Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report

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Daftar Isi

Article Submission

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Abstract

Background: Late diagnosis of COVID-19 in young patient with hypercoagulable state is a rare case. COVID-19 is a systemic hyperinflammation disease and can cause severe acute respiratory syndrome. Clinical manifestations of COVID-19 are fever, cough, shortness of breath, and extrapulmonary manifestations, such as thrombosis, elevated transaminase enzymes, and multiple-organ failure (MOF).

Case Report: A 34-year-old Indonesian man presented to the emergency room with high fever for two days, weakness, and flatulence. The patient was initially diagnosed as dengue haemorrhagic fever (DHF). However, after four days treated with suspected DHF, he was diagnosed with COVID-19. On day 7 of the treatment, the patient's condition did not improve and further deteriorated on day 13. On day 13, the oxygen saturation was approximately 80%, but the patient's family refused for intubation to be performed on the patient. The laboratory tests revealed leukocytes of 18,000 cells/µL, erythrocyte sedimentation rate of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, ALT level of 94 U/L, and AST level of 51 U/L. Radiologic evaluation indicated that the inhomogeneous radiopacity of the two lungs increased compared to the previous chest radiograph. The result of the PCR swab was negative. The chest CT scan revealed large ground-glass opacities in both lungs. On day 15, the patient passed away.

Conclusions: Thrombosis is partly responsible for the high mortality rate of COVID-19 patients. Early management of the thrombotic complications condition to prevent severity of COVID-19, including the use of LMWH prophylaxis, requires further clinical trials to confirm its effectiveness.

Keywords: Hypercoagulable state, late diagnosis, young patient

Background

Coronavirus disease 2019 (COVID-19) is caused by a highly pathogenic virus which can cause severe acute respiratory syndrome. The complications of thrombotic events which occur in COVID-19 patients could result in patient deterioration [1]. COVID-19 patients usually have symptoms of fever, cough, and shortness of breath. Other frequent symptoms are myalgia, fatigue, rhinorrhoea, sore throat, headache, and diarrhoea [2]. Laboratory findings include lymphocytopenia and elevated c-reactive protein (CRP). In terms of cases with coagulopathy complication, there were increases in D-dimers, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation reveals ground-glass opacities (GGO), bilateral multiple lobular and subsegmental consolidation [4]. To the best of our knowledge, there is no previous report of delayed diagnosis of COVID-19 in a young patient with hypercoagulable state. In this report, we report a patient who was initially diagnosed with dengue hemorrhagic fever (DHF), but then diagnosed with COVID-19 after four days of treatment, and died after fifteen days of hospitalization.

Case Report

A 34-year-old Indonesian man with high fever for two days, weakness, and flatulence was admitted to the emergency room in Bhayangkara Brimob Hospital (Depok, Indonesia). He had no medical history of comorbidities (e.g. hypertension, diabetes mellitus, autoimmune disease, or malignancy). The platelet count was below normal, hence suspected as DHF. Laboratory tests revealed monocytes of 20%, ALT level of 161 U/L, AST level of 52 U/L, and negative for PCR nasopharyngeal swab in two consecutive times. Radiologic evaluation revealed no abnormalities in the heart and lungs (Figure 1A). The patient was treated with a suspected DHF.

After four days of the treatment, the patient's condition did not improve. He still had daily high fever. Laboratory tests revealed oxygen saturation of 92%, leukocytes of 12,300 cells/µL, lymphocytes of 12%, erythrocyte sedimentation rate (ESR) of 40 mm/hour, monocytes of 11%, NLR of 6.24, AST level of 278 U/L, ALT level of 315 U/L, and potassium level of 3.16 mmol/L. PCR nasopharyngeal swabs were rechecked twice and the results were positive with CT value of ORF1ab Gen 19.14, Gen N19.21. The patient was subsequently diagnosed with confirmed COVID-19. The results of the PA chest X-ray did not show any radiological abnormalities in the heart and lungs (Figure 1B). Patients received symptomatic therapy to decrease the ALT and AST levels, and also antibiotics, remdesivir, steroids, and other therapies.

On day 7 of the treatment, the patient's condition still did not improve. He seemed short of breath. The oxygen saturation was 90-92%. He was subsequently subjected to oxygen therapy using non-rebreathing mask (NRM) of 15 litre/minute. Laboratory tests revealed ALT level of 87 U/L and AST 91 level of U/L. Chest radiograph observation indicated basal pulmonary fibrosis of the right lung and no pulmonary infiltrates (Figure 2A).

On day 10, the patient's condition declined. He seemed short of breath, and also suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84%, hence requiring ICU treatment using HFNC FiO2 100 Flow 60. Laboratory tests revealed leukocytes of 18,000 cells/µL, ESR of 95 mm/hour, D-dimers of 1,110 mg/L, ferritin of 2,553 ng/L, fibrinogen: > 500, and quantitative CRP of 75 mg/L.

On day 13, the patient's condition deteriorated. The oxygen saturation was approximately 80%. However, the patient's family refused for intubation to be performed on the patient. Laboratory tests revealed leukocytes of 18,000 cells/µL, ESR of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, ALT level of 94 U/L, and AST level of 51 U/L. Radiologic evaluation indicated that the inhomogeneous radiopacity of the two lungs increased compared to the previous chest radiograph (Figure 2B). The result of the PCR swab was negative. The chest CT scan revealed large GGO in both lungs (Figure 3). On day 15, the patient passed away.

Discussion

The incidence of thrombosis and hypercoagulation in COVID-19 patients was found in patients with poor clinical conditions [1]. Several studies showed that the pulmonary thrombosis condition in COVID-19 patients reached almost 79% [6]. The data of this thrombosis incidence were obtained from patients in non-intensive care units (ICU) and ICU. Studies reported that the incidence of thrombosis of COVID-19 patients who were admitted to the ICU was around 31-79% higher than the those treated in non-ICU [1,6]. Another study reported that thrombosis incidence of patients in non-ICU increased from 9.2% to 15% [7]. Additionally, the finding of COVIDl-19 patients autopsy revealed that 58% of patients had

undiagnosed venous thrombosis, with a direct cause of death of a massive pulmonary embolism in four patients [8]. The finding in this study is very important because the incidence of pulmonary thromboembolism is generally caused by bacterial or other viral pneumonia (only 1-2.6%) [9]. A conclusion which can be drawn from several studies was that critically ill patients have higher thrombosis risks than patients in non-ICU [1,6].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. Retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low level of lymphocytes, increased D-dimers, increased cardiac troponin, ferritin, lactate dehydrogenase, and IL-6 [10]. COVID-19 patients with coagulopathy complications were observed of having high D-dimers [3]. There was no previous study on the association between D-dimer increase and prediction of the level of severity of thrombotic complications, level of severity of COVID-19 of the patients in the ICU, and the potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of COVID-19 associated with liver injury. This liver injury is multifactorial attack, including drug-induced liver injury, systemic inflammatory reaction, hypoxia ischemia reperfusion liver injury, and possible direct injury from the SARS-CoV-2 virus to liver [11].

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are very important for regulating vascular permeability, maintaining haemostasis, and regulating haemolysis. Vascular endothelial injury due to the infection of SARS-CoV-2 virus can cause primary pulmonary thrombus [12]. The second mechanism is the formation of microvascular microthrombi which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome (ARDS) leads to an inflammatory feedback loop known as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions are increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased levels of serum lactate dehydrogenase and ferritin level are associated with an increased risk of death and microangiopathy in thrombotic complications of COVID-19 patients [10].

The use of low-molecular-weight heparin (LMWH) for prophylaxis of venous thromboembolism has been approved by WHO as the hypercoagulation management [13]. Besides having an anticoagulant effect, LWMH has also been demonstrated to have anti-inflammatory properties which might be beneficial against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses IL-6 reaction and IL-8 expression of pulmonary epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [14].

Conclusions

Late diagnosis of COVID-19 in young patient with hypercoagulable state is a rare incident. Further studies are required to understand the pathophysiology of thrombosis and hypercoagulation conditions in young patients. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is still not completely clear. It is clear that the state of thrombosis is partly responsible for the high mortality rate of COVID-19 patients. Several mechanisms involving vascular endothelial injury, proinflammatory cytokines, complement, and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the thrombotic complications condition to prevent severity of COVID-19, although the data are still limited

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and require further studies. Current treatment recommendations, including the use of LMWH prophylaxis, require further clinical trials to confirm its effectiveness.

Acknowledgment

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Conflicts of interest

No conflicts of interest to declare.

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Figure 1. (A) No abnormalities in the heart and lungs. (B) The second chest radiograph showed no radiological abnormalities in the heart and lungs.

Figure 2. (A) Chest radiograph indicated basal pulmonary fibrosis of the right lung and no pulmonary infiltrates. (B) Inhomogeneous radiopacity of the two lungs increased compared to the previous chest radiograph.

Figure 3. Large GGO in both lungs.

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Desdiani Desdiani

ARTICLE SUBMISSION

INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in the deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2].Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased Creactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after 4 days of treatment and died after 15 days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to the publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting 3 days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical history of comorbidities. The internist suspected DHF-based on laboratory results indicating a platelet count of 86,000 cells/µL, increased monocytes of 20%, an Alanine transaminase (ALT) level of 161 U/L, and an Aspartate transaminase (AST) level of 52 U/L due to a hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs, and COVD-19 was not suspected. The patient was treated for DHF and was given intravenous fluids, oxygen, antipyretic, and hepatoprotector.

After 4 days of DHF treatment, there was no improvement, and saturation tended to decrease. Therefore, the patient was referred to a pulmonologist in the main hospital.There, the patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The patient received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination showed that leukocytes were 12,300 cells/µL (normal value: 5.000-–10.000 cells/µL), lymphocytes were 12% (normal value: 20%–50%), erythrocyte sedimentation rate (ESR) was 40 mm/h (normal value: 0–15 mm/h), monocytes were 11% (normal value: 4% – 8%), Neutrophil

Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7-41 U/L), ALT level was 315 U/L (normal value: 12-–38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7 – 5.2 mmol/L). The posteroanterior chest X-ray results did not show any radiological abnormalities in the heart and lungs. On day 5, the D dimer examination was carried out, the sample was sent outside the hospital, and the results came 4 days later. Hospital facilities were limited, and, at that time, the national insurance did not cover the test cost. While waiting for the D dimer and PT results, the patient was given low molecular weight heparin (LMWH). The patient was experiencing hypoxemic respiratory failure and was in a hypercoagulable state due to the hyper inflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. Heexperienced shortness of breath. The oxygen saturation was 90% – 92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask of 15 L/min. Laboratory tests revealed an ALT level of 87 U/L and AST 91 level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g., Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring intensive care unit (ICU) treatment using high flow nasal cannula FiO_2 100% flow 60 L/min.

Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high-flow oxygen and could communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed ESR of 95 mm/h, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative CRPof 75 mg/L. The chest CT scan without intravenous contrast revealed large GGO in both lungs, such as Segment 1 (S1) and S2 left; S2, S3, and S6 right; S4, S5, and S6 left; S4, S5, S7, S8 right; S10 right and left (Figure 1)., representing anterior and posterior views of the pulmonary lobes and segments. The placement of the pulmonary segments and lobes on the anterior surface of the right and left lungs are depicted in a schematic drawing superimposedon a three-dimensional surface reformatted picture produced with a multidetector CT scanner. The apical (S1) and anterior (S3) segments of the right upper lobe, the lateral (S4) and medial (S5) segments of the right middle lobe, and the anterior basal (S8) segment of the right lower lobe make up the anterior surface of the right lung. The apicoposterior segment (S1 + S2), anterior (S3) segment, superior (S4) and inferior (S5) lingular segments of the left upper lobe, as well as the anteromedial segment (S6), the lateral basal (S9), and posterior basal (S10) segments.

The patient was then given additional medications, including Meropenem, Dexamethasone, Remdesivir, Ondansetron, Omeprazole,

and supplements (e.g., Vitamin C, Zinc, and Vitamin D3). The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyper inflammation process of COVID-19. A post mortem exam was not conducted because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions [1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non- ICUs and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31%–79% higher than that of non-ICU patients [1, 5]. Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis that directly caused a severe pulmonary embolism in four of those patients [7]. The findings of this study are important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1%– 2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1, 5].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A retrospective multicentre cohort study found that 54 COVID-19patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, cardiac troponin, ferritin, and lactate dehydrogenase [9]. Patients with coagulopathy complications have higher D-dimer levels [3].

In searching the current literature, no previous studies were found on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia, ischemia- reperfusion liver injury, and drug-induced hepatotoxicity, may direct injury from the virus to the liver [10]. This case report found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are important for regulating vascular permeability, maintaining hemostasis, and regulating hemolysis. Vascular endothelial injury due to the infection of the SARS CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions indicate increased D-dimer, moderate thrombocytopenia, and prolonged

PT [3]. Increased serum lactate dehydrogenase and ferritin levels are related to ahigh risk of death and microangiopathy in thrombotic complications of COVID-19 patients [9]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT due to hyperinflammatory reactions and vascular endothelial injury.

The use of LMWH for prophylaxis of venous thromboembolism has been approved by the World Health Organization for hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated anti-inflammatory attributes that might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with a lower incidence of mortality compared to standard DVT prophylaxis in hospitalized COVID-19 patients. In this case, the patient had been given LMWH, but not at the beginning of treatment; therefore, the administration of LMWH did not seem to improve the patient's condition [14].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is unclear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulation involving inflammatory cytokines, vascular endothelial injury, and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease the severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent the increasing severity of COVID-19, including the use of LMWH prophylaxis.

DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent for the publication of this case report was obtained from thepatient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

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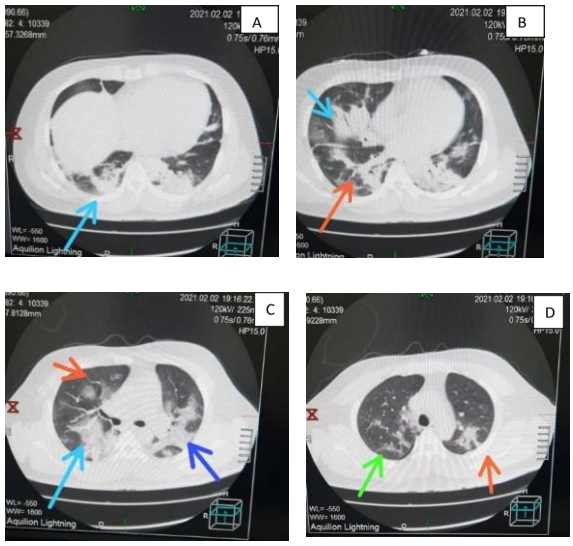
Figure 1. The chest CT scan without intravenous contrast revealed large ground-glass opacities in both lungs : (A)

S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow.



COVER LETTER

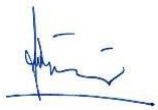
Dear Editor in Chief,

Canadian Journal of Respiratory Therapy

Here, we submit a manuscript entitled *"*Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report*"* for possible publication in Canadian Journal of Respiratory Therapy. Our study is original, has not already been published, and has not and will not be submitted for publication elsewhere as long as it is under consideration by Canadian Journal of Respiratory Therapy. All authors have read and approved the manuscript and take full responsibility for its content. All authors do not have conflict of interest in regard to this study or its funding.

Thank you very much for your attention,

Best regards,



Desdiani Desdiani, MD, PhD

Corresponding Author

ICMJE DISCLOSURE FORM

Date: May 14, 2021_ _ Your Name: Desdiani Desdiani _ Manuscript Title: Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report
Manuscript number (if known) _____ _____

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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__X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Re: Title page and Cover Letter

Dari: desdiani - (desdiani@ymail.com)

Kepada: editor@csrt.com

Tanggal: Selasa, 9 November 2021 pukul 14.21 GMT+7

Dear Editor Canadian Journal of Respiratory Therapy

Thank you for giving me the opportunity to submit my research manuscript. Please inform, currently, the status of my manuscript is still being reviewed, but there is no further information on the review process. Thank you for your attention.

Best Regards,
Desdiani Desdiani

> Pada Rabu, 19 Mei 2021 04.01.40 GMT+7, Editor <editor@csrt.com> menulis:
>
> Sorry for the delay responding – can you send the tle page? It was not in the aachments. And if there are any authors other than yourself, we need ICMJE statements signed from each author as well.
>
> Thanks,
>
> **Carly Brockington**
> Managing Editor, Canadian Journal of Respiratory Therapy
> (Pronouns: she, her)
> 201-2460 Lancaster Road Oawa, ON K1B 4S5
> Tel : (613) 808-8833
>
> **From:** desdiani - <desdiani@ymail.com>
> **Sent:** May 13, 2021 10:50 PM
> **To:** Editor <editor@csrt.com>
> **Subject:** Title page and Cover Leer
>
> Dear Managing Editor of Canadian Journal of Respiratory Therapy,
>
> Here, we submit title page and cover letter of our manuscript entitled "Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report" to Canadian Journal of Respiratory Therapy.
> Manuscript ID : 111
>
> Thank you for your attention.
>
> Best Regards,
> Desdiani Desdiani

RE: Title page and Cover Letter

Dari: Editor (editor@csrt.com)

Kepada: desdiani@ymail.com

Tanggal: Jumat, 12 November 2021 pukul 02.46 GMT+7

Sorry for taking so long to get back to you!

We have one completed review and I have had 6 others decline the invitation, so it has taken a really long time to get two reviews. Unfortunately, most of our reviewers are front line clinicians who have been swamped in the fourth wave in Canada. However, I think I may have a second person who will agree, so I should have feedback ready for the Associate Editor within the next 3 weeks.

Again, sincere apologies for the length of this process. If you have any questions let me know.

Kind regards,

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy
(Pronouns: she, her)
201-2460 Lancaster Road Ottawa, ON K1B 4S5
Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: November 9, 2021 2:22 AM
To: Editor <editor@csrt.com>
Subject: Re: Title page and Cover Letter

Dear Editor Canadian Journal of Respiratory Therapy

Thank you for giving me the opportunity to submit my research manuscript. Please inform, currently, the status of my manuscript is still beingreviewed, but there is no further information on the review process.

Thank you for your attention.

Best Regards,

Desdiani Desdiani

Pada Rabu, 19 Mei 2021 04.01.40 GMT+7, Editor <editor@csrt.com> menulis:

Re: Title page and Cover Letter

Dari: desdiani - (desdiani@ymail.com)

Kepada: editor@csrt.com

Tanggal: Jumat, 12 November 2021 pukul 08.57 GMT+7

Dear Dr. Carly Brockington,

Thank you for your attention
I hope my manuscript gets good reviews and gets a positive response from reviewers

Best Regards,
Desdiani Desdiani

> Pada Jumat, 12 November 2021 02.46.40 GMT+7, Editor <editor@csrt.com> menulis:
>
> Sorry for taking so long to get back to you!
>
> We have one completed review and I have had 6 others decline the invitation, so it has taken a really long time to get two reviews. Unfortunately, most of our reviewers are front line clinicians who have been swamped in the fourth wave in Canada. However, I think I may have a second person who will agree, so I should have feedback ready for the Associate Editor within the next 3 weeks.
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> Best Regards,
> Desdiani Desdiani
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> Pada Rabu, 19 Mei 2021 04.01.40 GMT+7, Editor <editor@csrt.com> menulis:
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> Sorry for the delay responding – can you send the title page? It was not in the attachments. And if there are any authors other than yourself, we need ICMJE statements signed from each author as well.
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> Thanks,

CJRT 2021-28 - Revision decision

Dari: Editor (editor@csrt.com)
Kepada: desdiani@ymail.com
Tanggal: Selasa, 23 November 2021 pukul 23.50 GMT+7

Hello,

Apologies again for the delay – please find a ached the two reviews – I sent this through the system, but I am a aching it by email as well just in case.

I invite you to resubmit your manuscript a er addressing the comments a ached. IMPORTANT - Please highlight your changes in yellow or using track changes to speed the decision process. When revising your manuscript, please outline every change made in response to their comments and provide suitable rebu als for any comments not addressed ("Response to Reviewers" document). Please note that your revised submission may need to be rereviewed.

Let me know if you have any ques ons!

Kind regards,

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy
(Pronouns: she, her)
201-2460 Lancaster Road O awa, ON K1B 4S5
Tel : (613) 808-8833

From: Editor
Sent: November 11, 2021 2:47 PM
To: desdiani - <desdiani@ymail.com>
Subject: RE: Title page and Cover Le er

Sorry for taking so long to get back to you!

