–
	HBG	123	108	0.01	131–172 g/L
	PLT	185	197	0.97	83–303 × 10 ⁹ /L
	INR	0.99	1.22	<0.01	0.85–1.15
	PT	12.19	14.49	<0.01	10.00–13.5 s
	APPT	31.28	34.30	0.08	23.9–33.5 s
	FBG	5.07	4.83	0.22	2.0–4.0 g/L
D-dimer*	825 (median, IQR 585–1104)	3755 (median, IQR 2020–8717)	<0.01	0–700 μg/L	

CAP: community-acquired pneumonia; HBG: hemoglobin; PLT: platelet; INR: international normalized ratio; PT: prothrombin time; APPT: activated partial thromboplastin time; FBG: fibrinogen; IQR: interquartile range; ICU: intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation.
Data are given as mean unless otherwise stated.

*Fifty results of D-dimer were available in patients with CAP and analyzed in this column.

Chicago, IL, USA). All tests were two-sided, and a P value less than 0.05 was considered statistically significant.

Results

Demographic information and comorbidities

A total of 34 patients in Group 1 and 51 patients in Group 2 were enrolled in this retrospective study. Their demographic information and comorbidities were summarized in Table 1. The mean age was 66 and 63 years in Groups 1 and 2, respectively. The majority of patients were male in both groups.

Patients with CAP tended to smoke and have chronic obstructive pulmonary disease (COPD). There was no other statistical difference in demographics and comorbidities detected.

Coagulation test

Results of coagulation tests on admission to our hospital and to the ICU were summarized in Table 2. Platelet was within the normal range, and fibrinogen was elevated in both groups. Hemoglobin level, PT, APTT and INR were almost normal in Group 1. For Group 2, however, the four test results were slightly out of the normal range with

Table 3. Advanced life support, VTE and hemorrhage.

Item	Group 1: Patients with COVID-19 (n=34)	Group 2: Patients with CAP (n=51)	P value
Incubation (%)	16 (47)	47 (92)	<0.01
ALS (%)	13 (38)	0 (0.0)	<0.01
ECMO (%)	12 (35)	10 (20)	0.13
CRRT (%)	12 (35)	13 (25)	0.34
VTE (%)	6 (18)	18 (35)	0.09
Hemorrhage* (%)	12 (35)	5 (10)	0.01

CAP: community-acquired pneumonia; ALS: artificial liver support; ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement treatment; VTE: venous thromboembolism.

Data are given as number (%) unless otherwise stated.

*The patients with hemorrhage met the International Society on Thrombosis and Haemostasis major bleeding criteria.

Table 4. VTE in the ICU.

Item		Group 1: Patients with COVID-19 (n=6)	Group 2: Patients with CAP (n=18)
Distal DVT	Intramuscular	5	16
	Tibial	0	5
	Peroneal	0	4
Proximal DVT		0	0
Internal jugular vein thrombosis (catheter-related)		3	1
PE		0	1

CAP: community-acquired pneumonia; DVT: deep venous thrombosis; PE: pulmonary embolism; IQR: interquartile range; VTE: venous thromboembolism; ICU: intensive care unit.

Data are given as number.

statistical significance detected. In terms of D-dimer, it was elevated in both groups with a greater increase in patients with CAP.

Advanced life support, VTE and hemorrhage

As summarized in Table 3, more ALS was used in patients with COVID-19, while patients with CAP received more intubation. Approximately a quarter of patients in both groups received ECMO or CRRT. VTE was detected in 6 (18%) patients with COVID-19 and 18 (35%) patients with CAP with no statistical significance ($P=0.09$). Most of the VTEs in both groups were distal deep venous thromboses (DVTs). There was no proximal DVT detected. Internal jugular vein thrombosis was discovered in three patients, all of which were catheter related. Only one low-risk pulmonary embolism (PE) in a patient with CAP was detected. Details were listed in Table 4. The treatments of VTE were individualized. If patients were already receiving ALS, ECMO and/or CRRT that required anticoagulation, no extra anticoagulant was administered. If not, the treatments would follow the guidelines.^{14,15} In terms of hemorrhage, 21 and 5 bleeding events occurred in 12 (35%) patients with COVID-19 and 5 (10%) patients with CAP, respectively ($P=0.01$). Details were listed in Table 5. Gastrointestinal bleeding was the most common in both groups. Compared with Group 2, more surgical/endoscopic treatments and more blood

transfusion were needed to control the bleeding in patients with COVID-19. Except the intracranial bleeding that caused one patient's death, all the remaining hemorrhages were restored by conservative treatments with or without surgical/endoscopic treatments.

