



# Source details

## Open Access Macedonian Journal of Medical Sciences

Formerly known as: Macedonian Journal of Medical Sciences

Scopus coverage years: from 2014 to 2022

(coverage discontinued in Scopus)

Publisher: Scientific Foundation SPIROSKI

E-ISSN: 1857-9655

Subject area: Medicine: General Medicine

Source type: Journal

CiteScore 2021

1.3



SJR 2021

0.257



SNIP 2021

0.603



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CiteScore 2021 counts the citations received in 2018-2021 to articles, reviews, conference papers, book chapters and data papers published in 2018-2021, and divides this by the number of publications published in 2018-2021. [Learn more >](#)

CiteScore 2021

$$1.3 = \frac{4,420 \text{ Citations 2018 - 2021}}{3,303 \text{ Documents 2018 - 2021}}$$

Calculated on 05 May, 2022

### CiteScore rank 2021

Category	Rank	Percentile
Medicine		
General Medicine	#416/826	49th

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### De Gruyter Academic Publishing

Open Access

The journal aims to change the current situation of weak direct academic exchanges

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## Open Access Macedonian Journal of Medical Sciences

COUNTRY	SUBJECT AREA AND CATEGORY	PUBLISHER	H-INDEX
<p>Macedonia</p> <ul style="list-style-type: none"> <li>Universities and research institutions in Macedonia</li> <li>Media Ranking in Macedonia</li> </ul>	<p>Medicine</p> <ul style="list-style-type: none"> <li>Medicine (miscellaneous)</li> </ul>		<h1>23</h1>
PUBLICATION TYPE	ISSN	COVERAGE	
Journals	18579655	2014-2021	

### Open Access

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The journal aims to change the current situation of weak direct academic exchanges

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### SCOPE

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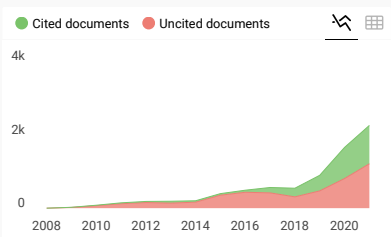
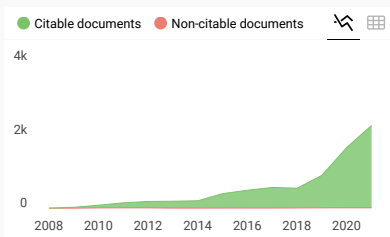
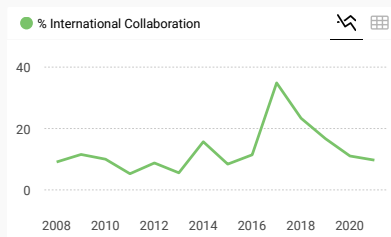
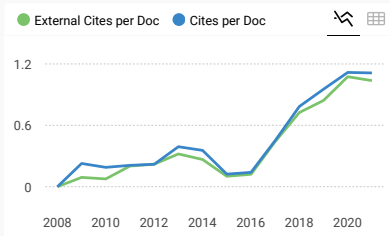
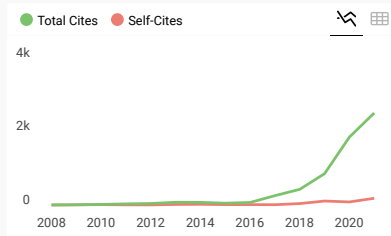
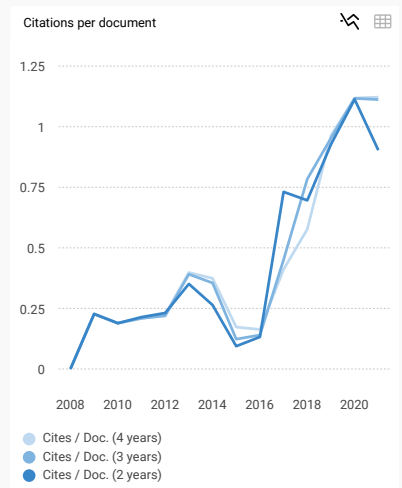
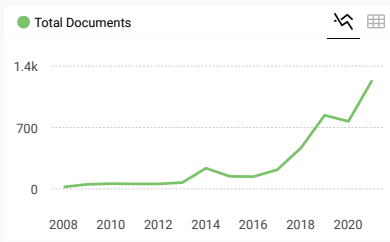
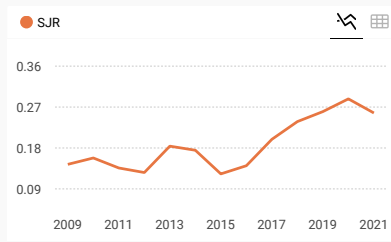
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Open Access Macedonian Journal of Medical Sciences