We have one completed review and I have had 6 others decline the invita on, so it has taken a really long me to get two reviews. Unfortunately, most of our reviewers are front line clinicians who have been swamped in the fourth wave in Canada. However, I think I may have a second person who will agree, so I should have feedback ready for the Associate Editor within the next 3 weeks.

Again, sincere apologies for the length of this process. If you have any ques ons let me know.

Kind regards,

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy

[CJRT] Editor Decision - Revisions requested

Dari: Carly Brockington (editor@csrt.com)

Kepada: nitayulianti_hmt@yahoo.com; aninditabasukidr@gmail.com; desdiani@ymail.comTanggal:

Selasa, 23 November 2021 pukul 03.22 GMT+7

Nita Yulianti, Anindita Basuki, Desdiani Desdiani:

The Associate Editor has reached a decision regarding your submission to Canadian Journal of Respiratory Therapy, "Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report ".

Please see attached for the editor and reviewer feedback. Can you address these suggestions and send a “Response to Reviewer” document answering each point, as well as a revised manuscript with changes highlighted (or a track changes version)? This helps speed the decision process.

Let me know if you have any questions!

Managing Editor

editor@csrt.com

Canadian Journal of Respiratory Therapy

E-CJRT 2021-28 Reviewer 1.docx
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18kB

Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report

ABSTRACT

Late diagnosis of COVID-19 in a young patient with hypercoagulable state can cause high mortality rate ~~of COVID-19 patients~~. Clinical manifestations of COVID-19 include ~~are~~ respiratory symptoms and extrapulmonary manifestations, such as hypercoagulable state, increased transaminase enzymes, and multiple-organ failure (MOF). A 34-year-old male presented to the emergency room of peripheral hospital with high fever for ~~three~~3 days, weakness, flatulence, thrombocytopenia and elevated liver transaminase enzymes. The patient was initially diagnosed as dengue haemorrhagic fever (DHF) and was given hydration intravenous fluids, oxygen, antipyretic and hepatoprotector. After ~~four~~ 4 days treated with suspected DHF, the patient was referred to a referral hospital because his condition did not improved and he was diagnosed with COVID-19 based on positive results of polymerase chain reaction (PCR) nasopharyngeal swabs. This patient received therapy to decrease the ALT and AST levels, azitromisin, N asetil sistein and multivitamins. On day 13, his condition~~s~~ deteriorated with cephalgia, shortness of breath, the oxygen saturation was approximately 84% room air, but the patient's family refused for intubation to be performed on the patient. The laboratory tests revealed leukocytes of 18,000 cells/µL, platelets 74,000 cells/µL, erythrocyte sedimentation rate of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, ALT level of 94 U/L, AST level of 51 U/L, ESR of 95 mm/hour, PT 15,3, aPTT 32,0, fibrinogen > 500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative CRP of 75 mg/L. The chest CT scan revealed large ground-glass opacities in both lungs. The patient was then subjected to additional drugs, such as meropenem, dexamethasone, remdesivir, low-molecular-weight heparin (LMWH). On day 15, the patient passed away. Hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of hypercoagulable state ~~to prevent severity of COVID-19~~, including the use of Low Molecular Weight Heparin prophylaxis, can be used to prevent the severity of COVID-19 symptoms.

Keywords: *Hypercoagulable state, late diagnosis, young patient*

INTRODUCTION

COVID-19 is caused by a contagious virus which can lead to severe respiratory problems. The complications of thrombotic events which occur in COVID-19 patients could result in patient deterioration [1]. COVID-19 patients usually have symptoms of shortness of breath fever, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhoea, and diarrhoea [2]. Laboratory findings include decreased lymphocyte and increased c-reactive protein (CRP). In terms of cases with coagulopathy complication, there were increases in D-dimer~~s~~, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation reveals ground-glass opacities (GGO), bilateral multiple lobular and subsegmental consolidation [4]. In this report, we report a patient who was initially diagnosed with dengue hemorrhagic fever (DHF), but was then diagnosed with COVID-19 after four days of treatment, and subsequently died after fifteen days of hospitalization.

ETHICS APPROVAL

The patients's elder sister consented to the publication of this deidentified case report. Institutional review board approval is not required for deidentified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man with high fever for ~~three~~ 3 days, weakness, and flatulence was admitted to the emergency room of a peripheral hospital. He had no medical history of comorbidities (e.g. hypertension, diabetes mellitus, autoimmune disease, or malignancy). The platelet count 86,000 cell/µl, hence suspected as DHF. Laboratory tests revealed monocytes of 20%, Alanine transaminase (ALT) level of 161 U/L, Aspartate transaminase (AST) level of 52 U/L. Radiologic evaluation revealed no abnormalities in the heart and lungs (Figure 1). The patient was treated with a suspected DHF and was given hydration intravenous fluids, oxygen, antipyretic and hepatoprotector.

After four days of being treated with suspected DHF, the patient was referred to a referral hospital because his condition did not improve~~d~~ ~~and~~. The patient was diagnosed with COVID-19 based on positive results of polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21 and oxygen saturation of 96% room air. Patients received hepatoprotector to decrease the ALT and AST levels, azitromisin, N asetil sistein and multivitamins. Laboratory tests revealed, leukocytes of 12,300

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Commented [4]: Since you used numerics throughout the article, stay consistent.

Commented [5]: Consider replacing "as" with "with"

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Commented [7]: Consider medications or pharmaceuticals and capitalize all of the listed medications

Commented [8]: To prevent severity of Covid-19 does not flow well.

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Commented [12]: Consider explaining the importance of these values, and if they are high/low

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cells/µL, lymphocytes of 12%, erythrocyte sedimentation rate (ESR) of 40 mm/hour, monocytes of 11%, Neutrophil Lymphocytes Ratio (NLR) of 6.24, AST level of 278 U/L, ALT level of 315 U/L, and potassium level of 3.16 mmol/L. The results of the Posteroanterior (PA) chest X-ray did not show any radiological abnormalities in the heart and lungs.

On day 7 of the treatment, the patient's condition still did not improve. He seemed shortness of breath. The oxygen saturation was 90-92% room air. He was subsequently subjected to oxygen therapy using non-rebreathing mask (NRM) of 15 litres/minute. Laboratory tests revealed ALT level of 87 U/L and AST 91 level of U/L. Chest radiograph indicated ~~showed~~ no radiological abnormalities in the heart and lungs (Figure 2A & B). The patient was given ~~treatments with~~ azithromycin, dexamethasone, remdesivir, ondansentron, omeprazole, and supplements (e.g. vitamin C, zinc, and vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He seemed shortness of breath, and also suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, hence requiring ICU treatment using HFNC FiO2 100% Flow 60 litres per minute. The patient's family refused for intubation to be performed on the patient. The laboratory tests revealed leukocytes of 18,000 cells/µL, platelets 74,000 cells/µL, erythrocyte sedimentation rate of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, ALT level of 94 U/L, AST level of 51 U/L, ESR of 95 mm/hour, PT 15,3, aPTT 32,0, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative CRP of 75 mg/L. The chest CT scan without intravenous contrast revealed large GGO in both lungs such as S1 and S2 left; S2 right, S3 and S6 right, S4, S5, S6 left; S4, S5, S7, S8 right; S 10 right and left (Figure 3). The patient was then subjected to additional drugs, such as meropenem, dexamethasone, remdesivir, low-molecular-weight heparin (LMWH), ondansentron, omeprazole, and supplements (e.g. vitamin C, zinc, and vitamin D3). On day 15, the patient passed away. Written informed consent this case was obtained from the patient's family.

DISCUSSION

Hypercoagulable state were found in COVID-19 patients with poor clinical conditions [1]. Several studies have shown~~ed~~ that ~~the~~ lung thrombosis conditions in patients with COVID-19 reached almost 79% [5]. The data of this thrombosis incidence were obtained from patients in non-intensive care units (ICU) and ICU's. Studies reported that the incidence of thrombosis of COVID-19 patients who were admitted to the ICU was around 31-79% higher than the those treated in non-ICU [1,5]. Another study reported that the thrombosis incidence of patients in non-ICU increased from 9.2% to 15% [6]. Additionally, the finding of COVID~~I~~-19 patients autopsy described that 58% of patients had undetected venous thrombosis, with a direct cause of death of a severe lung embolism in four patients [7]. The finding in this study ~~is~~ are very important because the incidence of pulmonary thromboembolism is generally caused by bacterial or other viral pneumonia (only 1-2.6%) [8]. In our case report, the patient had no medical history of comorbidities ~~(e.g. hypertension, diabetes mellitus, autoimmune disease, or malignancy)~~. A conclusion which can be obtained from several researches was that seriously ill patients have a higher risk factor for hypercoagulable and thrombosis than patients treated in non-ICU wards [1,5].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A Retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, ferritin, cardiac troponin, ferritin, lactate dehydrogenase [9]. Patients with coagulopathy complications were seen of having high D-dimers [3]. There was no previous ~~study~~ studies on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and the potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia and ischemia reperfusion liver injury, and drug-induced hepatotoxicity ~~and~~, may direct injury from the virus to liver [10]. In this patient, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are very important for regulating vascular permeability, maintaining haemostasis, and regulating haemolysis. Vascular endothelial injury due to the infection of SARS-CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome (ARDS) leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions are increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased of serum lactate dehydrogenase and ferritin level are related with a~~n~~ high risk of death and

Commented [15]: Again, consider explaining what these values mean instead of just listing off numbers so readers do not have to look up normal values if they are not familiar with all of these tests

Commented [16]: Consider another word. "Seemed" sounds subjective. Perhaps "He experienced"

Commented [17]: Capitalize drug names

Commented [18]: Same as above, consider using a word other than seemed

Commented [19]: Need to write out what this acronym stands for as it has not yet been used in the article

Commented [20]: Do we know why they refused?

Commented [21]: Please explain what this means

Commented [22]: Reword

Commented [23]: What happened prior to his death? How did he deteriorate? Was the family aware that the patient would likely die if not intubated?

Commented [24]: Is this necessary as it was already stated?

Commented [25]: Consider rewording, does not flow well or make sense

Commented [26]: I find this entire paragraph confusing. Consider rewording and emphasizing the key points you would like to make. ICU vs non ICU

Commented [27]: Reword

Commented [28]: State what acronym stands for

microangiopathy in thrombotic complications of COVID-19 patients [9].

The use of low-molecular-weight heparin (LMWH) for prophylaxis of venous thromboembolism has been approved by WHO as the hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated as anti-inflammatory attributes which might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates ~~of COVID-19 patients~~. Further studies are required to understand the pathophysiology of hyper coagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results will help us for the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is still not completely clear. It is clear that the state of ~~hypercoagulable~~ hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms involving complement, proinflammatory cytokines, vascular endothelial injury and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to prevent severity of COVID-19, although the data are still limited and require further studies. ~~This is very important to know~~ early detection and management of hypercoagulable state can be effective to prevent severity of COVID-19, including the use of Low Molecular Weight Heparin prophylaxis.

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DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for deidentified single case reports or histories based on institutional policies.

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FIGURE 1
Chest radiograph showed no radiological abnormalities in the heart and lungs.

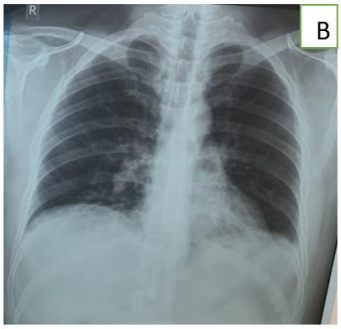


FIGURE 2.
(A) & (B) Chest radiograph indicated showed no radiological abnormalities in the heart and lungs

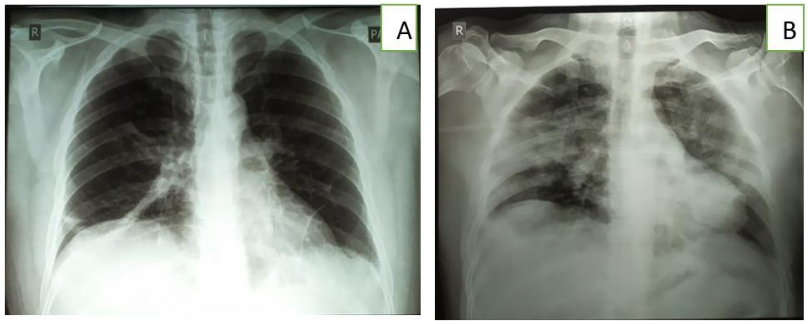
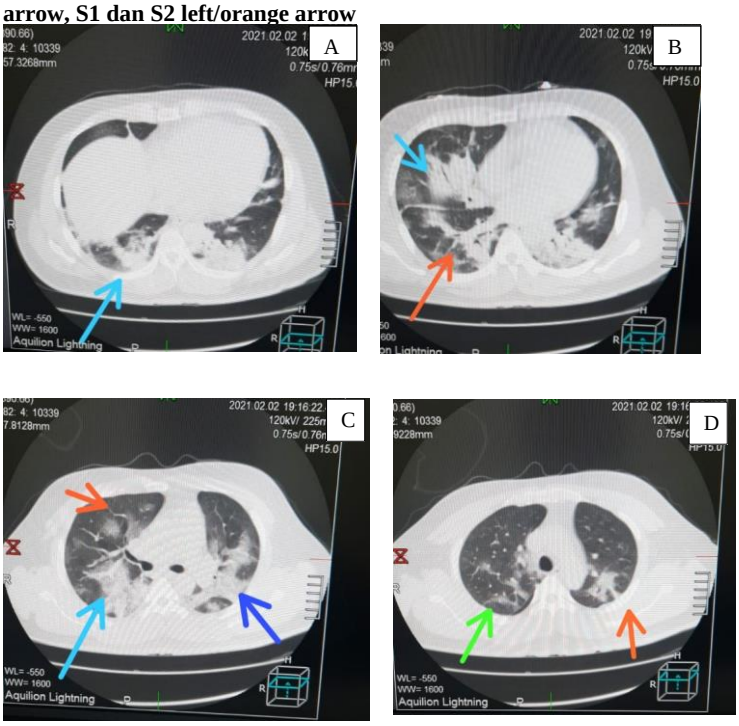


FIGURE 3. The chest CT scan without intravenous contrast revealed large GGO in both lungs : (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow



Comments to Reviewer 2 CJRT

Manuscript

Dear Manuscript's Reviewer

Thank you for allowing us the opportunity to submit a revised draft of the manuscript "Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report" for publication in the Canadian Journal of Respiratory Therapy. We appreciate the time and effort that you dedicated to providing feedback on our manuscript and are grateful for the insightful comments and valuable improvements to our paper. We have incorporated most of the suggestions made by the reviewers. Those changes are highlighted within the manuscript. Please see below, in blue, for a point-by-point response to the reviewers' comments and concerns. All page numbers refer to the revised manuscript file with tracked changes.

General Questions

Although I believe the case report does address important information and adds to the body of knowledge surrounding Covid-19 and hypercoagulable states, it seems that there are many gaps in the report that make the specific case hard to follow. I found that at the end of the report, I had many outlying questions that were not answered, such as:

1) Was the patient treated with additional or different medications/interventions as his condition worsened? The patient was then subjected to additional medications, such as Meropenem, Dexamethasone, Remdesivir, Low-molecular-weight heparin (LMWH), Ondansentron, Omeprazole, and Supplements (e.g. Vitamin C, Zinc, and Vitamin D3).

2) Why did the family refuse intubation? The patient's family refused for intubation to be performed on the patient, because they think the action will harm the patient.
   Was there more communication with the care team around this? Yes, already and the medical team have persuaded the patient and his family, but still refused to be intubated.
   If the patient was on heated high flow oxygen, couldn't he make medical decision and provide consent on his own? The patient's family, especially the patient's elder sister, determines the decision to treat this patient. The patient submits the decision of medical treatment to his elder sister.

3) Does the author think there was a role to treat this patient, possible with low molecular weight heparin, sooner? Initially this patient was treated by another specialist – an internist and the doctor thought that this patient was suffering from dengue fever, after there was no improvement and saturation tended to decrease, he was referred to a pulmonologist. The D dimer examination was carried out by sending the sample outside the hospital, because the hospital facilities were limited and the financing was not covered by the national insurance at that time. While waiting for the results of the D dimer and prothrombin time, the patient was still given low molecular weight-heparin.
   Would this have decreased the chance of mortality? In this case, LMWH was administered after the patient was treated by pulmologists and LMWH administration in this patient did not significantly improve the patient's condition.

   Was a post mortem exam done? The post mortem exam was not carried out, because it was not approved by the family.

4) Was the patient diagnosed with a hypercoagulable state prior to his hospital admission? No, Initially this patient was treated by another specialist – an internist and the doctor thought this patient was suffering from dengue fever, after there was no improvement, he was referred to a pulmonologist.,

and treated as covid-19.
Was this hypercoagulable state a long standing preexisting condition or was it due to Covid? This hypercoagulable state due to Covid19, clinical symptoms and blood laboratory results such as D dimer, prothrombin time have shown towards a hypercoagulable state.
Was it being treated or monitored? It has been managed after being consulted and referred to a pulmonologist, treated by the Covid-19 treatment standard.
What was the cause? hypoxemic respiratory failure, hypercoagulable state due to hyperinflammation process in Covid-19.

5) Why was the patient not tested for Covid initially (as his symptoms indicate he should have been)? Or was he tested and it took days for results to come back? Was the patient transferred to another site prior to the positive Covid test result? Or was this found by the receiving site? The patient was initially treated at the clinic with symptoms of fever and weakness, after there was no improvement, the patient was referred to a small hospital and treated by an internist and diagnosed as dengue haemorrhagic fever. After no improvement and the oxygen saturation tended to decrease, the patient was referred to a hospital, the patient was consulted to a pulmonologist, carried out a PCR test and treated as Covid-19.

I feel adding in details that better outline the case and interventions, as well as clearly outlining key points the author is portraying would make the article more impactful. Thank you for your suggestions.

Title
The title accurately reflects the purpose of the case report.

Abstract
The abstract summarizes the manuscript and can be understood without reading the manuscript. I did not find any discrepancies in the abstract and the remainder of the manuscript. However, I found lines 11 to 14 slightly unclear and was not sure if the patient was referred to another site due to the positive diagnosis or the fact they were not improving, or both. I am curious about why the patient was not tested or screened for Covid sooner and if they could have been managed at their original site once the Covid-19 diagnosis was made.

The patient was initially treated at the clinic with symptoms of fever and weakness, after there was no improvement, the patient was referred to a small hospital and treated by an internist and diagnosed as dengue haemorrhagic fever. After no improvement and the oxygen saturation tended to decrease , the patient was consulted to a pulmonologist, carried out a PCR test and treated as Covid-19.

Introduction
The introduction does define the problem in terms of Covid-19, however, there is less emphasis on hypercoagulable states. Consider defining what a hypercoagulable state means and why this is significant (especially in the context of Covid) as I think it would be helpful to the audience. The literature referenced in this section to provide context seem recent and valid, however, the flow of the information is hard to follow. Consider listing symptoms and lab findings, then discussing these in relation to a hypercoagulable state. There is no research question or hypothesis stated, however, this seems appropriate considering the article is a case report. Thanks for your suggestions. I've added the definition of hypercoagulable state and the importance of overcoming the condition as it can lead to death. Signs, symptoms and laboratory results that support a hypercoagulable state are listed in the case report sections line 77-89.

Methodology
The article does not contain results of experimental studies, therefore, no informed consent was required. Details of the ethics approval and consent from a family member of the patient discussed is clearly stated. As this article is a case report, there is no research design methodology or data collection and analysis described. The case report section of the article included many lab and vital signs values, for example lines 61-22 state the patient had an “oxygen saturation of 96% room air”. As a Respiratory Therapist, I understand the significance of this, however, other readers may not. I also found the listing of many values (lines 64-65) overwhelming, and would suggest only listing pertinent or significant lab values and in addition stating if

this is high/low in comparison to normal or why this is important in this specific case. The case report portion outlines the deterioration of the patient, however, I found it lacked in describing interventions and other details. For example, line 79 states “The patient’s family refused for intubation to be performed on the patient” but does not describe why or if there was discussion with the family about the repercussions of refusing to intubate the patient. The final paragraph of the case report describes the deterioration of the patient, a list of medications used and the subsequent death of the patient. However, it would be helpful to have more information about management and cause of death, for example, hypoxemic respiratory failure secondary to multiple pulmonary embolisms? Since there is an emphasis on using low molecular weight heparin in these patients later in the article, I am curious as to why this was not suggested or considered earlier in the patient’s management.