We used multivariable logistic regression model to explore risk factors with hemorrhage. Due to the amount of patients ($n=85$ in total) and previous findings, we included five variables, namely age, COVID-19, ALS, ECMO and CRRT. Multivariable logistic regression showed increasing odds of hemorrhage with ECMO ($P<0.01$, odds ratio (OR): 13.9, 95% confidence interval (CI): 4.0–48.1) and COVID-19 ($P<0.05$, OR: 4.7, 95% CI: 1.2–17.9).

Discussion

The COVID-19 pandemic, which is caused by the virus SARS-CoV-2, has put huge pressure on the medical system worldwide. The treatments for this disease are three-fold. For general population, it is important to keep social distancing, wash hands, cut travel¹⁹ and wear masks. For patients with mild and moderate COVID-19, Fangcang shelter hospitals, which are large, temporary hospitals built by converting public venues into health-care facilities, are necessary to isolate them from their families and communities and provide medical care.²⁰ For severe and critically ill patients, dedicated tertiary hospitals are needed to provide

Table 5. Hemorrhage in the ICU.

Item	Patients with COVID-19 (n = 12)		Patients with CAP (n = 5)		
	Conservative treatments alone	Surgical/endoscopic treatment	Conservative treatments alone	Surgical/endoscopic treatment	
Location	Gastrointestinal	3	6	2	0
	Tracheal and pulmonary	2	2	1	0
	Retroperitoneal	2	2	0	0
	Procedure-related	1	2	1	0
	Superficial	1	0	0	0
	Intracranial	0	0	1	0
Transfusion (median, IQR)—U*	21.5 (10–33)		2.0 (0.0–3.5)		

CAP: community-acquired pneumonia; IQR: interquartile range; ICU: intensive care unit.

Data are given as number unless otherwise stated.

*One unit (U) of blood transfusion was 200 mL.

intensive care and advanced life supports. Approximately 5% patients with COVID-19 are critically ill and require ICU admission.² With strong life supports and treatments, the mortality of COVID-19 can be decreased to a low level.

In this study, we compared the demographics, results of coagulation tests as well as the incidence and consequence of hemorrhage and VTE between the two groups. One particular interest of our study was the VTE and hemorrhage, the two common complications occurring during critical care.

VTE included DVT and PE. The incidence of DVT could be over 30% among patients in the ICU despite thromboprophylaxis.^{21,22} DVT would lead to swollen extremities and was closely related to PE in the short term. It also might result in post-thrombotic syndrome in the long term. Our results showed that most of the VTE detected in the two groups belonged to distal DVT, especially intramuscular venous thrombosis, which was considered to have a low risk of progression.²¹ Proximal DVT and PE were rare. The sole PE detected was stratified as low risk.¹⁵ A few catheter-related internal jugular vein thromboses were detected. Its incidence would be high if patients received thoracic or cardiovascular surgery.^{23,24} Among patients without surgery in ICU, symptomatic deep vein thrombosis related to catheters was as low as 1%.²⁵ The high incidence and low mortality risk of VTE in this study may be explained by use of a pneumatic compression device and prophylactic anticoagulation, close monitoring including D-dimers and ultrasonography as well as anticoagulants used during advanced life supports.