Medicine (miscellaneous)

Q3 best quartile

SJR 2021 0.26

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**nathaniel** 2 months ago

Thanks for the information you shared I appreciate your efforts and taking the time and sharing this content.

reply



**Melanie Ortiz** 2 months ago

SCImago Team

Dear Nathaniel, welcome and thanks for your participation! Best Regards, SCImago Team

A

**Ahmed Alshewered** 2 months ago

Dear Authors and members of SJR

This journal was out of scopus.

Open Access Macedonian Journal of Medical Sciences was discontinued from SCOPUS.

I contacted with SCOPUS team and they surly said that.

Regards

← reply

A

**Ahmed Samir** 2 months ago

Dear Dr Ahmed

What can I do now?

I send them the fees as it is covered by scopus

E

**Efrida Efrida** 3 months ago

Dear Scimago team and Prof. Dr Mirko Spiroski

I am the author of a paper named "Adiponectin is a single parameter that most correlates with Castelli Risk Index-II on Laboratory Woorkers who had Vitamin D Deficiency at M. Djamil General Hospital West Sumatera", Manuscript ID = OJS9522,. the paper was accepted on April 2022 by Open Access Macedonian Journal of Medical Sciences, also the payment of the regular publication fee was done on April 2022.

7 months till now and the paper is not yet published.

We have sent emails to the Chief Editor, Prof dr. Mirko Spiroski, but we have not received any information.

Appreciate your advice

← reply



**Melanie Ortiz** 3 months ago

SCImago Team

Dear Efrida,

Thank you for contacting us. Unfortunately, SCImago cannot help you with your request.

SJR is committed to help decision-making through scientometric indicators.

Best Regards, SCImago Team

G

**Guspianto** 4 months ago

Dear Scimago team and Prof. Dr Mirko Spiroski

I am the author of a paper named "Quality of service and its effect on patient value, patient satisfaction and revisit intention: Investigation of the Public Health Center (PHC) in Jambi Province", Manuscript ID = OJS8666,. the paper was accepted on 1st of Feb 2022 by Open Access Macedonian Journal of Medical Sciences. The payment of the regular publication fee was done on 1st of March, 2022.

7 months till now and the paper is not yet published.

We have sent many emails to the Chief Editor, Prof dr. Mirko Spiroski, but we have not received any information.

Appreciate your advice.

← reply



**Melanie Ortiz** 4 months ago

SCImago Team

Dear Guspianto,

Thank you for contacting us. Unfortunately, SCImago cannot help you with your request.

Best Regards, SCImago Team

W

**WAHYU DN** 5 months ago

hello,

Open Access Macedonian Journal of Medical Sciences discontinued status at Scopus due to issues with the publication concern in August. what about journals that are in the review process. thanks

← reply



**Salma A** 5 months ago

Hello, I am sorry but could you please include proof of this information to avoid misinformation, because from what I see on the Scopus website, <https://www.scopus.com/sourceid/21100824403>, the Journal is still Scopus Indexed since 2014- Present.

It would be beneficial if anyone else here could provide a valid update here. since I am planning to pay for the payment fee but I still have to make sure if it is still Scopus indexed or not.