The patient’s family refused for intubation to be performed on the patient, because they think the action will harm the patient. Yes, already and the medical team have persuaded the patient and his family, but still refused to be intubated. The patient's family, especially the patient's elder sister, determines the decision to treat this patient. The patient submits the decision of medical treatment to his elder sister. The patient was initially treated at the clinic with symptoms of fever and weakness, after there was no improvement, the patient was referred to a small hospital and treated by an internist and diagnosed as dengue haemorrhagic fever. After no improvement and the oxygen saturation tended to decrease, the patient was referred to a hospital, the patient was consulted to a pulmonologist, carried out a PCR test and treated as Covid-19. The D dimer examination was carried out by sending the sample outside the hospital, because the hospital facilities were limited and the financing was not covered by the national insurance at that time. While waiting for the results of the D dimer and prothrombin time, the patient was still given low molecular weight-heparin. This hypercoagulable state due to Covid19, clinical symptoms and blood laboratory results such as D dimer, prothrombin time have shown towards a hypercoagulable state. The cause of death in this patient is hypoxemic respiratory failure, hypercoagulable state due to hyperinflammation process in Covid-19.

Results
Not applicable, no results section (case review).

Discussion / Conclusion
Lines 104-106 state “A conclusion which can be obtained from several researches was that seriously ill patients have a higher risk factor for hypercoagulable and thrombosis than patients treated in non-ICU wards.” Although this relates to the observations in the case report to the literature and studies, I find the flow and wording difficult to understand and would consider rewording to make the statement more impactful. The discussion touches on mechanisms of the pathophysiology of hypercoagulability in COVID-19 and the use of Heparin, however, this information is not discussed in relation to the case or patient (besides the use of this for treatment on the patients final days of life).
Thank you fo your suggestions. Here, we submit rewording first paragraph in discussion section

The hypercoagulable state was found in COVID-19 patients with poor clinical conditions[1]. Several studies have shown that the pulmonary thrombosis rate of covid-19 patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-intensive care units (ICU) and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31-79% higher than that of non-ICU patients [1,5] . Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis, and 4 patients directly caused a severe pulmonary embolism[7]. The findings of this study are very important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1-2.6%)[8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1,5].

In this patient, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT. In this case, the patient has been given LMWH, but not since the beginning of treatment, therefore the administration of LMWH does not seem to improve the

patient's condition

Illustrations
The figures are appropriately labeled. I would consider removing Figure 1 and 2 from the Appendices as they are "normal findings". The arrows in Figure 3 are helpful, however, I am unsure if the description of the photo could be understood without referring to the manuscript. I do appreciate the use of arrows in the CT images. Thank you for the suggestions. We have removed figure 1 and 2. Figure 3 shows large Ground Glass Opacities in both lungs and already listed on the line number 86-89.

Style
I found that the flow, grammar and redundancy of this case review difficult to follow and think it took away from key messages the writer is trying to portray.

References
The references are timely as the Covid-19 pandemic is a recent issue. The references seem as though they are properly quoted and the manuscript contains an appropriate amount. However, I did notice a few lines that likely require the addition of a citation, for example lines 135-136 and 141-142. Thanks for your suggestion, I've added a citation to complete the discussion sections.

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report

ABSTRACT

Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure (MOF).

Case and outcomes: A 34-year-old male presented to the emergency room after three days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hemorrhagic fever (DHF). He was given hydration intravenous fluids, oxygen, antipyretic and hepatoprotector. On day four, the patient was diagnosed with COVID-19 and received therapy to decrease the Alanine transaminase (ALT) and Aspartate transaminase (AST) levels. While waiting for outsourced D dimer and prothrombin time results, the patient was given low molecular weight-heparin (LMWH) on day 5. On day 13, his condition deteriorated with cephalgia and shortness of breath, but the patient's family refused intubation. The chest CT scan revealed large ground-glass opacities in both lungs. The patient was given additional medications, such as Meropenem, Dexamethasone, and Remdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence than standard DVT prophylaxis in hospitalized COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH at the beginning of treatment.

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of the hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Keywords: *Hypercoagulable state, late diagnosis, young patient*

Commented [30]: Do we know what day they were given LMWH?

Commented [31R30]: The patient was given LMWH on day 5 and we have adjusted in manuscript. Thank you

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INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased c-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after four days of treatment and died after fifteen days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting three days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical history of comorbidities. Dengue Haemorrhagic Fever (DHF) was suspected by the internist based on laboratory results indicating a platelet count of 86,000 cells/µl, increased monocytes of 20%, an ALT level of 161 U/L, and an AST level of 52 U/L due to a hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs, and COVD-19 was not suspected. The patient was treated for DHF and was given intravenous fluids, oxygen, antipyretic, and hepatoprotector.

There was no improvement after four days of DHF treatment, and saturation tended to decrease. Therefore, the patient was referred to a pulmonologist in the main hospital. The patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The patient received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination show that leukocytes were 12,300 cells/µL (normal value: 5.000-10.000 cells/µL), lymphocytes were 12% (normal value: 20-50%), erythrocyte sedimentation rate (ESR) was 40 mm/hour (normal value: 0-15 mm/hour), monocytes were 11% (normal value: 4-8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7-41 U/L), ALT level was 315 U/L (normal value: 12-38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7 – 5.2 mmol/L). The results of the Posteroanterior (PA) chest X-ray did not show any radiological abnormalities in the heart and lungs.

On day 5, D dimer examination was carried out, the sample was sent outside the hospital and the results came out 4 days later. Hospital facilities were limited, and at that time, the national insurance did not cover the financing. While waiting for the D dimer and prothrombin time results, the patient was given low molecular weight-heparin (LMWH). The patient was experiencing hypoxemic respiratory failure, and was in a hypercoagulable state due to the hyperinflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90-92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask (NRM) of 15 litres/minute. Laboratory tests revealed an ALT level of 87 U/L and AST 91 level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g., Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring ICU treatment using High Flow Nasal Cannula FiO2 100% Flow 60 litres per minute.

Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high flow oxygen and was able to communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed erythrocyte sedimentation rate of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative C-Reactive protein of 75 mg/L. The chest CT scan without intravenous contrast revealed large Ground Glass Opacities in both lungs such as Segment 1 (S1) and S2 left; S2 right, S3 and S6 right, S4, S5, S6 left; S4, S5, S7, S8 right; S 10 right and left (Figure 1). The patient was then given additional medications including Meropenem, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and Supplements (e.g., Vitamin C, Zinc, and Vitamin D3).

The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyperinflammation process of COVID-19. A post mortem exam was not carried out because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions[1].

Commented [33]: Consider explaining the importance of these values, and if they are high/low

Commented [34R33]:

Commented [35R33]: SARS-etiology CoV-2's is not fully known. The genome sequences of SARS-CoV and SARS-CoV-2, on the other hand, exhibit a high degree of homology (about 79 percent homologous). These laboratory findings matched those of patients who had been infected with SARS-CoV in 2003. As a result, the two viruses may share similar processes. The virus is known to infect a variety of tissues and organs, particularly those of the respiratory and immune systems, such as lymph nodes, tonsils, spleen, and bone marrow, causing viral pneumonia, immunosuppression, liver injury, cardiac injury, and other complications. Multiple organ damage are reflected in these laboratory findings.

Commented [36]: Can you confirm this is the right place for this paragraph in the timeline – what day of treatment was the D dimer exam? What day did results come back?

Commented [37R36]: We have updated. On day 5, D dimer examination was carried out, the sample was sent outside the hospital and the results came out 4 days later. Hospital facilities were limited, and at that time, the national insurance did not cover the financing.

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Commented [47R46]: Yes, we have updated. Thank you for your suggestion

Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-intensive care units (ICU) and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31-79% higher than that of non-ICU patients [1,5]. Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis that directly caused a severe pulmonary embolism in four of those patients [7]. The findings of this study are important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1-2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1,5].

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The use of LMWH for prophylaxis of venous thromboembolism has been approved by WHO for hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated anti-inflammatory attributes that might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with a lower incidence of mortality compared to standard DVT prophylaxys in hospitalized COVID-19 patients. In this case, the patient had been given LMWH, but not at the beginning of treatment; therefore the administration of LMWH did not seem to improve the patient's condition [14].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is still not completely clear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulations involving inflammatory cytokines, vascular endothelial injury and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent increasing severity of COVID-19, including the use of LMWH prophylaxis.

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DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

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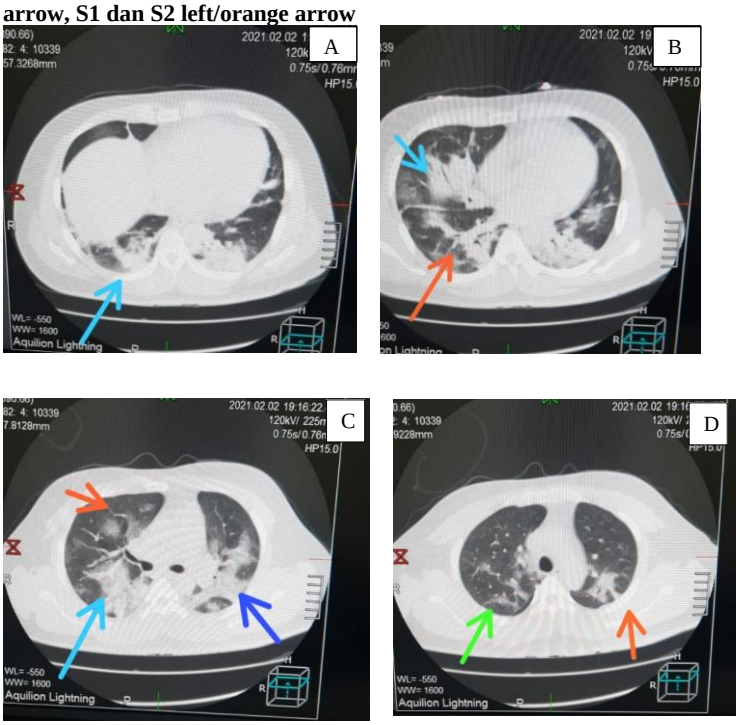
FIGURE 1. The chest CT scan without intravenous contrast revealed large GGO in both lungs : (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow



CJRT 2021-28R1 - Reviewer feedback - Clean Final

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report

ABSTRACT

Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure (MOF).

Case and outcomes: A 34-year-old male presented to the emergency room after three days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hemorrhagic fever (DHF). He was given hydration intravenous fluids, oxygen, antipyretic and hepatoprotector. On day four, the patient was diagnosed with COVID-19 and received therapy to decrease the Alanine transaminase (ALT) and Aspartate transaminase (AST) levels. While waiting for outsourced D dimer and prothrombin time results, the patient was given low molecular weight-heparin (LMWH) on day 5. On day 13, his condition deteriorated with cephalgia and shortness of breath, but the patient's family refused intubation. The chest CT scan revealed large ground-glass opacities in both lungs. The patient was given additional medications, such as Meropenem, Dexamethasone, and Remdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence than standard DVT prophylaxis in hospitalized COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH at the beginning of treatment.

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of the hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Keywords: *Hypercoagulable state, late diagnosis, young patient*

INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased c-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after four days of treatment and died after fifteen days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting three days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical history of comorbidities. Dengue Haemorrhagic Fever (DHF) was suspected by the internist based on laboratory results indicating a platelet count of 86,000 cells/µl, increased monocytes of 20%, an ALT level of 161 U/L, and an AST level of 52 U/L due to a hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs, and COVD-19 was not suspected. The patient was treated for DHF and was given intravenous fluids, oxygen, antipyretic, and hepatoprotector.

There was no improvement after four days of DHF treatment, and saturation tended to decrease. Therefore, the patient was referred to a pulmonologist in the main hospital. The patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The patient received hepatoprotector to decrease the ALT and

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Commented [55R53]: SARS-etiology CoV-2's is not fully known. The genome sequences of SARS-CoV and SARS-CoV-2, on the other hand, exhibit a high degree of homology (about 79 percent homologous). These laboratory findings matched those of patients who had been infected with SARS-CoV in 2003. As a result, the two viruses may share similar processes. The virus is known to infect a variety of tissues and organs, particularly those of the respiratory and immune systems, such as lymph nodes, tonsils, spleen, and bone marrow, causing viral pneumonia, immunosuppression, liver injury, cardiac injury, and other complications. Multiple organ damage are reflected in these laboratory findings.

AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination show that leukocytes were 12,300 cells/µL (normal value: 5.000-10.000 cells/µL), lymphocytes were 12% (normal value: 20-50%), erythrocyte sedimentation rate (ESR) was 40 mm/hour (normal value: 0-15 mm/hour), monocytes were 11% (normal value: 4-8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7-41 U/L), ALT level was 315 U/L (normal value: 12-38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7 – 5.2 mmol/L). The results of the Posteroanterior (PA) chest X-ray did not show any radiological abnormalities in the heart and lungs.

On day 5, D dimer examination was carried out, the sample was sent outside the hospital and the results came out 4 days later. Hospital facilities were limited, and at that time, the national insurance did not cover the financing. While waiting for the D dimer and prothrombin time results, the patient was given low molecular weight-heparin (LMWH). The patient was experiencing hypoxemic respiratory failure, and was in a hypercoagulable state due to the hyperinflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90-92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask (NRM) of 15 litres/minute. Laboratory tests revealed an ALT level of 87 U/L and AST 91 level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g., Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring ICU treatment using High Flow Nasal Cannula FiO2 100% Flow 60 litres per minute.

Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high flow oxygen and was able to communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed erythrocyte sedimentation rate of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative C-Reactive protein of 75 mg/L. The chest CT scan without intravenous contrast revealed large Ground Glass Opacities in both lungs such as Segment 1 (S1) and S2 left; S2 right, S3 and S6 right, S4, S5, S6 left; S4, S5, S7, S8 right; S 10 right and left (Figure 1). The patient was then given additional medications including Meropenem, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and Supplements (e.g., Vitamin C, Zinc, and Vitamin D3).

The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyperinflammation process of COVID-19. A post mortem exam was not carried out because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions[1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-intensive care units (ICU) and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31-79% higher than that of non-ICU patients [1,5]. Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis that directly caused a severe pulmonary embolism in four of those patients [7]. The findings of this study are important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1-2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1,5].

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CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is still not completely clear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulations involving inflammatory cytokines, vascular endothelial injury and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent increasing severity of COVID-19, including the use of LMWH prophylaxis.

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DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

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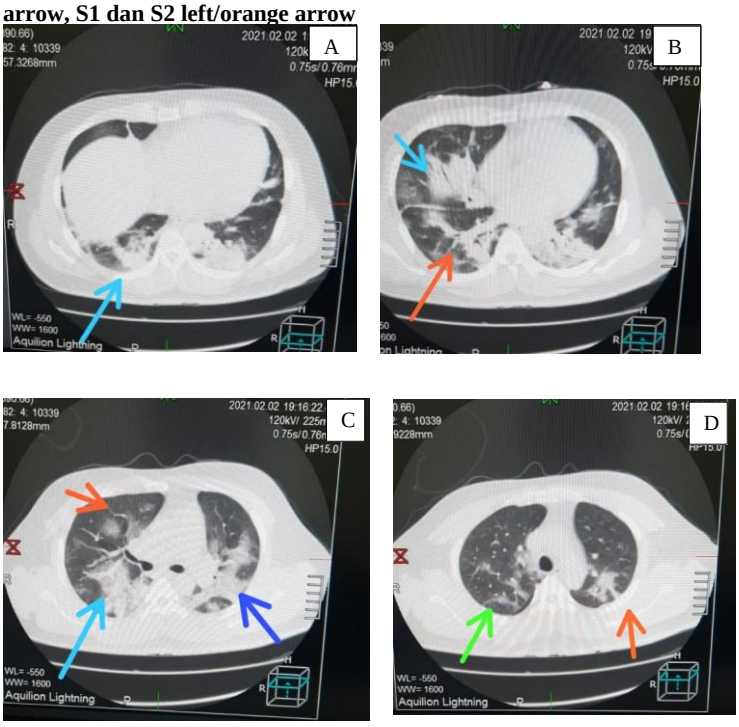

RE: [CJRT] Editor Decision - Revisions requested

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Tanggal: Sabtu, 4 Desember 2021 pukul 03.46 GMT+7

Thanks, I got these two attachments through the system so I will send off to the editor for decision now.
You can send the revised title page and cover letter to me; I can add it to your file.

Have a great weekend,

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy
(Pronouns: she, her)
201-2460 Lancaster Road Ottawa, ON K1B 4S5
Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
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To: Editor <editor@csrt.com>
Subject: Re: [CJRT] Editor Decision - Revisions requested

Dear Carly,

I'm having trouble submitting my manuscript revision. I tried submitting manuscript revisions via revisions-review in workflow, but it doesn't work. Would you like to help me? Please let me send the manuscript via this email.

Thank you for your helping and attention.

Best Regards,

Desdiani Desdiani

Pada Selasa, 23 November 2021 03.22.36 GMT+7, Carly Brockington <editor@csrt.com> menulis:

Nita Yulianti, Anindita Basuki, Desdiani Desdiani:

The Associate Editor has reached a decision regarding your submission to Canadian Journal of Respiratory Therapy, "Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report ".

Please see attached for the editor and reviewer feedback. Can you address these suggestions and send a "Response to Reviewer" document answering each point, as well as a revised manuscript with changes highlighted (or a track changes version)? This helps speed the decision process.

Let me know if you have any questions!

General Questions
Although I believe the case report does address important information and adds to the body of knowledge surrounding Covid-19 and hypercoagulable states, it seems that there are many gaps in the report that make the specific case hard to follow. I found that at the end of the report, I had many outlying questions that were not answered, such as:

1) Was the patient treated with additional or different medications/interventions as his condition worsened?
2) Why did the family refuse intubation? Was there more communication with the care team around this? If the patient was on heated high flow oxygen, couldn't he make medical decision and provide consent on his own?
3) Does the author think there was a role to treat this patient, possible with low molecular weight heparin, sooner? Would this have decreased the chance of mortality? What was the cause of death? Was a post mortem exam done?
4) Was the patient diagnosed with a hypercoagulable state prior to his hospital admission? Was this hypercoagulable state a long standing preexisting condition or was it due to Covid? Was it being treated or monitored? What was the cause?
5) Why was the patient not tested for Covid initially (as his symptoms indicate he should have been)? Or was he tested and it took days for results to come back? Was the patient transferred to another site prior to the positive Covid test result? Or was this found by the receiving site?

I feel adding in details that better outline the case and interventions, as well as clearly outlining key points the author is portraying would make the article more impactful.

Title
The title accurately reflects the purpose of the case report.

Abstract
The abstract summarizes the manuscript and can be understood without reading the manuscript. I did not find any discrepancies in the abstract and the remainder of the manuscript. However, I found lines 11 to 14 slightly unclear and was not sure if the patient was referred to another site due to the positive diagnosis or the fact they were not improving, or both. I am curious about why the patient was not tested or screened for Covid sooner and if they could have been managed at their original site once the Covid-19 diagnosis was made.

Introduction
The introduction does define the problem in terms of Covid-19, however, there is less emphasis on hypercoagulable states. Consider defining what a hypercoagulable state means and why this is significant (especially in the context of Covid) as I think it would be helpful to the audience. The literature referenced in this section to provide context seem recent and valid, however, the flow of the information is hard to follow. Consider listing symptoms and lab findings, then discussing these in relation to a hypercoagulable state. There is no research question or hypothesis stated, however, this seems appropriate considering the article is a case report.

Methodology

The article does not contain results of experimental studies, therefore, no informed consent was required. Details of the ethics approval and consent from a family member of the patient discussed is clearly stated. As this article is a case report, there is no research design methodology or data collection and analysis described. The case report section of the article included many lab and vital signs values, for example lines 61-22 state the patient had an "oxygen saturation of 96% room air". As a Respiratory Therapist, I understand the significance of this, however, other readers may not. I also found the listing of many values (lines 64-65) overwhelming, and would suggest only listing pertinent or significant lab values and in addition stating if this is high/low in comparison to normal or why this is important in this specific case. The case report portion outlines the deterioration of the patient, however, I found it lacked in describing interventions and other details. For example, line 79 states "The patient's family refused for intubation to be performed on the patient" but does not describe why or if there was discussion with the family about the repercussions of refusing to intubate the patient. The final paragraph of the case report describes the deterioration of the patient, a list of medications used and the subsequent death of the patient. However, it would be helpful to have more information about management and cause of death, for example, hypoxemic respiratory failure secondary to multiple pulmonary embolisms? Since there is an emphasis on using low molecular weight heparin in these patients later in the article, I am curious as to why this was not suggested or considered earlier in the patient's management.

Results

Not applicable, no results section (case review).