Hemorrhage was another major concern in the ICU. Except intubation and mechanical ventilation, other advanced life supports including ALS, CRRT and ECMO usually required anticoagulation, which might cause hemorrhage. The stress ulcer incurred by the pneumonia and procedures such as catheterization in central veins and femoral arteries might also lead to bleeding. In our study, 12 (35%) patients with COVID-19 and 5 (10%) patients with CAP suffered hemorrhage. Approximately half of the bleeding in patients with COVID-19 needed surgical/endoscopic

treatments. The intracranial bleeding resulted in one death, while the remaining patients survived this adverse event, which suggested that a combination of conservative treatments and surgical/endoscopic treatments could deal with the bleeding in most cases.

To explore the risk factors for bleeding, we used the multivariable logistic regression model. Five possible factors, namely age, COVID-19, ALS, ECMO and CRRT, were analyzed. Its results showed only ECMO (OR: 13.9, 95% CI: 4.0–48.1) and COVID-19 (OR: 4.7, 95% CI: 1.2–17.9) were risk factors of hemorrhage in patients in the ICU.

Age was frequently related to adverse events and poor prognosis. Previous studies reported that age was a risk factor for mortality in patients with COVID-19.¹⁷ Our study showed that age did not contribute to the hemorrhage, suggesting that the hemorrhage could happen in any patient.

According to the regression analysis, the ALS was also not related to hemorrhage. The ALS system was useful for clearing cytokine storm and exchanging plasma, which could filter toxic metabolites, balance fluid volume and provide serum albumin and coagulation factors.¹³ Although heparinization was needed for the system, massive plasma (approximately 2000 mL) could be exchanged into the patient and protamines would be used to neutralize heparin, which contributed to hemostasis. In terms of CRRT, there were three widely used anticoagulants, namely, unfractionated heparin, low-molecular-weight heparin and citrate. Heparin and citrate could be regionally administered. Compared with heparin, high-quality evidence demonstrated that regional citrate had a bleeding rate less than 5% in critically ill patients and had a low risk of circuit loss, filter failure and heparin-induced thrombocytopenia.^{26–29} Therefore, it was considered a satisfactory anticoagulant. With the developments of anticoagulants in CRRT, our regression analysis excluded the CRRT as a risk factor for bleeding in critically ill patients with pneumonia.

ECMO was another vital life-saving technique. Venovenous ECMO was able to provide oxygenation in

respiratory failure,^{30,31} and venoarterial ECMO could be a complementary strategy for high-risk PE,^{32,33} cardiogenic shock³⁴ and lung transplantation.³⁵ Complications including limb ischemia, brain injury and hemorrhage were prevalent.^{36,37} Thrombocytopenia, acquired von Willebrand syndrome and anticoagulation during the procedure might explain its bleeding tendency.^{38,39} Reduction from standard to low anticoagulation regimens decreased incidence of bleeding in half to approximately 20%.⁴⁰ Short-term heparin-free operation may be performed to control fatal bleeding.¹¹ Although the bleeding was common, days on ECMO was not associated with a decrease in the platelet count, and death due to hemorrhage accounted for approximately 3% reasons for discontinuation of ECMO.^{38,41} Our results also showed that ECMO was a risk factor for bleeding and most patients would survive this adverse event with a combination of conservative treatments and surgical/endoscopic treatments.

The regression results indicated that COVID-19 was a risk factor for bleeding as well. The COVID-19 tended to affect multiple organs that expressed angiotensin-converting enzyme 2 (ACE2), such as the lungs, heart, gastrointestinal tract and kidney.⁴² In severe patients with COVID-19, abnormal coagulation and low level of platelets were observed.^{2,5} Pathology results also showed a reduction of blood cells in the all three classes in bone marrow.⁴³ In critically ill patients, end-stage disseminated intravascular coagulation might take place and lead to bleeding.⁴⁴ All these might explain the probability of hemorrhage in patients with COVID-19.

This study had three main limitations. First, it was a retrospective study, which indicated the level of evidence could be improved further. The baseline of the two groups was not the same in some aspects. More smoking, more COPD, lower hemoglobin and higher D-dimer were noted in Group 2, which might be confounding factors. Second, it must be noted that the capacity of the study hospital was not overwhelmed. We had ample supply of devices, medicine and blood transfusion, which was vital to treat critically ill patients. Third, the Chinese government covered all the medical expense of patients with COVID-19. Since there was no restriction of costs and the only aim was to save patients' lives, the treatments for patients with COVID-19 might be more aggressive compared with patients with CAP. In addition, there was no power calculation taken for estimation of sample size, which was also a limitation.