Thank you very much in advance.



**Ghada Elgarawany** 6 months ago

Dear Scimago team,

I am the author of a paper named "Impact of high aspartame and high fructose diet on vascular reactivity, glucose metabolism and liver structure in diabetic rats", Manuscript ID = OJS8810. the paper was accepted on 22th of March 2022 by Open Access Macedonian Journal of Medical Sciences.

The payment of the fee was done on 8th of April, 2022.

5 months till now and the paper is not yet published.

Me and the corresponding author have sent many emails to the Chief Editor, Prof dr. Mirko Spiroski, and I tried to contact by phone, but unfortunately, until now, we have not received any information. Appreciate your advice.

← reply



**Soha** 4 months ago

Dear dr ghadai have the same problem as yours with my paper i would appreciate it for you to tell me if you figured to solve the publishing issue ..thank you



**Hamid Khaleel AL-tameemi** 5 months ago

Dear Author,

I suggest sending the journal team directly.



**Melanie Ortiz** 6 months ago

SCLmago Team

Dear Ghada,

Thank you for contacting us. Unfortunately, SCLmago cannot help you with your request.

SJR is committed to help decision-making through scientometric indicators.

Best Regards, SCLmago Team



**Mira** 6 months ago

Dear schimagojr team,

Kindly please check the Open Access Macedonian Journal of Medical Sciences Scopus ranking, it is still Q3 ?

← reply



**Melanie Ortiz** 6 months ago

SCLmago Team

Dear Mira,

Thank you for contacting us. Our data come from Scopus, they annually send us an update of the data. This update is sent to us around April / May every year. The SJR for 2021 was released on 11 May 2022 (based on Scopus data as of April 2022). Therefore, the indicators for 2022 will be available in May/June 2023 and before that date we can't know what will happen with this journal.

Best Regards, SCLmago Team



**Geralt of Rivia** 7 months ago

Dear colleagues

Just inform you

Open Access Macedonian Journal of Medical Sciences has been discontinued from scopus since June 2022 for "publication concern" reason. You could find it at the scopus discontinued source list june 2022 from scopus website.

← reply

**A** **Ardia** 7 months ago

Dear Geralt

How about a paper that is published before June 2022? Will it publish in Scopus or not?  
Thank you for your information...



**Melanie Ortiz** 7 months ago

SCImago Team

Dear Ardia,

Thank you for contacting us. A paper will be considered as Scopus indexed as long as it has been published in the same period in which Scopus has indexed the journal. For this reason, we always recommend to consult the Scopus database directly to see the current status of a journal.

Best Regards, SCImago Team



**Melanie Ortiz** 7 months ago

SCImago Team

Dear Geralt, thanks for your participation! Best Regards, SCImago Team

**M**

**moonlight** 10 months ago

Dear editors,

I have revised and submitted the manuscript ID 7736 entitled "Correlation between level of Serum Transaminases and Duration of Antiepileptic Drugs in Epilepsy Children in Sanglah" in October 2021 and made the payment in January 2022. The editors team replied in March stated its awaiting final edits before publication.

Its been 2 months, I wonder hows the progression of the manuscript, could you please help me to check the progression? thank you in advance.

Best regards,  
purnama

← reply



**Melanie Ortiz** 10 months ago

SCImago Team

Dear Purnama,

Thank you for contacting us.

We are sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.

We suggest you contact the journal's editorial staff , so they could inform you more deeply.

Best Regards, SCImago Team

**D**

**drg. Rachmady nofriansyah** 10 months ago

Hi team how to do submit manuscript in here?