Discussion / Conclusion

Lines 104-106 state "A conclusion which can be obtained from several researches was that seriously ill patients have a higher risk factor for hypercoagulable and thrombosis than patients treated in non-ICU wards." Although this relates to the observations in the case report to the literature and studies, I find the flow and wording difficult to understand and would consider rewording to make the statement more impactful. The discussion touches on mechanisms of the pathophysiology of hypercoagulability in COVID-19 and the use of Heparin, however, this information is not discussed in relation to the case or patient (besides the use of this for treatment on the patients final days of life).

Illustrations

The figures are appropriately labeled. I would consider removing Figure 1 and 2 from the Appendices as they are "normal findings". The arrows in Figure 3 are helpful, however, I am unsure if the description of the photo could be understood without referring to the manuscript. I do appreciate the use of arrows in the CT images.

Style

I found that the flow, grammar and redundancy of this case review difficult to follow and think it took away from key messages the writer is trying to portray.

References

The references are timely as the Covid-19 pandemic is a recent issue. The references seem as though they are properly quoted and the manuscript contains an appropriate amount. However, I

did notice a few lines that likely require the addition of a citation, for example lines 135-136 and 141-142.

RE: [CJRT] Editor Decision - Revisions requested Jan 20th

Dari: Editor (editor@csrt.com)

Kepada: desdiani@ymail.com

Tanggal: Jumat, 21 Januari 2022 pukul 01.48 WIB

Hello Desidani,

Below are the Reviewer's comments. They attached a marked up copy of further suggestions – can you make these minor revisions, and then I can run it past the Associate Editor for final approval and publication? If you could accept all changes and send back a clean version with **just the latest changes highlighted**, that would be great. Also, a response to the comment below. You can send it directly to me.

Although the author addressed many of the comments I made in the review, I still have some concerns with the article in terms of the overall flow. I noticed there are still long lists of lab values within the article, which are hard to follow and take away from key messages. There is also still a significant amount of grammatical issues and use of present tense. I have made a few more comments regarding this within the revised article, please find it attached. Hopefully this helps!

Once it is accepted, I can give it a further edit f or grammar before layout.

Kind regards,

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy
(Pronouns: she, her)
201-2460 Lancaster Road Ottawa, ON K1B 4S5
Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: December 4, 2021 9:52 PM
To: Editor <editor@csrt.com>
Subject: Re: [CJRT] Editor Decision - Revisions requested

Dear Carly,

After thoroughly reading the authorship guideline, I have decided to change the authorship. The first and second authors have not made a substantive intellectual contribution to the manuscript. In this study, they performed laboratory and radiological results assessment without any further intellectual work. Thus, I decided to put their names in the acknowledgment section instead.

Thank you for your attention.

Best Regards,
Desdiani Desdiani
Pada Sabtu, 4 Desember 2021 03.46.21 GMT+7, Editor <editor@csrt.com> menulis:

Thanks, I got these two attachments through the system so I will send off to the editor for decision now.
You can send the revised title page and cover letter to me; I can add it to your file.

Have a great weekend,

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy

(Pronouns: she, her)
201-2460 Lancaster Road Ottawa, ON K1B 4S5
Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: December 2, 2021 6:33 PM
To: Editor <editor@csrt.com>
Subject: Re: [CJRT] Editor Decision - Revisions requested

Dear Carly,

I'm having trouble submitting my manuscript revision. I tried submitting manuscript revisions via revisions-review in workflow, but it doesn't work. Would you like to help me? Please let me send the manuscript via this email.
Thank you for your helping and attention.

Best Regards,
Desdiani Desdiani
Pada Selasa, 23 November 2021 03.22.36 GMT+7, Carly Brockington <editor@csrt.com> menulis:

Nita Yulianti, Anindita Basuki, Desdiani Desdiani:

The Associate Editor has reached a decision regarding your submission to Canadian Journal of Respiratory Therapy, "Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report ".

Please see attached for the editor and reviewer feedback. Can you address these suggestions and send a “Response to Reviewer” document answering each point, as well as a revised manuscript with changes highlighted (or a track changes version)? This helps speed the decision process.

Let me know if you have any questions!

Managing Editor

editor@csrt.com

Canadian Journal of Respiratory Therapy

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Late diagnosis of COVID-19 in a 34-year-old man with hypercoagulable state: A case report

ABSTRACT

Late diagnosis of COVID-19 in a young patient with hypercoagulation state can cause high mortality rate. Clinical manifestations of COVID-19 include respiratory and extrapulmonary symptoms such as hypercoagulable state, increased transaminase enzymes, and multiple-organ failure (MOF). A 34-years-old male presented to the emergency room of peripheral hospital with high fever for 3 days, weakness, flatulence, thrombocytopenia, and elevated liver transaminase enzymes. The patient was initially diagnosed with dengue haemorrhagic fever (DHF) and was given hydration intravenous fluids, oxygen, antipyretic and hepatoprotector. After 4 days treated with suspected DHF, the patient was referred to another hospital because his condition did not improve and he was diagnosed with COVID-19 based on positive results of polymerase chain reaction (PCR) nasopharyngeal swabs. This patient received therapy to decrease the Alanine transaminase (ALT) and Aspartate transaminase (AST) levels, azithromycin, N acetyl cysteine and multivitamins. On day 13, his condition deteriorated with cephalgia, shortness of breath, the oxygen saturation was approximately 84% room air, but the patient's family refused for intubation to be performed on the patient. The laboratory tests revealed leukocytes of 18,000 cells/µL, platelets 74,000 cells/µL, erythrocyte sedimentation rate of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, ALT level of 94 U/L, AST level of 51 U/L, ESR of 95 mm/hour, PT 15,3, aPTT 32,0, fibrinogen > 500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative CRP of 75 mg/L. The chest CT scan revealed large ground-glass opacities in both lungs. The patient was then subjected to additional medications, such as Meropenem, Dexamethasone, Remdesivir, Low-molecular-weight heparin (LMWH). On day 15, the patient passed away. Hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of hypercoagulable state, including the use of Low Molecular Weight Heparin prophylaxis, can be used to prevent the severity of COVID-19 symptoms.

Keywords: *Hypercoagulable state, late diagnosis, young patient*

INTRODUCTION

COVID-19 is caused by a contagious virus which can lead to severe respiratory problems. The complications of thrombotic events which occur in COVID-19 patients could result in patient deterioration. Thrombotic and coagulation abnormalities promoting a hypercoagulable state [1]. COVID-19 patients usually have symptoms of shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhoea, and diarrhoea [2]. Laboratory findings include decreased lymphocyte and increased c-reactive protein (CRP). In terms of cases with coagulopathy complication, there were increases in D-dimers, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation reveals ground-glass opacities (GGO), bilateral multiple lobular and subsegmental consolidation [4]. We report a patient who was initially diagnosed with dengue hemorrhagic fever (DHF), but was then diagnosed with COVID-19 after four days of treatment, and subsequently died after fifteen days of hospitalization.

ETHICS APPROVAL

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The patients's elder sister consented to the publication of this deidentified case report. Institutional review board approval is not required for deidentified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man with high fever for 3 days, weakness, and flatulence was admitted to the emergency room of a peripheral hospital. He had no medical history of comorbidities. The platelet count is 86,000 cells/µl, hence suspected as Dengue Haemorrhagic Fever. Laboratory tests revealed increased monocytes of 20%, ALT level of 161 U/L, AST level of 52 U/L due to hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs. The patient was treated with a suspected DHF and was given hydration intravenous fluids, oxygen, antipyretic, and hepatoprotector.

After four days of being treated with suspected DHF, the patient was referred to a hospital because his condition did not improve. The patient was diagnosed with COVID-19 based on positive results of polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. Patients received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination show that leukocytes were 12,300 cells/µL (normal value: 5.000-10.000 cells/µL), lymphocytes were 12% (normal value: 20-50%), erythrocyte sedimentation rate (ESR) was 40 mm/hour (normal value: 0-15 mm/hour), monocytes were 11% (normal value: 4-8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7-41 U/L), ALT level was 315 U/L (normal value: 12-38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7 – 5.2 mmol/L). The results of the Posteroanterior (PA) chest X-ray did not show any radiological abnormalities in the heart and lungs.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90-92% room air. He was subsequently subjected to oxygen therapy using a non-rebreathing mask (NRM) of 15 liters/minute. Laboratory tests revealed an ALT level of 87 U/L and AST 91 level of U/L. Chest radiograph indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g., Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, Multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath, and also suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, hence requiring ICU treatment using High Flow Nasal Cannula FiO2 100% Flow 60 liters per minute. The patient's family refused for intubation to be performed on the patient, because they think the action will harm the patient. The laboratory tests revealed leukocytes of 18,000 cells/µL, platelets 74,000 cells/µL, erythrocyte sedimentation rate of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, ALT level of 94 U/L, AST level of 51 U/L, ESR of 95 mm/hour, Prothrombin Time 15,3, activated Partial Thromboplastin Time 32,0, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative C-Reactive Protein of 75 mg/L. The chest CT scan without intravenous contrast revealed large Ground Glass Opacities in both lungs such as Segment 1 (S1) and S2 left; S2 right, S3 and S6 right, S4, S5, S6 left; S4, S5, S7, S8 right; S 10 right and left (Figure 1). The patient was then subjected to additional medications, such as Meropenem, Dexamethasone, Remdesivir, Low-molecular-weight heparin (LMWH), Ondansetron, Omeprazole, and Supplements (e.g., Vitamin C, Zinc, and Vitamin D3). The patient's condition

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worsened, and the family asked to be referred and still refused to be intubated. On the 15th day, the patient passed away with hypoxemic respiratory failure.

DISCUSSION

The hypercoagulable state was found in COVID-19 patients with poor clinical conditions[1]. Several studies have shown that the pulmonary thrombosis rate of covid-19 patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-intensive care units (ICU) and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31-79% higher than that of non-ICU patients [1,5] . Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis, and 4 patients directly caused a severe pulmonary embolism [7]. The findings of this study are very important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1-2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1,5].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A Retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, , cardiac troponin, ferritin, lactate dehydrogenase [9]. Patients with coagulopathy complications have higher levels of D-dimers [3]. There were no previous studies on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and the potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia, and ischemia-reperfusion liver injury, and drug-induced hepatotoxicity, may direct injury from the virus to the liver [10]. In this patient, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are very important for regulating vascular permeability, maintaining hemostasis, and regulating hemolysis. Vascular endothelial injury due to the infection of the SARS CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome (ARDS) leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions are increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased of serum lactate dehydrogenase and ferritin levels are related to a high risk of death and microangiopathy in thrombotic complications of COVID-19 patients [9]. In this patient, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT, due to hyperinflammatory reactions and vascular endothelial injury .

The use of low-molecular-weight heparin (LMWH) for prophylaxis of venous thromboembolism has been approved by WHO as the hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated as anti-inflammatory

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attributes which might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with lower incidence of mortality compared to standard DVT prophylaxys in hospitalized COVID-19 patients. In this case, the patient has been given LMWH, but not since the beginning of treatment, therefore the administration of LMWH does not seem to improve the patient's condition [14].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hyper coagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results will help us for the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is still not completely clear. It is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms involving proinflammatory cytokines, vascular endothelial injury and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to prevent severity of COVID-19, although the data are still limited and require further studies. Early detection and management of hypercoagulable state can be effective to prevent severity of COVID-19, including the use of Low Molecular Weight Heparin prophylaxis.

DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for deidentified single case reports or histories based on institutional policies.

REFERENCES

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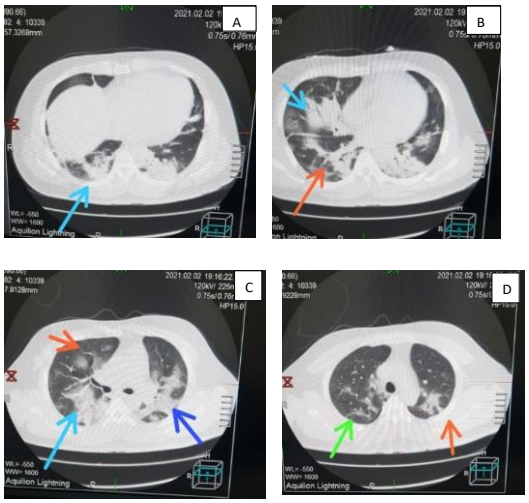
FIGURE 1. The chest CT scan without intravenous contrast revealed large GGO in both lungs : (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow



RE: Revision of Manuscript CJRT 2021-28 20 Feb 2022

Dari: Editor (editor@csrt.com)

Kepada: desdiani@ymail.com

Tanggal: Minggu, 20 Februari 2022 pukul 23.51 WIB

Hello Desdiani,

I have given the manuscript a bit of an edit and tried to incorporate some of your responses to the reviewers into the text. Can you make sure this looks correct? There are a few remaining questions from the reviewers that should be easier to see now.

If you can send me a revision and a response to these comments, I can run it past the editor for final approval.

Kind regards,

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy
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From: desdiani - <desdiani@ymail.com>
Sent: February 7, 2022 1:57 AM
To: Editor <editor@csrt.com>
Subject: Re: Revision of Manuscript

Dear Carly,

Thank you for your email

Best Regards,
Desdiani Desdiani

Pada Senin, 7 Februari 2022 00.59.02 GMT+7, Editor <editor@csrt.com> menulis:

Sorry for the delay – I am going through the suggestions and will edit the manuscript and send you a version to approve shortly.

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Regarding reviewer"s comment, there is still minor revision, but sorry I can"t find it attached from email.
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Best Regards
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CJRT 2021-28R1 - Reviewer feedback - Clean.docx
1.1MB

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report

ABSTRACT

Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure (MOF).

Case and outcomes: A 34-year-old male presented to the emergency room after three days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hemorrhagic fever (DHF). He was given hydration intravenous fluids, oxygen, antipyretic and hepatoprotector. On day four, the patient was diagnosed with COVID-19 and received therapy to decrease the Alanine transaminase (ALT) and Aspartate transaminase (AST) levels. While waiting for outsourced D dimer and prothrombin time results, the patient was given low molecular weight-heparin (LMWH). On day 13, his condition deteriorated with cephalgia and shortness of breath, but the patient's family refused intubation. The chest CT scan revealed large ground-glass opacities in both lungs. The patient was given additional medications, such as Meropenem, Dexamethasone, and Remdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence than standard DVT prophylaxis in hospitalized COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH at the beginning of treatment.

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of the hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Keywords: *Hypercoagulable state, late diagnosis, young patient*

INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased c-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after four days of treatment and died after fifteen days of hospitalization.

ETHICS APPROVAL

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The patients' elder sister consented to publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting three days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical history of comorbidities. Dengue Haemorrhagic Fever (DHF) was suspected by the internist based on laboratory results indicating a platelet count of 86,000 cells/µl, increased monocytes of 20%, an ALT level of 161 U/L, and an AST level of 52 U/L due to a hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs, and COVD-19 was not suspected. The patient was treated for DHF and was given intravenous fluids, oxygen, antipyretic, and hepatoprotector.

There was no improvement after four days of DHF treatment, and saturation tended to decrease. Therefore, the patient was referred to a pulmonologist in the main hospital. The patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The patient received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination show that leukocytes were 12,300 cells/µL (normal value: 5.000-10.000 cells/µL), lymphocytes were 12% (normal value: 20-50%), erythrocyte sedimentation rate (ESR) was 40 mm/hour (normal value: 0-15 mm/hour), monocytes were 11% (normal value: 4-8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7-41 U/L), ALT level was 315 U/L (normal value: 12-38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7 – 5.2 mmol/L). The results of the Posteroanterior (PA) chest X-ray did not show any radiological abnormalities in the heart and lungs.

A D dimer examination was carried out, and the sample was sent outside the hospital. Hospital facilities were limited, and at that time, the national insurance did not cover the financing. While waiting for the D dimer and prothrombin time results, the patient was given low molecular weight-heparin (LMWH). The patient was experiencing chypoxemic respiratory failure, and was in a hypercoagulable state due to the hyperinflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90-92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask (NRM) of 15 litres/minute. Laboratory tests revealed an ALT level of 87 U/L and AST 91 level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g., Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring ICU treatment using High Flow Nasal Cannula FiO2 100% Flow 60 litres per minute.

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Commented [A8]: Can you confirm this is the right place for this paragraph in the timeline – what day of treatment was the D dimer exam? What day did results come back?

Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high flow oxygen and was able to communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed leukocytes of 18,000 cells/μL, platelets 74,000 cells/μL, erythrocyte sedimentation rate of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, ALT level of 94 U/L, AST level of 51 U/L, ESR of 95 mm/hour, Prothrombin Time 15,3, activated Partial Thromboplastin Time 32,0, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative C-Reactive protein of 75 mg/L. The chest CT scan without intravenous contrast revealed large Ground Glass Opacities in both lungs such as Segment 1 (S1) and S2 left; S2 right, S3 and S6 right, S4, S5, S6 left; S4, S5, S7, S8 right; S 10 right and left (Figure 1). The patient was then given additional medications including Meropenem, Dexamethasone, Remdesivir, Low-molecular-weight heparin (LMWH), Ondansetron, Omeprazole, and Supplements (e.g., Vitamin C, Zinc, and Vitamin D3).

The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyperinflammation process of COVID-19. A post mortem exam was not carried out because the family did not approve it.

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DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions[1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-intensive care units (ICU) and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31-79% higher than that of non-ICU patients [1,5]. Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis that directly caused a severe pulmonary embolism in four of those patients [7]. The findings of this study are important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1-2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1,5].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, cardiac troponin, ferritin, and lactate dehydrogenase [9]. Patients with coagulopathy complications have higher D-dimer levels [3].

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In searching the current literature, no previous studies were found on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia, ischemia-reperfusion liver injury, and drug-induced hepatotoxicity, may direct injury from the virus to

the liver [10]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are important for regulating vascular permeability, maintaining hemostasis, and regulating hemolysis. Vascular endothelial injury due to the infection of the SARS CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome (ARDS) leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions indicate increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased serum lactate dehydrogenase and ferritin levels are related to a high risk of death and microangiopathy in thrombotic complications of COVID-19 patients [9]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT due to hyperinflammatory reactions and vascular endothelial injury.

The use of LMWH for prophylaxis of venous thromboembolism has been approved by WHO for hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated anti-inflammatory attributes that might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with a lower incidence of mortality compared to standard DVT prophylaxys in hospitalized COVID-19 patients. In this case, the patient had been given LMWH, but not at the beginning of treatment, therefore the administration of LMWH did not seem to improve the patient's condition [14].

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CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is still not completely clear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms involving proinflammatory cytokines, vascular endothelial injury and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent increasing severity of COVID-19, including the use of LMWH prophylaxis.

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DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

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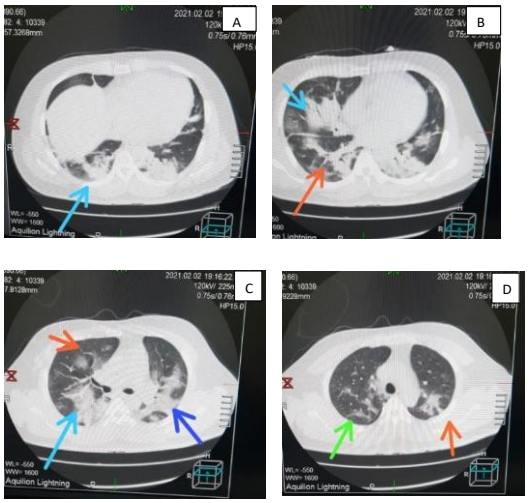
FIGURE 1. The chest CT scan without intravenous contrast revealed large GGO in both lungs : (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow



Re: Revision of Manuscript CJRT 2021-28 24 Feb 2022

Dari: desdiani - (desdiani@ymail.com)

Kepada: editor@csrt.com

Tanggal: Kamis, 24 Februari 2022 pukul 08.44 WIB

Dear Carly,

Here i submit and revised all responses to all reviewer's comments. I hope that all the revisions submitted are appropriate. Thank you for your attention.

Best Regards,

Desdiani Desdiani

> Pada Minggu, 20 Februari 2022 23.51.17 GMT+7, Editor <editor@csrt.com> menulis:
>
> Hello Desdiani,
>
> I have given the manuscript a bit of an edit and tried to incorporate some of your responses to the reviewers into the text. Can you make sure this looks correct? There are a few remaining questions from the reviewers that should be easier to see now.
>
> If you can send me a revision and a response to these comments, I can run it past the editor for final approval.
>
> Kind regards,
>
> **Carly Brockington**
> Managing Editor, Canadian Journal of Respiratory Therapy
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CJRT 2021-28R1 - Reviewer feedback - Clean Final.docx
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Commented [A1]: Do we know what day they were given LMWH?