Conclusion

VTE and hemorrhage were common in both groups. The predominant type of VTE was distal DVT, which presented a low risk of progression. COVID-19 and ECMO were risk factors for hemorrhage. Blood transfusion with or without surgical/endoscopic treatments was able to manage it in most cases.

Author contributions

Conception and design were performed by H.Z. and C.Q. Analysis and interpretation were performed by C.Q., G.W., J.X., W.Y., Z.W., Y.H., T.C., J.Z., X.H., J.H., J.F. and H.Z. Data collection and final approval of the article were performed by C.Q., T.L., G.W., J.X., W.Y., Z.W., Y.H., T.C., J.Z., X.H., J.H., J.F. and H.Z. The article was written by H.Z., T.L. and C.Q. Critical revision of the article was performed by G.W., J.X., W.Y., Z.W., Y.H., T.C., J.Z., X.H., J.H., J.F. and H.Z. Statistical analysis was performed by C.Q., T.L., G.W., J.X., W.Y., Z.W., Y.H., T.C., J.Z., X.H., J.H. and J.F. C.Q. and H.Z. obtained funding. H.Z. took the overall responsibility.

Declaration of conflicting interests

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Ethical approval

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Informed consent

Written informed consent was waived due to the urgent need to collect data. Approved within the ethical approval (APPROVAL NUMBER: IIT20200438A).

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References

1. World Health Organization. Coronavirus disease (COVID-19) outbreak situation, <https://www.who.int/emergencies/diseases/novel-coronavirus-2019> (accessed 1 October 2020).
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382: 1708–1720.
3. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; 5: 802–810.
4. Madjid M, Safavi-Naeini P, Solomon SD, et al. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol* 2020; 5: 831–840.
5. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020; 18: 844–847.
6. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* 2020; 69: 1002–1009.