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INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased c-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

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The patients' elder sister consented to publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

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On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90-92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask (NRM) of 15 litres/minute. Laboratory tests revealed an ALT level of 87 U/L and AST 91 level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g., Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

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Commented [A6R4]: SARS-etiology CoV-2's is not fully known. The genome sequences of SARS-CoV and SARS-CoV-2, on the other hand, exhibit a high degree of homology (about 79 percent homologous). These laboratory findings matched those of patients who had been infected with SARS-CoV in 2003. As a result, the two viruses may share similar processes. The virus is known to infect a variety of tissues and organs, particularly those of the respiratory and immune systems, such as lymph nodes, tonsils, spleen, and bone marrow, causing viral pneumonia, immunosuppression, liver injury, cardiac injury, and other complications. Multiple organ damage are reflected in these laboratory findings.

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Commented [A8R7]: We have updated. On day 5, D dimer examination was carried out, the sample was sent outside the hospital and the results came out 4 days later. Hospital facilities were limited, and at that time, the national insurance did not cover the financing.

Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high flow oxygen and was able to communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed erythrocyte sedimentation rate of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative C-Reactive protein of 75 mg/L. The chest CT scan without intravenous contrast revealed large Ground Glass Opacities in both lungs such as Segment 1 (S1) and S2 left; S2 right, S3 and S6 right, S4, S5, S6 left; S4, S5, S7, S8 right; S 10 right and left (Figure 1). The patient was then given additional medications including Meropenem, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and Supplements (e.g., Vitamin C, Zinc, and Vitamin D3).

The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyperinflammation process of COVID-19. A post mortem exam was not carried out because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions[1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-intensive care units (ICU) and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31-79% higher than that of non-ICU patients [1,5]. Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis that directly caused a severe pulmonary embolism in four of those patients [7]. The findings of this study are important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1-2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1,5].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, cardiac troponin, ferritin, and lactate dehydrogenase [9]. Patients with coagulopathy complications have higher D-dimer levels [3].

In searching the current literature, no previous studies were found on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia, ischemia-reperfusion liver injury, and drug-induced hepatotoxicity, may direct injury from the virus to the liver [10]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

Commented [A9]: Please confirm this paragraph is correct. Was the family aware that the patient would likely die if not intubated?

Commented [A10R9]: The medical team have already persuaded the patient and his family that patient would likely die if not intubated, but still refused to be intubated.

Commented [A11]: Although this information is useful, having a list of values may be overwhelming to the reader. I suggest only including pertinent and abnormal values and why these are significant

Commented [A12R11]: Thank you for your suggestions. We have adjusted

Commented [A13R11]:

Commented [A14]: Please explain what this means

Commented [A15R14]: Anterior and posterior views of the pulmonary lobes and segments. The placement of the pulmonary segments and lobes on the anterior surface of the right and left lungs is depicted in a schematic drawing superimposed on a three-dimensional surface reformatted picture produced with a multidetector CT scanner. The apical (S1) and anterior (S3) segments of the right upper lobe, the lateral (S4) and medial (S5) segments of the right middle lobe, and the anterior basal (S8) segment of the right lower lobe make up the anterior surface of the right lung. The apicoposterior segment (S1 + 2), anterior (S3) segment, superior (S4) and inferior (S5) lingular segments of the left upper lobe, as well as the anteromedial segment (S6), the lateral basal (S9) and posterior basal (S10) segments.

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Commented [A17]: Can this be removed here because the patient was given LMWH on day 5, or is it only on day 13 they were given LMWH?

Commented [A18R17]: Yes, we have updated. Thank you for your suggestion

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are important for regulating vascular permeability, maintaining hemostasis, and regulating hemolysis. Vascular endothelial injury due to the infection of the SARS CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome (ARDS) leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions indicate increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased serum lactate dehydrogenase and ferritin levels are related to a high risk of death and microangiopathy in thrombotic complications of COVID-19 patients [9]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT due to hyperinflammatory reactions and vascular endothelial injury.

The use of LMWH for prophylaxis of venous thromboembolism has been approved by WHO for hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated anti-inflammatory attributes that might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with a lower incidence of mortality compared to standard DVT prophylaxys in hospitalized COVID-19 patients. In this case, the patient had been given LMWH, but not at the beginning of treatment; therefore the administration of LMWH did not seem to improve the patient's condition [14].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is still not completely clear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulations involving inflammatory cytokines, vascular endothelial injury and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent increasing severity of COVID-19, including the use of LMWH prophylaxis.

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DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

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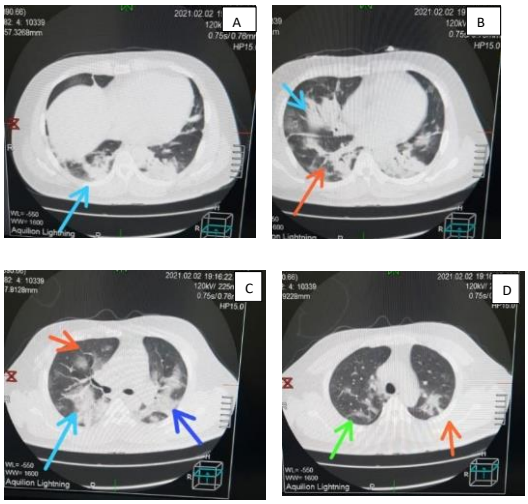
FIGURE 1. The chest CT scan without intravenous contrast revealed large GGO in both lungs : (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow



RE: Revision of Manuscript CJRT 2021-28 26 feb 2022

Dari: Editor (editor@csrt.com)

Kepada: desdiani@ymail.com

Tanggal: Sabtu, 26 Februari 2022 pukul 01.34 WIB

Thanks! I have sent this to the editor and I will get right back to you with a decision.

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy
(Pronouns: she, her)
201-2460 Lancaster Road Ottawa, ON K1B 4S5
Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: February 23, 2022 8:45 PM
To: Editor <editor@csrt.com>
Subject: Re: Revision of Manuscript CJRT 2021-28

Dear Carly,

Here i submit and revised all responses to all reviewer's comments. I hope that all the revisions submitted are appropriate. Thank you for your attention.

Best Regards,

Desdiani Desdiani

Pada Minggu, 20 Februari 2022 23.51.17 GMT+7, Editor <editor@csrt.com> menulis:

Hello Desdiani,

I have given the manuscript a bit of an edit and tried to incorporate some of your responses to the reviewers into the text. Can you make sure this looks correct? There are a few remaining questions from the reviewers that should be easier to see now.

If you can send me a revision and a response to these comments, I can run it past the editor for final approval.

Kind regards,

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy
(Pronouns: she, her)
201-2460 Lancaster Road Ottawa, ON K1B 4S5

Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: February 7, 2022 1:57 AM
To: Editor <editor@csrt.com>
Subject: Re: Revision of Manuscript

Dear Carly,

Thank you for your email

Best Regards,
Desdiani Desdiani

Pada Senin, 7 Februari 2022 00.59.02 GMT+7, Editor <editor@csrt.com> menulis:

Sorry for the delay – I am going through the suggestions and will edit the manuscript and send you a version to approve shortly.

Carly Brockington

Managing Editor, Canadian Journal of Respiratory Therapy

(Pronouns: she, her)

201-2460 Lancaster Road Ottawa, ON K1B 4S5

Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: February 2, 2022 3:16 AM
To: Editor <editor@csrt.com>
Subject: Revision of Manuscript

Dear Carly,

Regarding reviewer"s comment, there is still minor revision, but sorry I can"t find it attached from email.

Would you please help me.

Thank you for your attention

Best Regards

Desdiani Desdiani

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report

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[2] Department of Pulmonology and Respiratory Medicine, Bhayangkara Brimob Hospital, Cimanggis, Depok, West Java, Indonesia

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ABSTRACT

Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure (MOF).

Case and outcomes: A 34-year-old male presented to the emergency room after three days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hemorrhagic fever (DHF). He was given hydration intravenous fluids, oxygen, antipyretic, and hepatoprotector. On day four4, the patient was diagnosed with COVID-19 and received therapy to decrease the Alanine transaminase (ALT) and Aspartate transaminase (AST) levels. While waiting for outsourced D dimer and prothrombin time results, the patient was given low molecular weight- heparin (LMWH) on day 5. On day 13, his condition deteriorated with cephalgia and shortness of breath, but the patient's family refused intubation. The chest CT scan revealed large ground-glass opacities in both lungs. The patient was given additional medications, such as Meropenem, Dexamethasone, and Remdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence than standard DVT prophylaxis in hospitalized COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH at the beginning of treatment.

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of the hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Key wWords: Hhypercoagulable state, ; late diagnosis, ; young patient

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Commented [A2]: Author: Please define DVT. DVT is Deep Vine Thrombosis

Commented [A3]: Please provide 5–10 keywods. COVID-19, hypercoagulable state, late diagnosis, LMWH, young patient

INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in the deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased Cc-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4]. This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after four 4 days of treatment and died after fifteen 15 days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to the publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting three 3 days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical history of comorbidities. The internist suspected Dengue Haemorrhagic Fever (DHF) based on laboratory results indicating a platelet count of 86,000 cells/µlL, increased monocytes of 20%, and an Alanine transaminase (ALT) level of 161 U/L, and an Aspartate transaminase (AST) level of 52 U/L due to a hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs, and COVD-19 was not suspected. The patient was treated for DHF and was given intravenous fluids, oxygen, antipyretic, and hepatoprotector.

After four 4 days of DHF treatment, there was no improvement, and saturation tended to decrease. Therefore, the patient was referred to a pulmonologist in the main hospital. There, the patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The patient received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination showed that leukocytes were 12,300 cells/µL (normal value: 5.000-–10.000 cells/µL), lymphocytes were 12% (normal value: 20% -– 50%), erythrocyte sedimentation rate (ESR) was 40 mm/hour (normal value: 0-–15 mm/hour), monocytes were 11% (normal value: 4% -– 8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7-–41 U/L), ALT level was 315 U/L (normal value: 12-–38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7 – 5.2 mmol/L). The posteroanterior (PA) chest X-ray results did not show any radiological abnormalities in the heart and lungs.

On day 5, the D dimer examination was carried out, the sample was sent outside the hospital, and the results came four 4 days later. Hospital facilities were limited, and, at that time, the national insurance did not cover the financingtest cost. While waiting for the D dimer and prothrombin timePT results, the patient was given low molecular weight heparin

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Yes it is(LMWH). The patient was experiencing hypoxemic respiratory failure and was in a hypercoagulable state due to the hyper inflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90% -– 92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask (NRM) of 15 Llitres/minute. Laboratory tests revealed an ALT level of 87 U/L and AST 91 level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g., Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring intensive care unit (ICU) treatment using Hhigh Fflow Nnasal cCannula FiO_2 100% Fflow 60 lL/itres per minute.

Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high-flow oxygen and could communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed erythrocyte sedimentation rateESR of 95 mm/hour, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2,553 ng/L, and quantitative CRPC-Reactive protein of 75 mg/L. The chest CT scan without intravenous contrast revealed large Ground Glass OpacitiesGGO in both lungs, such

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The patient was then given additional medications, including Meropenem, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and Ssupplements (e.g., Vitamin C, Zinc, and Vitamin D3). The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyper inflammation process of COVID-19. A post mortem exam was not conducted because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions [1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non intensive care units (ICUs) and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31% -– 79% higher than that of non-ICU patients [1, 5]. Another study reported that the incidence of thrombosis in non-ICU patients

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CONCLUSION Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is unclear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulation involving inflammatory cytokines, vascular endothelial injury, and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease the severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent the increasing severity of COVID-19, including the use of LMWH prophylaxis.

DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

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Figure 1. The chest CT scan without intravenous contrast revealed large ground-glass opacitiesGGO in both lungs : (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow.

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Kepada: desdiani@ymail.com

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Here i submit and revised all responses to all reviewer's comments. I hope that all the revisions submitted are appropriate. Thank you for your attention.

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If you can send me a revision and a response to these comments, I can run it past the editor for final approval.

Kind regards,

Response needed: CJRT-2021-028 edited manuscript and proof 7 April 2022

Dari: Danhua Wang (danhua.wang@cdnsciencepub.com)

Kepada: desdiani@ymail.com

Tanggal: Kamis, 7 April 2022 pukul 01.17 WIB

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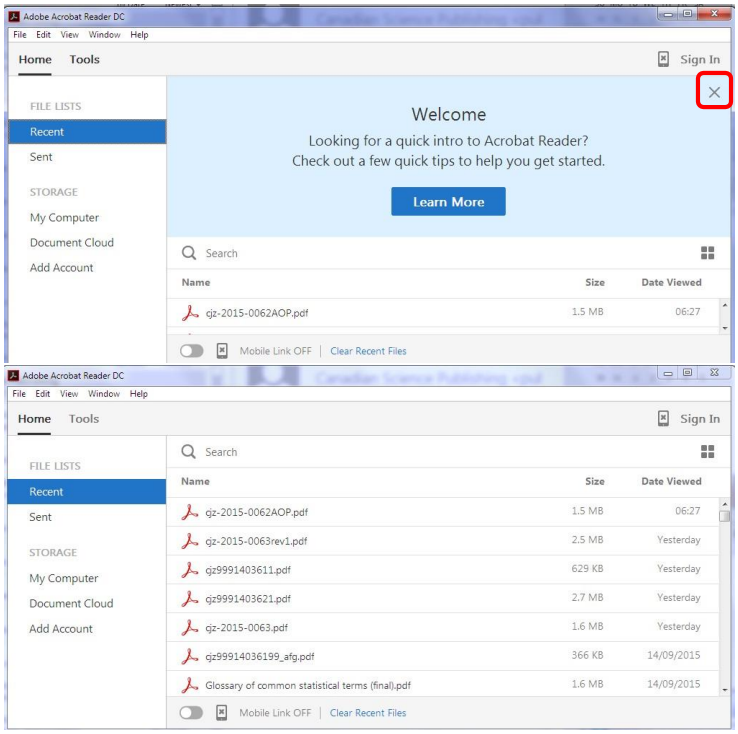

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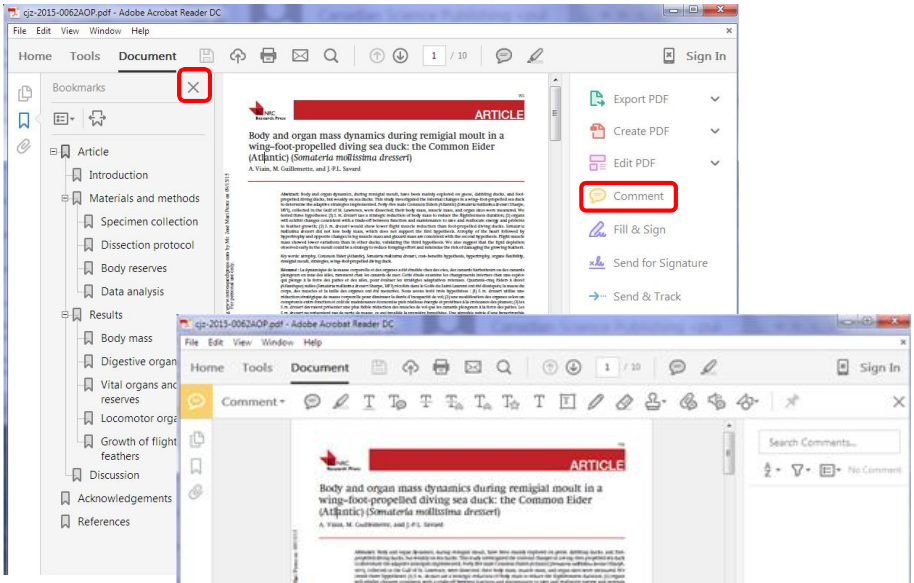

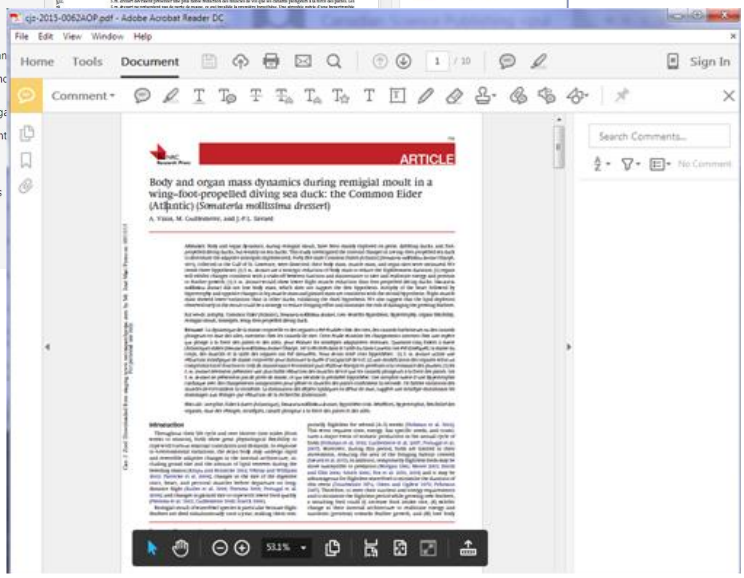

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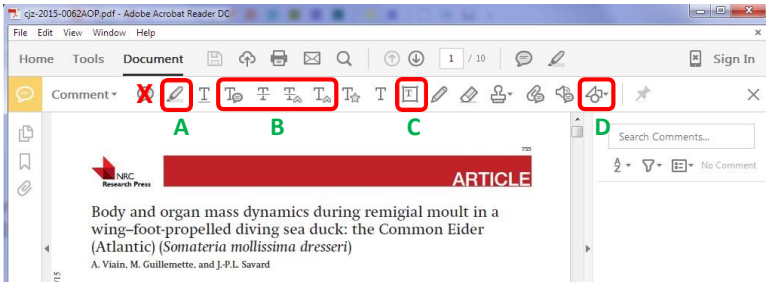

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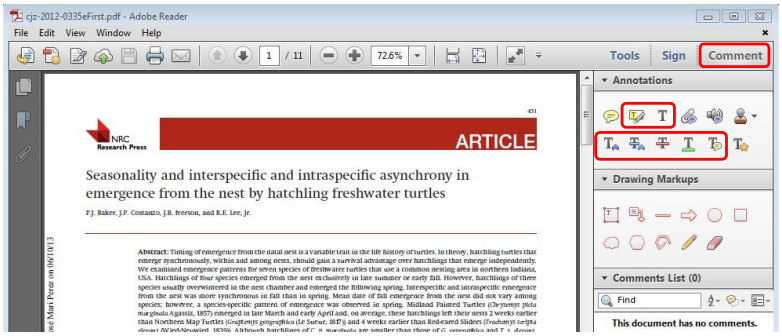

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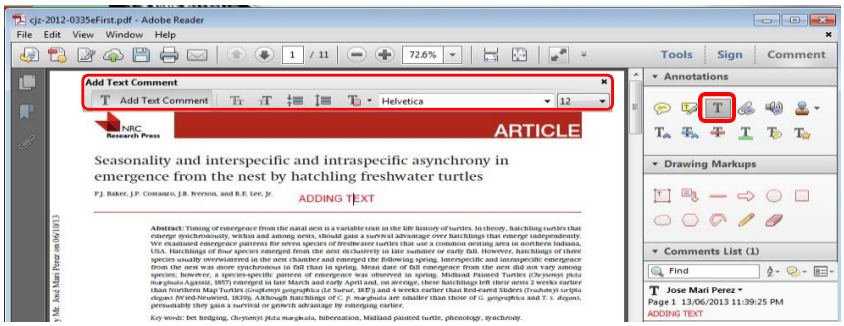

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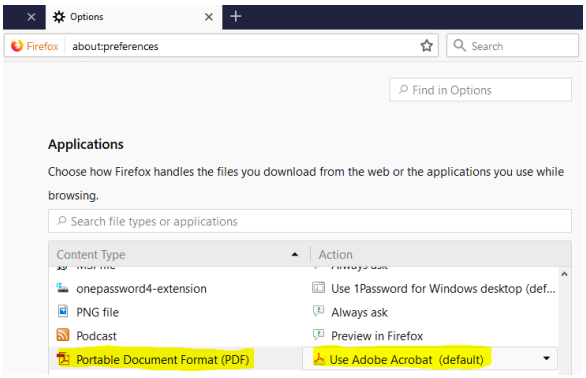

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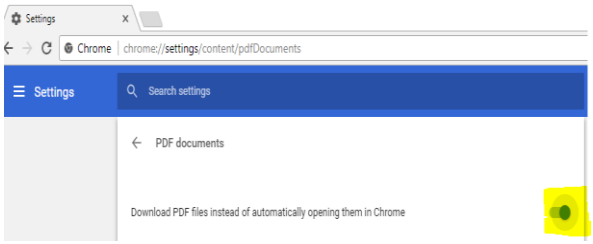

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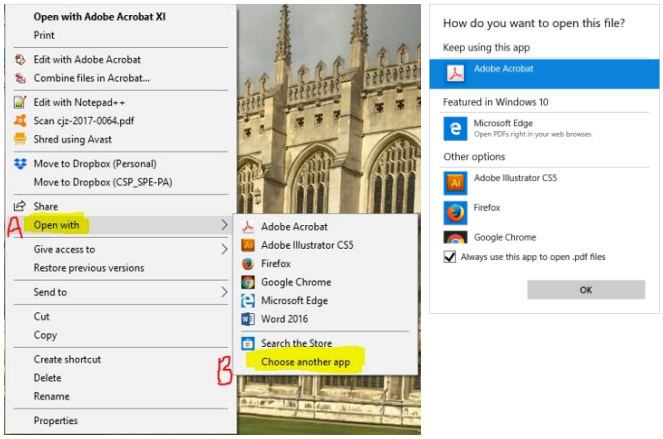

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Kepada: danhua.wang@cdnsciencepub.com

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Late diagnosis of COVID-19 in a 34-year-old man

Desdiani ~~Desdiani~~

-Case Report

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report

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~~ABSTRACT~~

Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and

extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure ~~(MOF)~~.

Case and outcomes: A 34-year-old male presented to the emergency room after three days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hemorrhagic fever ~~(DHF)~~. He was given hydration intravenous fluids, oxygen, antipyretic, and hepatoprotector. On day ~~four~~4, the patient was diagnosed with COVID-19 and received therapy to decrease the Alanine transaminase ~~(ALT)~~ and Aspartate transaminase ~~(AST)~~ levels. While waiting for outsourced D dimer and prothrombin time results, the patient was given low molecular weight- heparin (LMWH) on day 5. On day 13, his condition deteriorated with cephalgia and shortness of breath, but the patient's family refused intubation. The chest CT scan revealed large ground-glass opacities in both lungs. The patient was given additional medications, such as Meropenem, Dexamethasone, and Remdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence than standard DVT prophylaxis in hospitalized COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH at the beginning of treatment.

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of the hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Key ~~w~~Words: ~~H~~*hypercoagulable state*~~,~~, *late diagnosis*~~,~~, *young patient*

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INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in the deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased C~~c~~-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after ~~four~~ 4 days of treatment and died after ~~fifteen~~ 15 days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to the publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting ~~three~~ 3 days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical

history of comorbidities. The internist suspected ~~Dengue Haemorrhagic Fever (~~DHF~~)~~ based on laboratory results indicating a platelet count of 86,000 cells/µ~~H~~L, increased monocytes of 20%, ~~and~~ an Alanine transaminase (ALT) level of 161 U/L, and an Aspartate transaminase (AST) level of 52 U/L due to a hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs, and COVD-19 was not suspected. The patient was treated for DHF and was given intravenous fluids, oxygen, antipyretic, and hepatoprotector.

After ~~four~~ 4 days of DHF treatment, there was no improvement, and saturation tended to decrease. Therefore, the patient was referred to a pulmonologist in the main hospital. There, the patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The patient received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination showed that leukocytes were 12,300 cells/µL (normal value: 5.000–10.000 cells/µL), lymphocytes were 12% (normal value: 20%–50%), erythrocyte sedimentation rate (ESR) was 40 mm/h~~our~~ (normal value: 0–15 mm/h~~our~~), monocytes were 11% (normal value: 4%–8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7–41 U/L), ALT level was 315 U/L (normal value: 12–38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7–5.2 mmol/L). The posteroanterior ~~(PA)~~ chest X-ray results did not show any radiological abnormalities in the heart and lungs.

On day 5, the D dimer examination was carried out, the sample was sent outside the hospital, and the results came ~~four~~ 4 days later. Hospital facilities were limited, and, at that time, the national insurance did not cover the ~~financing~~test cost. While waiting for the D dimer and ~~prothrombin time~~PT results, the patient was given low molecular weight heparin

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(LMWH). The patient was experiencing hypoxemic respiratory failure and was in a hypercoagulable state due to the hyper inflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90%~~, ,~~ ~~,~~92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask ~~(NRM)~~ of 15 L~~litres~~/min~~ute~~. Laboratory tests revealed an ALT level of 87 U/L and AST 91 level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g.~~,~~ Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring intensive care unit (ICU) treatment using ~~H~~high ~~F~~flow ~~N~~nasal c~~C~~annula FiO_2 100% ~~F~~flow 60 ~~l~~L/~~itres per~~ min~~ute~~.

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Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high-flow oxygen and could communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed ~~erythrocyte sedimentation rate~~ESR of 95 mm/h~~our~~, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2~~,~~553 ng/L, and quantitative CRP~~C-Reactive protein~~ of 75 mg/L. The chest CT scan without intravenous contrast revealed large ~~Ground Glass Opacities~~GGO in both lungs~~,~~ such

as Segment 1 (S1) and S2 left; S2 ~~right~~, S3, and S6 right; ~~-~~ S4, S5, and S6 left; S4, S5, S7, S8 right; ~~–~~ S~~–~~10 right and left (Figure 1)~~.~~, representing anterior and posterior views of the pulmonary lobes and segments. The placement of the pulmonary segments and lobes on the anterior surface of the right and left lungs are depicted in a schematic drawing superimposed on a three-dimensional surface reformatted picture produced with a multidetector CT scanner. The apical (S1) and anterior (S3) segments of the right upper lobe, the lateral (S4) and medial (S5) segments of the right middle lobe, and the anterior basal (S8) segment of the right lower lobe make up the anterior surface of the right lung. The apicoposterior segment (S1 + S2), anterior (S3) segment, superior (S4) and inferior (S5) lingular segments of the left upper lobe, as well as the anteromedial segment (S6), the lateral basal (S9), and posterior basal (S10) segments.

The patient was then given additional medications, including Meropenem, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and ~~S~~supplements (e.g., Vitamin C, Zinc, and Vitamin D3). The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyper inflammation process of COVID-19. A post mortem exam was not conducted because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions [1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-~~intensive care units (~~ICU~~s)~~ and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31% ~~–~~ ~~–~~79% higher than that of non-ICU

patients [1, 5]. Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis that directly caused a severe pulmonary embolism in four of those patients [7]. The findings of this study are important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1% – 2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1, 5].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, cardiac troponin, ferritin, and lactate dehydrogenase [9]. Patients with coagulopathy complications have higher D-dimer levels [3].

In searching the current literature, no previous studies were found on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia, ischemia-reperfusion liver injury, and drug-induced hepatotoxicity, may direct injury from the virus to the liver [10]. This case report found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are important for regulating vascular permeability, maintaining hemostasis, and regulating hemolysis. Vascular endothelial injury

due to the infection of the SARS CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome ~~(ARDS)~~ leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions indicate increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased serum lactate dehydrogenase and ferritin levels are related to a high risk of death and microangiopathy in thrombotic complications of COVID-19 patients [9]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT due to hyperinflammatory reactions and vascular endothelial injury.

The use of LMWH for prophylaxis of venous thromboembolism has been approved by ~~WHO~~ the World Health Organization for hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated anti-inflammatory attributes that might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with a lower incidence of mortality compared to standard DVT prophylaxis in hospitalized COVID-19 patients. In this case, the patient had been given LMWH, but not at the beginning of treatment; therefore, the administration of LMWH did not seem to improve the patient's condition [14].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is unclear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulation involving inflammatory cytokines, vascular endothelial injury, and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease the severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent the increasing severity of COVID-19, including the use of LMWH prophylaxis.

DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

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Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

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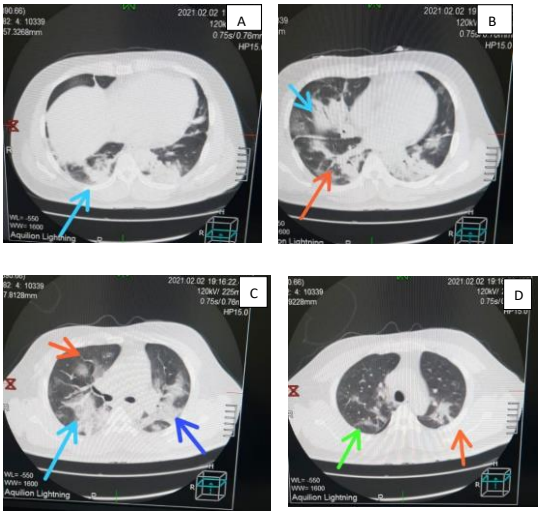
Figure 1. The chest CT scan without intravenous contrast revealed large ground-glass opacities(C) S4, S5, S7, S8 right/blue
arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow.



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CASE REPORT

Late diagnosis of COVID-19 in a 34-year-old man in ahypercoagulable state: A case report

Desdiani Desdiani[1,2]

D Desdiani. Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report. Can J Respir Ther 2022;58:1–4. doi: 10.29390/cjrt-2021-028.

Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure.

Case and outcomes: A 34-year-old male presented to the emergency room after ~~three~~ days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hem[illegible] nous fluids, oxygen, antipyretic, and hepatoprotector. On day 4, the patient was diagnosed with CO[illegible] Alanine transaminase and Aspartate transaminase levels. While waiting for outsourced D dimer and [illegible] low molecular weight heparin (LMWH) on day 5. On day 13, his condition deteriorated with cephalgia[illegible] refused intubation. The chest CT scan revealed large ground-glass opacities in both lungs. The pati[illegible] Meropenem, Dexamethasone, and Remdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence t[illegible] COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH a[illegible]

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 p[illegible] hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Key Words: *hypercoagulable state; late diagnosis; young patient*

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INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in the deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased C-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after 4 days of treatment and died after 15 days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to the publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting 3 days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical history of comorbidities. The internist suspected DHFbased on laboratory results indicating a platelet count of 86,000 cells/µL, increa[illegible] (ALT) level of 161 U/[illegible] 52 U/L due to a hyperi[illegible] revealed no abnormali[illegible] suspected. The patient [illegible] fluids, oxygen, antipyr[illegible] ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination showed that leukocytes were 12,300 cells/µL (normal value: 5.000–10.000 cells/µL), lymphocytes were 12% (normal value: 20%–50%), erythrocyte sedimentation rate (ESR) was 40 mm/h (normal value: 0–15 mm/h), monocytes were 11% (normal value: 4%–8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7–41 U/L), ALT level was

After 4 days of D[illegible] HF treatment, there was no improvement, and saturation tended to de[illegible] crease. Therefore, the patient was referred to a pulmonologist in the [illegible] main hospital. There, the patient was diagnosed with COVID-19 based[illegible] on a positive result from polymerase chain reaction (PCR) nasopharyn[illegible] geal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The pa[illegible] tient received hepatoprotector to decrease the

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315 U/L (normal value: 12–38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7–5.2 mmol/L). The posteroanterior chest X-ray results did not show any radiological abnormalities in the heart and lungs.

On day 5, the D dimer examination was carried out, the sample was sent outside the hospital, and the results came 4 days later. Hospital facilities were limited and, at that time, the national insurance did not cover the test cost. While waiting for the D dimer and PT results, the patient was given low molecular weight heparin (LMWH). The patient was experiencing hypoxemic respiratory failure and was in a hypercoagulable state due to the hyper inflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90%–92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask of 15 L/min. Laboratory tests revealed an ALT level of 87 U/L and AST ~~91~~ level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g. Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring intensive care unit (ICU) treatment using high flow nasal cannula FiO_2 100% flow 60 L/min.

Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high-flow oxygen and could communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed ESR of 95 mm/h, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2553 ng/L, and quantitative CRP of 75 mg/L. The chest CT scan without intravenous contrast revealed large GGO in both lungs, such as Segment 1 (S1) and S2 left; S2, S3, and S6 right; S4, S5, and S6 left; S4, S5, S7, S8 right; S10 right and left (Figure 1), representing anterior and posterior views of the pulmonary lobes and segments. The placement of the pulmonary segments and lobes on the anterior surface of the right and left lungs are depicted in a schematic drawing superimposed on a three-dimensional surface-reformatted picture produced with a multidetector CT scanner. Th
right upper lobe, the la
middle lobe, and the a
make up the anterior s
ment (S1 + S2), anteri
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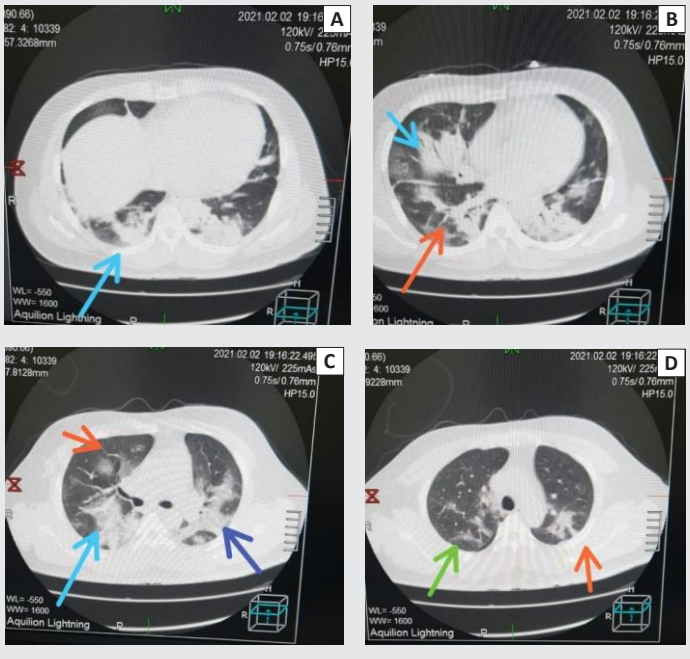
FIGURE 1

The chest CT scan without intravenous contrast revealed large ground-glass opacities in both lungs. (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow.



and supplements (e.g., Vitamin C, Zinc, and Vitamin D3). The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyper inflammation process of COVID-19. A post mortem exam was not conducted because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions [1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-ICUs and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31%–79% higher than that of non-ICU patients [1, 5]. Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis that directly caused a severe pulmonary embolism in four of those patients [7]. The findings of this study are important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1%–2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1, 5].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, cardiac troponin, ferritin, and lactate dehydrogenase [9]. Patients with coagulopathy complications have higher D-dimer levels [3].

In searching the current literature, no previous studies were found on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia, ischemia-reperfusion liver injury, and drug-induced hepatotoxicity, may direct injury from the virus to the liver [10]. This case report found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are important for regulating vascular permeability, maintaining hemostasis, and regulating hemolysis. Vascular endothelial injury due to the infection of the SARS CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions indicate increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased serum lactate dehydrogenase and ferritin levels are related to a high risk of death and microangiopathy in thrombotic complications of COVID-19 patients [9]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT due to hyperinflammatory reactions and vascular endothelial injury.

The use of LMWH for prophylaxis of venous thromboembolism has been approved by the World Health Organization for hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated anti-inflammatory attributes that might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with a lower incidence of mortality compared to standard DVT prophylaxis in hospitalized COVID-19 patients. In this case, the patient had been given LMWH, but not at the beginning of treatment; therefore, the administration of LMWH did not seem to improve the patient's condition [14].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is unclear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulation involving inflammatory cytokines, vascular endothelial injury, and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease the severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent the increasing severity of COVID-19, including the use of LMWH prophylaxis.

DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

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Informed consent

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Late diagnosis of COVID-19 in a 34-year-old man

Desdiani

Case Report

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulablestate: A case report

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Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure MOF

Case and outcomes: A 34-year-old male presented to the emergency room after three days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hemorrhagic fever. He was given hydration intravenous fluids, oxygen, antipyretic, and hepatoprotector. On day 4, the patient was diagnosed withCOVID-19 and received therapy to decrease the Alanine transaminase and Aspartate transaminase levels. While waiting foroutsourced D dimer and prothrombin time results, the patient was given low molecular weight- heparin (LMWH) on day 5. On day 13,his condition deteriorated with cephalgia and shortness of breath, but the patient's family refused intubation. The chest CT scan revealedlarge ground-glass opacities in both lungs. The patient was given additional medications, such as Meropenem, Dexamethasone, andRemdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence than standard DVT (Deep Vein

Thrombosis) prophylaxis in hospitalized COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH at the beginning of treatment.

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of the hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Key Words: *COVID-19; hypercoagulable state ; late diagnosis; LMWH; young patient*

CASE REPORT

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report

Desdiani Desdiani[1,2]

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Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence than standard DVT (Deep Vein Thrombosis prophylaxis in hospitalized COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH at the beginning of treatment.

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of the hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Key Words: *COVID-19, hypercoagulable state; late diagnosis; LMWH; young patient*

INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in the deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased C-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after 4 days of treatment and died after 15 days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to the publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting 3 days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical history of comorbidities. The internist suspected DHF based on laboratory results indicating a platelet count of 86,000 cells/µL, increased monocytes of 20%, an Alanine transaminase (ALT) level of 161 U/L, and an Aspartate transaminase (AST) level of 52 U/L due to a hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs, and COVD-19 was not suspected. The patient was treated for DHF and was given intravenous fluids, oxygen, antipyretic, and hepatoprotector.

After 4 days of DHF treatment, there was no improvement, and saturation tended to decrease. Therefore, the patient was referred to a pulmonologist in the main hospital. There, the patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, CoV Gen 19.21. The patient received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination showed that leukocytes were 12,300 cells/µL (normal value: 5.000–10.000 cells/µL), lymphocytes were 12% (normal value: 20%–50%), erythrocyte sedimentation rate (ESR) was 40 mm/h (normal value: 0–15 mm/h), monocytes were 11% (normal value:4%–8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7–41 U/L), ALT level was

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315 U/L (normal value: 12–38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7–5.2 mmol/L). The posteroanterior chest X-ray results did not show any radiological abnormalities in the heart and lungs.

On day 5, the D dimer examination was carried out, the sample was sent outside the hospital, and the results came 4 days later. Hospital facilities were limited and, at that time, the national insurance did not cover the test cost. While waiting for the D dimer and PT results, the patient was given low molecular weight heparin (LMWH). The patient was experiencing hypoxemic respiratory failure and was in a hypercoagulable state due to the hyper inflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90%–92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask of 15 L/min. Laboratory tests revealed an ALT level of 87 U/L and AST level of 91 U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g, Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring intensive care unit (ICU) treatment using high flow nasal cannula FiO_2 100% flow 60 L/min.

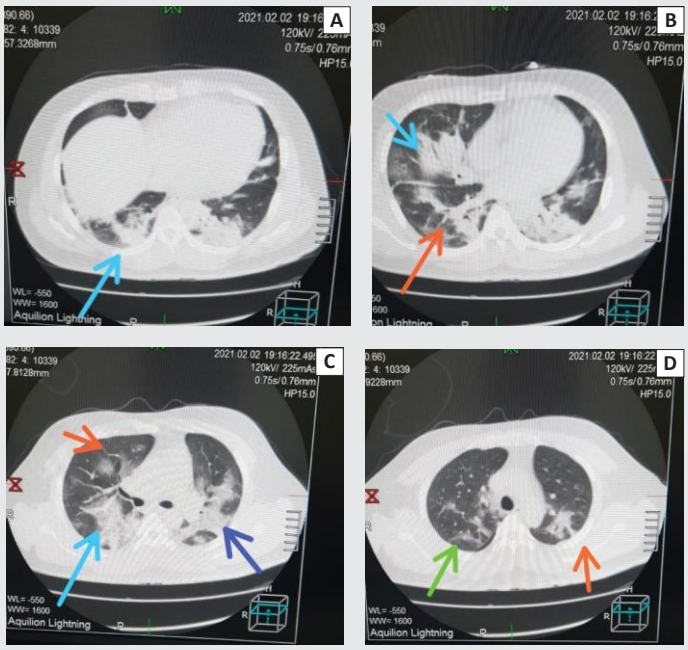
Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on that intubation would further harm the patient. Although the patient was on heated high-flow oxygen and could communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed ESR of 95 mm/h, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2553 ng/L, and quantitative CRP of 75 mg/L. The chest CT scan without intravenous contrast revealed large GGO in both lungs, such as Segment 1 (S1) and S2 left; S2, S3, and S6 right; S4, S5, and S6 left; S4, S5, S7, S8 right; S10 right and left (Figure 1), representing anterior and posterior views of the pulmonary lobes and segments. The placement of the pulmonary segments and lobes on the anterior surface of the right and left lungs are depicted in a schematic drawing superimposed on a three-dimensional surface reformatted picture produced with a multidetector CT scanner. The apical (S1) and anterior (S3) segments of the right upper lobe, the lateral (S4) and medial (S5) segments of the right middle lobe, and the anterior basal (S8) segment of the right lower lobe make up the anterior surface of the right lung. The apicoposterior segment (S1 + S2), anterior (S3) segment, superior (S4) and inferior (S5) lingular segments of the left upper lobe, as well as the anteromedial segment (S6), the lateral basal (S9), and posterior basal (S10) segments.