7. Dashraath P, Wong JJJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol* 2020; 222: 521–531.
8. Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. *Am J Transplant* 2020; 20: 1859–1863.
9. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020; 395: 809–815.
10. Chinese Thoracic Society. Diagnosis and treatment of Chinese adults with community-acquired pneumonia. *Chin J Tuberc Resp D* 2016; 39: 253–279 (in Chinese).
11. Tingbo L. *Handbook of COVID-19 prevention and treatment*, 2020, https://globalcc.org/downloads/Handbook_of_COVID_19_Prevention_en_Mobile.pdf
12. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; 200: e45–e67.
13. Zhang Y, Yu L, Tang L, et al. A promising anti-cytokine-storm targeted therapy for COVID-19: the artificial-liver blood-purification system. *Engineering* 2021; 7: 11–13.
14. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; 149: 315–352.
15. Konstantinides SV, Barco S, Lankeit M, et al. Management of pulmonary embolism: an update. *J Am Coll Cardiol* 2016; 67: 976–990.
16. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180: 934–943.
17. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–1062.
18. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol* 2020; 75: 2950–2973.
19. Kraemer MUG, Yang CH, Gutierrez B, et al. The effect of human mobility and control measures on the COVID-19 epidemic in China. *Science* 2020; 368: 493–497.
20. Chen S, Zhang Z, Yang J, et al. Fangcang shelter hospitals: a novel concept for responding to public health emergencies. *Lancet* 2020; 395: 1305–1314.
21. Kaplan D, Casper TC, Elliott CG, et al. VTE incidence and risk factors in patients with severe sepsis and septic shock. *Chest* 2015; 148(5): 1224–1230.
22. Minet C, Potton L, Bonadona A, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. *Crit Care* 2015; 19: 287.
23. Oh CS, Rhee KY, Yoon TG, et al. Assessment of thrombosis in right internal jugular vein after percutaneous superior vena cava catheter insertion during cardiovascular surgery with cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2016; 152(6): 1592–1599.
24. Chen PT, Chang KC, Hu KL, et al. Catheter-related right internal jugular vein thrombosis after chest surgery. *Br J Anaesth* 2017; 119: 192–199.
25. Parienti JJ, Mongardon N, Megarbane B, et al. Intravascular complications of central venous catheterization by insertion site. *N Engl J Med* 2015; 373: 1220–1229.
26. Bai M, Zhou M, He L, et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs. *Intensive Care Med* 2015; 41(12): 2098–2110.
27. Liu C, Mao Z, Kang H, et al. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials. *Crit Care* 2016; 20: 144.
28. Zhang W, Bai M, Yu Y, et al. Safety and efficacy of regional citrate anticoagulation for continuous renal replacement therapy in liver failure patients: a systematic review and meta-analysis. *Crit Care* 2019; 23: 22.
29. Tsujimoto H, Tsujimoto Y, Nakata Y, et al. Pharmacological interventions for preventing clotting of extracorporeal circuits during continuous renal replacement therapy. *Cochrane Database Syst Rev* 2020; 3: CD012467.
30. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378: 1965–1975.
31. Yeo HJ, Kim D, Jeon D, et al. Extracorporeal membrane oxygenation for life-threatening asthma refractory to mechanical ventilation: analysis of the Extracorporeal Life Support Organization registry. *Crit Care* 2017; 21: 297.
32. Corsi F, Lebreton G, Brechot N, et al. Life-threatening massive pulmonary embolism rescued by venoarterial-extracorporeal membrane oxygenation. *Crit Care* 2017; 21: 76.
33. Meneveau N, Guillon B, Planquette B, et al. Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases. *Eur Heart J* 2018; 39: 4196–4204.
34. Russo JJ, Aleksova N, Pitcher I, et al. Left ventricular unloading during extracorporeal membrane oxygenation in patients with cardiogenic shock. *J Am Coll Cardiol* 2019; 73: 654–662.
35. Hayanga AJ, Du AL, Joubert K, et al. Mechanical ventilation and extracorporeal membrane oxygenation as a bridging strategy to lung transplantation: significant gains in survival. *Am J Transplant* 2018; 18(1): 125–135.
36. Luyt CE, Brechot N, Demondion P, et al. Brain injury during venovenous extracorporeal membrane oxygenation. *Intensive Care Med* 2016; 42: 897–907.
37. Bonicolini E, Martucci G, Simons J, et al. Limb ischemia in peripheral veno-arterial extracorporeal membrane oxygenation: a narrative review of incidence, prevention, monitoring, and treatment. *Crit Care* 2019; 23: 266.
38. Abrams D, Baldwin MR, Champion M, et al. Thrombocytopenia and extracorporeal membrane oxygenation in adults with acute respiratory failure: a cohort study. *Intensive Care Med* 2016; 42(5): 844–852.
39. Kalbhenn J, Schlagenhaut A, Rosenfelder S, et al. Acquired von Willebrand syndrome and impaired platelet function during venovenous extracorporeal membrane oxygenation: rapid onset and fast recovery. *J Heart Lung Transplant* 2018; 37(8): 985–991.
40. Raman J, Alimohamed M, Dobrilovic N, et al. A comparison of low and standard anti-coagulation regimens in extracorporeal membrane oxygenation. *J Heart Lung Transplant* 2019; 38(4): 433–439.

41. Posluszny J, Rycus PT, Bartlett RH, et al. Outcome of adult respiratory failure patients receiving prolonged (≥ 14 Days) ECMO. *Ann Surg* 2016; 263(3): 573–581.
42. Letko M, Marzi A and Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 2020; 5(4): 562–569.
43. National Health Commission of the People's Republic of China, National Administration of Traditional Chinese Medicine. Guideline for diagnosis and treatment of COVID-19 (7th version). *J Cardiovasc Pulmon Dis* 2020, 39(2). (in Chinese).
44. Lin L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect* 2020; 9(1): 727–732.