The patient was then given additional medications, including Meropenem, Dexamethasone, Remdesivir, Ondansetron, Omeprazole,

FIGURE 1

The chest CT scan without intravenous contrast revealed large ground-glass opacitiesin both lungs: (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow.



and supplements (e.g., Vitamin C, Zinc, and Vitamin D3). The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyper inflammation process of COVID-19. A post mortem exam was not conducted because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions [1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-ICUs and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31%–79% higher than that of non-ICU patients [1, 5]. Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis that directly caused a severe pulmonary embolism in four of those patients [7]. The findings of this study are important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1%–2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1, 5].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, cardiac troponin, ferritin, and lactate dehydrogenase [9]. Patients with coagulopathy complications have higher D-dimer levels [3].

In searching the current literature, no previous studies were found on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia, ischemia-reperfusion liver injury, and drug-induced hepatotoxicity, may direct injury from the virus to the liver [10]. This case report found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are important for regulating vascular permeability, maintaining hemostasis, and regulating hemolysis. Vascular endothelial injury due to the infection of the SARS CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions indicate increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased serum lactate dehydrogenase and ferritin levels are related to a high risk of death and microangiopathy in thrombotic complications of COVID-19 patients [9]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT due to hyperinflammatory reactions and vascular endothelial injury.

The use of LMWH for prophylaxis of venous thromboembolism has been approved by the World Health Organization for hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated anti-inflammatory attributes that might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with a lower incidence of mortality compared to standard DVT prophylaxis in hospitalized COVID-19 patients. In this case, the patient had been given LMWH, but not at the beginning of treatment; therefore, the administration of LMWH did not seem to improve the patient's condition [14].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is unclear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulation involving inflammatory cytokines, vascular endothelial injury, and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease the severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent the increasing severity of COVID-19, including the use of LMWH prophylaxis.

DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

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The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

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Late diagnosis of COVID-19 in a 34-year-old man

Desdiani ~~Desdiani~~

-Case Report

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report

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~~ABSTRACT~~

Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and

extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure ~~(MOF)~~.

Case and outcomes: A 34-year-old male presented to the emergency room after three days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hemorrhagic fever ~~(DHF)~~. He was given hydration intravenous fluids, oxygen, antipyretic, and hepatoprotector. On day ~~four~~4, the patient was diagnosed with COVID-19 and received therapy to decrease the Alanine transaminase ~~(ALT)~~ and Aspartate transaminase ~~(AST)~~ levels. While waiting for outsourced D dimer and prothrombin time results, the patient was given low molecular weight- heparin (LMWH) on day 5. On day 13, his condition deteriorated with cephalgia and shortness of breath, but the patient's family refused intubation. The chest CT scan revealed large ground-glass opacities in both lungs. The patient was given additional medications, such as Meropenem, Dexamethasone, and Remdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence than standard DVT prophylaxis in hospitalized COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH at the beginning of treatment.

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of the hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Key ~~w~~Words: ~~H~~*hypercoagulable state*, ~~-~~, *late diagnosis*, ~~-~~, *young patient*

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INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in the deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased C~~c~~-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after ~~four~~ 4 days of treatment and died after ~~fifteen~~ 15 days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to the publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting ~~three~~ 3 days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical

history of comorbidities. The internist suspected ~~Dengue Haemorrhagic Fever (~~DHF~~)~~ based on laboratory results indicating a platelet count of 86,000 cells/µ~~H~~L, increased monocytes of 20%, ~~and~~ an Alanine transaminase (ALT) level of 161 U/L, and an Aspartate transaminase (AST) level of 52 U/L due to a hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs, and COVD-19 was not suspected. The patient was treated for DHF and was given intravenous fluids, oxygen, antipyretic, and hepatoprotector.

After ~~four~~ 4 days of DHF treatment, there was no improvement, and saturation tended to decrease. Therefore, the patient was referred to a pulmonologist in the main hospital. There, the patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The patient received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination showed that leukocytes were 12,300 cells/µL (normal value: 5.000–10.000 cells/µL), lymphocytes were 12% (normal value: 20%–~~-~~50%), erythrocyte sedimentation rate (ESR) was 40 mm/h~~our~~ (normal value: 0–15 mm/h~~our~~), monocytes were 11% (normal value: 4%–~~-~~8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value:– <5), AST level was 278 U/L (normal value: 7–41 U/L), ALT level was 315 U/L (normal value: 12–38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7–~~-~~5.2 mmol/L). The posteroanterior ~~(PA)~~ chest X-ray results did not show any radiological abnormalities in the heart and lungs.

On day 5, the D dimer examination was carried out, the sample was sent outside the hospital, and the results came ~~four~~ 4 days later. Hospital facilities were limited, and, at that time, the national insurance did not cover the ~~financing~~test cost. While waiting for the D dimer and ~~prothrombin time~~PT results, the patient was given low molecular weight heparin

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Yes it is

(LMWH). The patient was experiencing hypoxemic respiratory failure and was in a hypercoagulable state due to the hyper inflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90% ~~– –~~92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask ~~(NRM)~~ of 15 L~~litres~~/min~~ute~~. Laboratory tests revealed an ALT level of 87 U/L and AST 91 level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g.~~,~~ Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring intensive care unit (ICU) treatment using ~~H~~high ~~F~~flow ~~N~~nasal c~~C~~annula FiO_2 100% ~~F~~flow 60 ~~l~~L/~~itres per~~ min~~ute~~.

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Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high-flow oxygen and could communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed ~~erythrocyte sedimentation rate~~ESR of 95 mm/h~~our~~, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2~~,~~553 ng/L, and quantitative CRP~~C-Reactive protein~~ of 75 mg/L. The chest CT scan without intravenous contrast revealed large ~~Ground Glass Opacities~~GGO in both lungs, such

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The patient was then given additional medications, including Meropenem, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and ~~S~~supplements (e.g., Vitamin C, Zinc, and Vitamin D3). The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyper inflammation process of COVID-19. A post mortem exam was not conducted because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions [1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-~~intensive care units (~~ICU~~s)~~ and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31% ~~–~~ ~~-~~79% higher than that of non-ICU

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Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, cardiac troponin, ferritin, and lactate dehydrogenase [9]. Patients with coagulopathy complications have higher D-dimer levels [3].

In searching the current literature, no previous studies were found on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia, ischemia-reperfusion liver injury, and drug-induced hepatotoxicity, may direct injury from the virus to the liver [10]. This case report found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are important for regulating vascular permeability, maintaining hemostasis, and regulating hemolysis. Vascular endothelial injury

due to the infection of the SARS CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome ~~(ARDS)~~ leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions indicate increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased serum lactate dehydrogenase and ferritin levels are related to a high risk of death and microangiopathy in thrombotic complications of COVID-19 patients [9]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT due to hyperinflammatory reactions and vascular endothelial injury.

The use of LMWH for prophylaxis of venous thromboembolism has been approved by ~~WHO~~ the World Health Organization for hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated anti-inflammatory attributes that might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with a lower incidence of mortality compared to standard DVT prophylaxis in hospitalized COVID-19 patients. In this case, the patient had been given LMWH, but not at the beginning of treatment; therefore, the administration of LMWH did not seem to improve the patient's condition [14].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is unclear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulation involving inflammatory cytokines, vascular endothelial injury, and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease the severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent the increasing severity of COVID-19, including the use of LMWH prophylaxis.

DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

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Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

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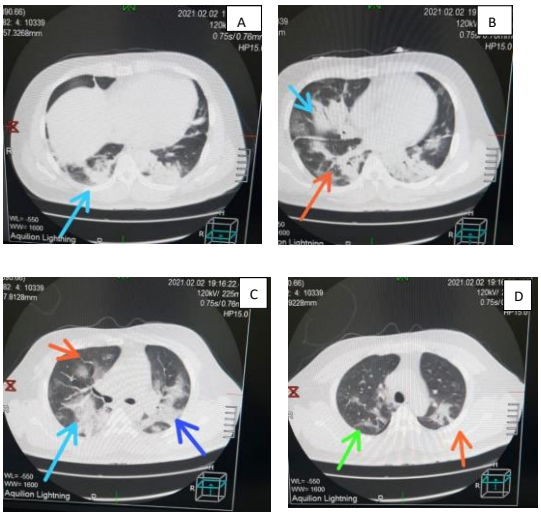
Figure 1. The chest CT scan without intravenous contrast revealed large ground-glass opacities~~GGO~~ in both lungs : (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow.



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RE: Response needed: CJRT-2021-028 edited manuscript and proof 11 April 2022

Dari: Danhua Wang (danhua.wang@cdnsciencepub.com)

Kepada: desdiani@ymail.com

Tanggal: Senin, 11 April 2022 pukul 18.54 WIB

Dear Dr. Desdiani,
Thanks for confirming that no additional change required. There is a query about DVT in the abstract. Is “Deep Vine Thrombosis” the correct definition? Please see attached.

Thanks

Danhua

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Subject: Re: Response needed: CJRT-2021-028 edited manuscript and proof

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Thank you for your attention

Best Regards,

Desdiani Desdiani

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Please let me know if you have any questions.

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To: Danhua Wang <danhua.wang@cdnsciencepub.com>
Subject: Re: Response needed: CJRT-2021-028 edited manuscript and proof

Dear Danhua

Thank you for your email. I send corrections of my manuscript, but I"m sorry because i"ve edited with manual setting.
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Best Regards,
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CASE REPORT

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report

Desdiani Desdiani[1,2]

D Desdiani. Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report. Can J Respir Ther 2022;58:1–4. doi: 10.29390/cjrt-2021-028.

Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure.

Case and outcomes: A 34-year-old male presented to the emergency room after three days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hem nous fluids, oxygen, antipyretic, and hepatoprotector. On day 4, the patient was diagnosed with C Alanine transaminase and Aspartate transaminase levels. While waiting for outsourced D dimer and low molecular weight heparin (LMWH) on day 5. On day 13, his condition deteriorated with cephalgia refused intubation. The chest CT scan revealed large ground-glass opacities in both lungs. The pati Meropenem, Dexamethasone, and Remdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence t COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH a

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 p hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms

Key Words: *hypercoagulable state; late diagnosis; young patient*

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Deep Vine Thrombosis)

CASE REPORT

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INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in the deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased C-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after 4 days of treatment and died after 15 days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to the publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

A 34-year-old Indonesia man reporting 3 days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical history of comorbidities. The internist suspected DHFbased on laboratory results indicating a platelet count of 86,000 cells/µL, increa (ALT) level of 161 U/ 52 U/L due to a hyperl revealed no abnormaliti suspected. The patient s treated for DHF and was given intravenous fluids, oxygen, antipyr tic, and hepatoprotector.

After 4 days of DH F treatment, there was no improvement, and saturation tended to de crease. Therefore, the patient was referred to a pulmonologist in the m ain hospital. There, the patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The patient received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination showed that leukocytes were 12,300 cells/µL (normal value: 5.000–10.000 cells/µL), lymphocytes were 12% (normal value: 20%–50%), erythrocyte sedimentation rate (ESR) was 40 mm/h (normal value: 0–15 mm/h), monocytes were 11% (normal value: 4%–8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7–41 U/L), ALT level was

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Correspondence: Desdiani Desdiani, Faculty of Medicine, Universitas Sultan Ageng Tirtayasa, Jalan Jend. Sudirman No.20, RT.10/RW.5, Kotabumi, Cilegon, Banten, Indonesia 42434. Tel: (+62-254) 280330, Fax: (+62-254) 281254, E-mail: desdiani@ymail.com

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315 U/L (normal value: 12–38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7–5.2 mmol/L). The posteroanterior chest X-ray results did not show any radiological abnormalities in the heart and lungs.

On day 5, the D dimer examination was carried out, the sample was sent outside the hospital, and the results came 4 days later. Hospital facilities were limited and, at that time, the national insurance did not cover the test cost. While waiting for the D dimer and PT results, the patient was given low molecular weight heparin (LMWH). The patient was experiencing hypoxemic respiratory failure and was in a hypercoagulable state due to the hyper inflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90%–92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask of 15 L/min. Laboratory tests revealed an ALT level of 87 U/L and AST ~~91~~ level of U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g. Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring intensive care unit (ICU) treatment using high flow nasal cannula FiO_2 100% flow 60 L/min.

Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high-flow oxygen and could communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed ESR of 95 mm/h, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2553 ng/L, and quantitative CRP of 75 mg/L. The chest CT scan without intravenous contrast revealed large GGO in both lungs, such as Segment 1 (S1) and S2 left; S2, S3, and S6 right; S4, S5, and S6 left; S4, S5, S7, S8 right; S10 right and left (Figure 1), representing anterior and posterior views of the pulmonary lobes and segments. The placement of the pulmonary segments and lobes on the anterior surface of the right and left lungs are depicted in a schematic drawing superimposed on a three-dimensional surface-reformatted picture produced with a multidetector CT scanner. Th
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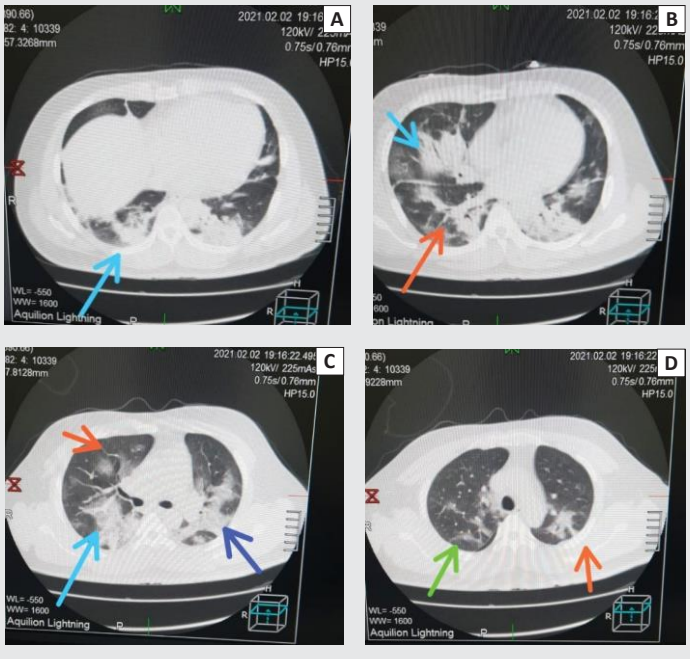
FIGURE 1

The chest CT scan without intravenous contrast revealed large ground-glass opacities in both lungs: (A) S10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow.



and supplements (e.g., Vitamin C, Zinc, and Vitamin D3). The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyper inflammation process of COVID-19. A post mortem exam was not conducted because the family did not approve it.

DISCUSSION

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CONCLUSION

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DISCLOSURE

Author contributions
All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests
No conflicts of interest to declare.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

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Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

REFERENCES

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Re: Response needed: CJRT-2021-028 edited manuscript and proof

Dari: desdiani - (desdiani@ymail.com)

Kepada: danhua.wang@cdnsciencepub.com

Tanggal: Senin, 11 April 2022 pukul 19.57 WIB

Dear Danhua,

I am very sorry, i typed the wrong word. The correct word is " Deep Vein Thrombosis".
Thank you very much.

Desdiani

> Pada Senin, 11 April 2022 18.54.22 GMT+7, Danhua Wang <danhua.wang@cdnsciencepub.com> menulis:
>
> Dear Dr. Desdiani,
> Thanks for confirming that no additional change required. There is a query about DVT in the abstract. Is "Deep Vine Thrombosis" the correct definition? Please see attached.
>
> Thanks
>
> Danhua
>
> **From:** desdiani - <desdiani@ymail.com>
> **Sent:** Friday, April 8, 2022 7:07 PM
> **To:** Danhua Wang <danhua.wang@cdnsciencepub.com>
> **Subject:** Re: Response needed: CJRT-2021-028 edited manuscript and proof
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> Dear Danhua,
>
> Thank you for your email. I try to send corrections of my manuscript, and answer all comments on the track change future. I agree with CJRT-2021-028pr.PDF.
> Thank you for your attention
>
> Best Regards,
> Desdiani Desdiani
>
> Pada Jumat, 8 April 2022 21.01.25 GMT+7, Danhua Wang <danhua.wang@cdnsciencepub.com> menulis:
>
> Dear Dr. Desdiani,
>
> No changes are marked up in cjrt-2021-028 (edit).pdf you returned. Actually the few minor corrections I marked up are removed. Final_Late diagnosis of COVID.doc doesn't have track changes shown so I have no way to tell what changes you have made. If you cannot annotate the PDF, could you please send me a list of corrections via email or turn on the track change feature when update the Word file?
>
> Please let me know if you have any questions.
>
> Thanks
>
> Danhua
>
> **From:** desdiani - <desdiani@ymail.com>
> **Sent:** Friday, April 8, 2022 4:02 AM
> **To:** Danhua Wang <danhua.wang@cdnsciencepub.com>
> **Subject:** Re: Response needed: CJRT-2021-028 edited manuscript and proof
>
> Dear Danhua
>
> Thank you for your email. I send corrections of my manuscript, but I"m sorry because i"ve edited with manual setting.

Thank you for your attention

Best Regards,
Desdiani Desdiani

Pada Kamis, 7 April 2022 01.17.08 GMT+7, Danhua Wang <danhua.wang@cdnsciencepub.com> menulis:

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Danhua

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Danhua Wang

Publishing Coordinator

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RE: Revision of Manuscript CJRT 2021-28 21 April 2022

Dari: Editor (editor@csrt.com)

Kepada: desdiani@ymail.com

Tanggal: Kamis, 21 April 2022 pukul 03.34 WIB

Hi Desdiani,

I just posted the final article online at www.cjrt.ca! I tweeted about it (https://twitter.com/CJRTeditor).

Link to PDF: https://www.cjrt.ca/wp-content/uploads/cjrt-2021-028.pdf

I attached a PDF copy as well.

Have a great

day

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy
(Pronouns: she, her)
201-2460 Lancaster Road Ottawa, ON K1B 4S5
Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: March 20, 2022 3:24 AM
To: Editor <editor@csrt.com>
Subject: Re: Revision of Manuscript CJRT 2021-28

Dear Carly,

Thank you so much

Regards,

Desdiani Desdiani

Pada Jumat, 18 Maret 2022 02.20.05 GMT+7, Editor <editor@csrt.com> menulis:

Your paper has been accepted! I will be sending it to our publisher today for layout. I'll send the official notification through the system now.

Congratulations!

Carly Brockington
Managing Editor, Canadian Journal of Respiratory Therapy

(Pronouns: she, her)
201-2460 Lancaster Road Ottawa, ON K1B 4S5
Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: February 23, 2022 8:45 PM
To: Editor <editor@csrt.com>
Subject: Re: Revision of Manuscript CJRT 2021-28

Dear Carly,

Here i submit and revised all responses to all reviewer's comments. I hope that all the revisions submitted are appropriate. Thank you for your attention.

Best Regards,

Desdiani Desdiani

Pada Minggu, 20 Februari 2022 23.51.17 GMT+7, Editor <editor@csrt.com> menulis:

Hello Desdiani,

I have given the manuscript a bit of an edit and tried to incorporate some of your responses to the reviewers into the text. Can you make sure this looks correct? There are a few remaining questions from the reviewers that should be easier to see now.

If you can send me a revision and a response to these comments, I can run it past the editor for final approval.

Kind regards,

Carly Brockington

Managing Editor, Canadian Journal of Respiratory Therapy

(Pronouns: she, her)

201-2460 Lancaster Road Ottawa, ON K1B 4S5

Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: February 7, 2022 1:57 AM
To: Editor <editor@csrt.com>
Subject: Re: Revision of Manuscript

Dear Carly,

Thank you for your email

Best Regards,

Desdiani Desdiani

Pada Senin, 7 Februari 2022 00.59.02 GMT+7, Editor <editor@csrt.com> menulis:

Sorry for the delay – I am going through the suggestions and will edit the manuscript and send you a version to approve shortly.

Carly Brockington

Managing Editor, Canadian Journal of Respiratory Therapy

(Pronouns: she, her)

201-2460 Lancaster Road Ottawa, ON K1B 4S5

Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: February 2, 2022 3:16 AM
To: Editor <editor@csrt.com>
Subject: Revision of Manuscript

Dear Carly,

Regarding reviewer"s comment, there is still minor revision, but sorry I can"t find it attached from email.

Would you please help me.

Thank you for your attention

Response needed: CJRT-2022-033 edited manuscript and proof

Dari: Danhua Wang (danhua.wang@cdnsciencepub.com)

Kepada: desdiani@ymail.com

Tanggal: Jumat, 15 Juli 2022 pukul 08.40 GMT+7

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Dari: desdiani - (desdiani@ymail.com)

Kepada: danhua.wang@cdnsciencepub.com

Tanggal: Sabtu, 16 Juli 2022 pukul 23.17 GMT+7

Dear Danhua,

Here we submit a correction of our manuscript.

Thank you for your attention

Best Regards,
Desdiani

Pada Jumat, 15 Juli 2022 08.40.56 GMT+7, Danhua Wang <danhua.wang@cdnsciencepub.com> menulis:

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Kepada: danhua.wang@cdnsciencepub.com

Tanggal: Sabtu, 16 Juli 2022 pukul 23.17 GMT+7

Dear Danhua,

Here we submit a correction of our manuscript.

Thank you for your attention

Best Regards,
Desdiani

Pada Jumat, 15 Juli 2022 08.40.56 GMT+7, Danhua Wang <danhua.wang@cdnsciencepub.com> menulis:

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RE: [CJRT] Article Review Request

Dari: Editor (editor@csrt.com)

Kepada: desdiani@ymail.com

Tanggal: Selasa, 4 Oktober 2022 pukul 22.21 GMT+7

Thank you! I accepted the review invite on your behalf in the system, your comments are due Oct 20th. If you prefer, you can send a list of numbered comments directly to me (or insert comments into the Word document), and I can load your feedback into the system.

Thanks again!

Carly Brockington
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201-2460 Lancaster Road Ottawa, ON K1B 4S5
Tel : (613) 808-8833

From: desdiani - <desdiani@ymail.com>
Sent: September 29, 2022 9:12 PM
To: Editor <editor@csrt.com>
Subject: Re: [CJRT] Article Review Request

Okay Carly, i agree to review this manuscript

Pada Jumat, 30 September 2022 03.13.28 GMT+7, Carly Brockington <editor@csrt.com> menulis:

Desdiani Desdiani:

I believe that you would serve as an excellent reviewer of the manuscript, "Antifibrotic Effect of Ciplukan (Physalis angulata Linn.) Against Bleomycin-Induced Pulmonary Fibrosis in Mice via Alveolar Regeneration and Anti-Inflammatory," which has been submitted to Canadian Journal of Respiratory Therapy. The submission's abstract is inserted below, and I hope that you will consider undertaking this important task for us.

Please log into the journal web site by 2022-10-06 to indicate whether you will undertake the review or not, as well as to access the submission and to record your review and recommendation.

The review itself is due 2022-10-20.

Submission URL: https://cjrtmanuscript.com/index.php/CJRT/reviewer/submission?submissionId=227&reviewId=334&key=dEifC9

Thank you for considering this request.

Carly Brockington
editor@csrt.com

CASE REPORT

Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report

Desdiani Desdiani[1,2]

D Desdiani. Late diagnosis of COVID-19 in a 34-year-old man in a hypercoagulable state: A case report. Can J Respir Ther 2022;58:49–52. doi: 10.29390/cjrt-2021-028.

Background: Late diagnosis of COVID-19 in young patients in a hypercoagulable state can cause a high mortality rate. Clinical manifestations of COVID-19 include respiratory and extrapulmonary symptoms such as a hypercoagulable state, increased transaminase enzymes, and multiple-organ failure.

Case and outcomes: A 34-year-old male presented to the emergency room after 3 days of high fever, weakness, and flatulence. The patient had thrombocytopenia and elevated liver transaminase enzymes and was initially diagnosed with dengue hemorrhagic fever. He was given hydration intravenous fluids, oxygen, antipyretic, and hepatoprotector. On day 4, the patient was diagnosed with COVID-19 and received therapy to decrease the Alanine transaminase and Aspartate transaminase levels. While waiting for outsourced D dimer and prothrombin time results, the patient was given low molecular weight heparin (LMWH) on day 5. On day 13, his condition deteriorated with cephalgia and shortness of breath, but the patient's family refused intubation. The chest CT scan revealed large ground-glass opacities in both lungs. The patient was given additional medications, such as Meropenem, Dexamethasone, and Remdesivir. On day 15, the patient passed away.

Discussion: Intermediate LMWH dosage seems to be associated with a lower mortality incidence than standard Deep Vein Thrombosis (DVT) prophylaxis in hospitalized COVID-19 patients. However, due to the late COVID-19 diagnosis, the patient was not given LMWH at the beginning of treatment.

Conclusion: A hypercoagulable state is partly responsible for the high mortality rate of COVID-19 patients. Early detection and management of the hypercoagulable state, including the use of LMWH, can decrease the severity of COVID-19 symptoms.

Key Words: *COVID-19*; *hypercoagulable state*; *late diagnosis*; *LMWH*; *young patient*

INTRODUCTION

COVID-19 is caused by a contagious virus that can lead to severe respiratory problems. The complications of thrombotic events frequently result in the deterioration of COVID-19 patients. Thrombotic and coagulation abnormalities can lead to a hypercoagulable state [1]. COVID-19 patients usually have shortness of breath, cough, and fever. Other frequent symptoms are sore throat, myalgia, fatigue, headache, rhinorrhea, and diarrhea [2]. Laboratory findings in COVID-19 patients generally indicate decreased lymphocyte and increased C-reactive protein (CRP). In cases with coagulopathy complications, there are increases in D-dimer, prolonged prothrombin time (PT), fibrinogen, lactate dehydrogenase, and ferritin levels [3]. Radiologic evaluation of these patients frequently reveals ground-glass opacities (GGO) and bilateral multiple lobular and subsegmental consolidation [4].

This case report details a patient initially diagnosed with dengue hemorrhagic fever (DHF), who was then diagnosed with COVID-19 after 4 days of treatment and died after 15 days of hospitalization.

ETHICS APPROVAL

The patients' elder sister consented to the publication of this de-identified case report. Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

CASE REPORT

A 34-year-old Indonesian man reporting 3 days of high fever, weakness, and flatulence was admitted to the emergency room of a small, peripheral hospital. He had no medical history of comorbidities. The internist suspected DHF-based on laboratory results indicating a platelet count of 86,000 cells/µL, increased monocytes of 20%, an Alanine transaminase (ALT) level of 161 U/L, and an Aspartate transaminase (AST) level of 52 U/L due to a hyperinflammation condition. A radiologic evaluation revealed no abnormalities in the heart and lungs, and COVD-19 was not suspected. The patient was treated for DHF and was given intravenous fluids, oxygen, antipyretic, and hepatoprotector.

After 4 days of DHF treatment, there was no improvement, and saturation tended to decrease. Therefore, the patient was referred to a pulmonologist in the main hospital. There, the patient was diagnosed with COVID-19 based on a positive result from polymerase chain reaction (PCR) nasopharyngeal swabs with CT value of ORF1ab Gen 19.14, Gen N 19.21. The patient received hepatoprotector to decrease the ALT and AST levels, azithromycin, N-acetylcysteine, and multivitamins. Laboratory examination showed that leukocytes were 12,300 cells/µL (normal value: 5.000–10.000 cells/µL), lymphocytes were 12% (normal value: 20%–50%), erythrocyte sedimentation rate (ESR) was 40 mm/h (normal value: 0–15 mm/h), monocytes were 11% (normal value: 4%–8%), Neutrophil Lymphocytes Ratio (NLR) was 6.24 (normal value: <5), AST level was 278 U/L (normal value: 7–41 U/L), ALT level was

[1]*Faculty of Medicine, Universitas Sultan Ageng Tirtayasa, Cilegon, Banten, Indonesia*

[2]*Department of Pulmonology and Respiratory Medicine, Bhayangkara Brimob Hospital, Cimanggis, Depok, West Java, Indonesia*

Correspondence: Desdiani Desdiani, Faculty of Medicine, Universitas Sultan Ageng Tirtayasa, Jalan Jend. Sudirman No.20, RT.10/RW.5, Kotabumi, Cilegon, Banten, Indonesia 42434. Tel: (+62-254) 280330, Fax: (+62-254) 281254, E-mail: desdiani@ymail.com

Published online at https://www.cjrt.ca on 20 April 2022

315 U/L (normal value: 12–38 U/L), and potassium level was 3.16 mmol/L (normal value: 3.7–5.2 mmol/L). The posteroanterior chest X-ray results did not show any radiological abnormalities in the heart and lungs.

On day 5, the D dimer examination was carried out, the sample was sent outside the hospital, and the results came 4 days later. Hospital facilities were limited and, at that time, the national insurance did not cover the test cost. While waiting for the D dimer and PT results, the patient was given low molecular weight heparin (LMWH). The patient was experiencing hypoxemic respiratory failure and was in a hypercoagulable state due to the hyper inflammation process associated with COVID-19.

On day 7 of the treatment, the patient's condition still did not improve. He experienced shortness of breath. The oxygen saturation was 90%–92% room air. Subsequently, he was subjected to oxygen therapy using a non-rebreathing mask of 15 L/min. Laboratory tests revealed an ALT level of 87 U/L and AST level of 91 U/L. Chest radiographs indicated no radiological abnormalities in the heart and lungs. The patient was given Azithromycin, Dexamethasone, Remdesivir, Ondansetron, Omeprazole, and supplements (e.g., Vitamin C, Zinc, and Vitamin D3), N-acetyl cysteine, multivitamins, and other supporting medications.

On day 13, the patient's condition declined. He experienced shortness of breath and suffered from fever, abdominal bloating, headache, and tingling of limbs. The oxygen saturation was 84% room air, requiring intensive care unit (ICU) treatment using high flow nasal cannula FiO_2 100% flow 60 L/min.

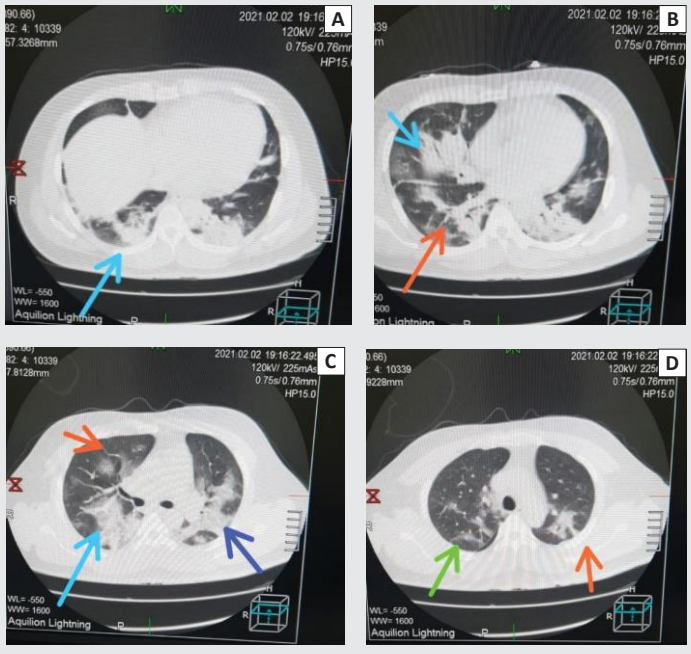
Intubation was recommended as a next step; after communication with the patient's family about this procedure, they refused based on the belief that intubation would further harm the patient. Although the patient was on heated high-flow oxygen and could communicate, the patient's family, especially the patient's elder sister, determined the treatment decisions. The patient deferred all decisions regarding medical treatment to the elder sister.

The laboratory tests revealed ESR of 95 mm/h, lymphocytes of 3%, NLR of 30.7, fibrinogen >500 mg/dL, D-dimers of 11,110 mg/L, ferritin of 2553 ng/L, and quantitative CRP of 75 mg/L. The chest CT scan without intravenous contrast revealed large GGO in both lungs, such as Segment 1 (S1) and S2 left; S2, S3, and S6 right; S4, S5, and S6 left; S4, S5, S7, S8 right; S10 right and left (Figure 1), representing anterior and posterior views of the pulmonary lobes and segments. The placement of the pulmonary segments and lobes on the anterior surface of the right and left lungs are depicted in a schematic drawing superimposed on a three-dimensional surface reformatted picture produced with a multidetector CT scanner. The apical (S1) and anterior (S3) segments of the right upper lobe, the lateral (S4) and medial (S5) segments of the right middle lobe, and the anterior basal (S8) segment of the right lower lobe make up the anterior surface of the right lung. The apicoposterior segment (S1 + S2), anterior (S3) segment, superior (S4) and inferior (S5) lingular segments of the left upper lobe, as well as the anteromedial segment (S6), the lateral basal (S9), and posterior basal (S10) segments.

The patient was then given additional medications, including Meropenem, Dexamethasone, Remdesivir, Ondansetron, Omeprazole,

FIGURE 1

The chest CT scan without intravenous contrast revealed large ground-glass opacitiesin both lungs: (A) S 10 right and left; (B) S4, S5, S7, S8 right/blue arrows and S10 right and left/orange arrows; (C) S3 right/orange arrow, S2, S4, S5, S6 right/blue arrow, S4, S5, S6 left/blue arrow; (D) S2 right/green arrow, S1 dan S2 left/orange arrow.



and supplements (e.g., Vitamin C, Zinc, and Vitamin D3). The patient's condition worsened, and the family still refused intubation. On the 15th day, the patient passed away. The cause of death was hypoxemic respiratory failure, a hypercoagulable state due to the hyper inflammation process of COVID-19. A post mortem exam was not conducted because the family did not approve it.

DISCUSSION

A hypercoagulable state has been reported in COVID-19 patients with poor clinical conditions [1]. Several studies have shown that the pulmonary thrombosis rate of these patients reaches nearly 79% [5]. The thrombosis rate data comes from patients in non-ICUs and ICU. The study reported that the incidence of thrombosis in COVID-19 patients admitted to the ICU is about 31%–79% higher than that of non-ICU patients [1, 5]. Another study reported that the incidence of thrombosis in non-ICU patients increased from 9.2% to 15% [6]. In addition, the autopsy findings of COVID-19 patients showed that 58% of patients had undetected venous thrombosis that directly caused a severe pulmonary embolism in four of those patients [7]. The findings of this study are important because pulmonary thromboembolism is usually caused by bacteria or other viral pneumonia (only 1%–2.6%) [8]. In our case report, the patient had no history of comorbidities. Several studies have concluded that compared with patients receiving treatment in non-ICU wards, critically ill patients have higher risk factors for hypercoagulability and thrombosis [1, 5].

Increased proinflammatory and anti-fibrinolytic conditions were observed in patients with severe infection. A retrospective multicentre cohort study found that 54 COVID-19 patients who died were more likely to have low levels of lymphocytes, increased D-dimers, interleukin-6, cardiac troponin, ferritin, and lactate dehydrogenase [9]. Patients with coagulopathy complications have higher D-dimer levels [3].

In searching the current literature, no previous studies were found on the association between D-dimer increase and prediction of the level of severity of hypercoagulation complications, level of COVID-19 severity of the patients in the ICU, and potential mortality. The elevation of the transaminase enzyme in these patients is related to the incidence of liver injury in COVID-19. This liver injury, including systemic inflammatory, hypoxia, ischemia-reperfusion liver injury, and drug-induced hepatotoxicity, may direct injury from the virus to the liver [10]. This case report found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT.

The first mechanism of the pathophysiology of hypercoagulability in COVID-19 is vascular endothelial injury. Vascular endothelial cells are important for regulating vascular permeability, maintaining hemostasis, and regulating hemolysis. Vascular endothelial injury due to the infection of the SARS CoV-2 virus can cause primary pulmonary thrombus [11]. The second mechanism is the formation of microvascular microthrombi, which triggers the expression of active tissue factors in macrophages and endothelial cells. The increase in tissue hypoxic factors due to acute respiratory distress syndrome leads to an inflammatory process as a cytokine storm. The laboratory results of COVID-19 patients with hypercoagulation conditions indicate increased D-dimer, moderate thrombocytopenia, and prolonged PT [3]. Increased serum lactate dehydrogenase and ferritin levels are related to a high risk of death and microangiopathy in thrombotic complications of COVID-19 patients [9]. In this case report, we found increased transaminase enzymes, hypercoagulation conditions such as increased D-dimer, moderate thrombocytopenia, and prolonged PT due to hyperinflammatory reactions and vascular endothelial injury.

The use of LMWH for prophylaxis of venous thromboembolism has been approved by the World Health Organization for hypercoagulation management [12]. Besides having an anticoagulant effect, LWMH has demonstrated anti-inflammatory attributes that might be helpful against inflammatory conditions caused by the COVID-19 virus. Heparin also suppresses interleukin-6 reaction and interleukin-8 expression of lung epithelial cells, thereby reducing the risks of the emergence of thrombotic complications and cytokine storms [13]. Intermediate LMWH dosage seems to be associated with a lower incidence of mortality compared to standard DVT prophylaxis in hospitalized COVID-19 patients. In this case, the patient had been given LMWH, but not at the beginning of treatment; therefore, the administration of LMWH did not seem to improve the patient's condition [14].

CONCLUSION

Late diagnosis of COVID-19 in young patients with a hypercoagulable state can cause high mortality rates. Further studies are required to understand the pathophysiology of hypercoagulation conditions in young patients. The role of laboratory results such as elevated D dimer, ferritin, CRP and fibrinogen, thrombocytopenia and CT scan results help identify the hypercoagulable state. The relationship between hypercoagulation conditions and thrombotic complications in COVID-19 patients is unclear. However, it is clear that the state of hypercoagulation is partly responsible for the high mortality rate of COVID-19 patients. The mechanisms of hypercoagulation involving inflammatory cytokines, vascular endothelial injury, and serum procoagulants have been frequently discussed and investigated. These data can help the early management of the hypercoagulable state to decrease the severity of COVID-19, although the data are still limited and require further studies. Early detection and management of a hypercoagulable state can be an effective way to prevent the increasing severity of COVID-19, including the use of LMWH prophylaxis.

DISCLOSURE

Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Declaration of conflicting interests

No conflicts of interest to declare.

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Informed consent

Written informed consent for the publication of this case report was obtained from the patient's family. A copy of the consent form is available upon request.

Ethical approval

Institutional review board approval is not required for de-identified single case reports or histories based on institutional policies.

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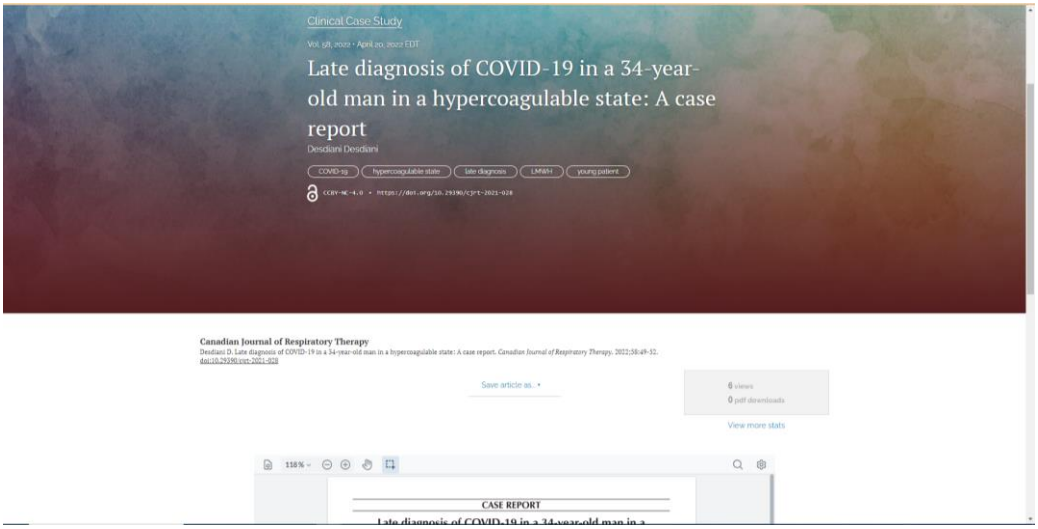

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