← reply



**Melanie Ortiz** 10 months ago

SCImago Team

Dear Drg. Rachmady , thank you very much for your comment, we suggest you look for the author's instructions/submission guidelines in the journal's website. Best Regards,  
SCImago Team

**J**

**Junita Indarti** 10 months ago

Dear Prof Mirko Spiroski

My name is Junita Indarti, Thank you for the opportunity to be able to publish on OAMJMS, I ask for confirmation for my article oamjms.2022.8509

I received information from OAMJMS that my article [oamjms.2022.8509] had been accepted and asked to make payment in March 9, 2022 01:03 AM  
Then I made a payment via VISA credit card in the same day (2022-03-09 04:22 PM) , after making the payment I confirmed through the system on the website

On March 14, 2022 i recieved an email, asking the credit card payment I made for which article.  
Then I reply the payment for Manuscript Number 8509

But after that there has been no answered from OAMJMS, and it's been a month since my article status is still copyediting.

I would ask, when would the article be available online? Thank you

← reply

M

**Mei neni** 10 months ago

I am a corresponding author of the manuscript entitled "Needs of Parents of Children with Cancer for a Parent Supportive Meeting" that was accepted on OAMJS on 27 December 2021 (oamjms.2021.8042), and I have paid the APC on 30 December. However, until now, I have not been informed of the current status. I have sent an email to Chief Editor, Prof dr. Mirko Spiroski 4 times and also sent messages by the online system, but unfortunately, until now, I have not received any information.

I would ask how is the status of our manuscript.

best regard

Mei Neni Sitaresmi



**Melanie Ortiz** 10 months ago

SCLMago Team

Dear Junita,

Thank you for contacting us. Please see comments below.

Best Regards, SCLMago Team

H

**Hotma Rumahorbo** 1 year ago

I am the author of an article in the Open Access Macedonian Journal of Medical Sciences who has received a letter that the article has been accepted for publication. We received the letter on August 24, 2021, and I have already transferred the bank transfer the funds amounting to the publication fee (400 euros) on August 26, 2021. I have sent the proof of transfer. On October 16, 2021, I received a letter that my payment had not been received and requested online payment within 2 days, otherwise, the publication of the article was canceled. I immediately wrote to the editor-in-chief and assistant editor (October 17, 2021), stating that I had transferred the payment on August 26 and included proof of the transfer. I have also gone to the bank where the delivery was sent to clarify the transfer problem. According to the bank, there is no problem, the funds have been sent. I was given proof that the funds had been sent and I immediately sent the bank statement to the editor-in-chief via email. However, until now I have not received any information, even though I have written to provide information.

Through my letter, maybe someone can share their experiences on how to solve problems like this? because I was confused about how to ask for clarification, the letter was not answered.

thank you

← reply

A

**asep** 1 year ago

Dear Hotma

I think your manuscript has been published by Journal of Macedonia...Just they needed time to process it

C

**chris** 1 year ago

It takes time, just be more patient Actually you manuscript has been published. So You can give the information more completely.



**Melanie Ortiz** 1 year ago

SCLMago Team

Dear Hotma,

Thank you for contacting us. Unfortunately, SCLMago cannot help you with your request. SJR is committed to help decision-making through scientometric indicators.

Best Regards, SCLMago Team

K

**Kuat Oshakbayev** 2 years ago

Our manuscript has been accepted (#6164) and the APC is paid (order-28S-CG81NFH-ITJ2MUW) on June 3, 2021. However, the editor (Dr Mirko Spiroski) is ignored it and didn't reply any email nor phone call. I am as corresponding author three times had written email-letters to the editor, and to web-site of the journal, but no one time is not answered. Today is already June 28. Can Scimago check this journal credibility?

Thank you in advance.

Bests, Kuat

← reply





**Tommy** 1 year ago

Hi I am experiencing the same thing,

Have you got any solution? can you please share it with me, thank you.



**Satriya Pranata** 2 years ago

please ask directly to the university (Cyril and Methodius University in Skopje) where Dr Spiroski works via email. This is very influential on his credibility as a scholar and his place of work must be aware of this problem because many people have experienced the same thing, not only you. good luck



**Melanie Ortiz** 2 years ago

**SCImago Team**

Dear Kuat,  
thank you for your comment.  
Our data source is Scopus, SCImago doesn't participate in the journal's selection.  
SCImago has no authority to include or exclude SJR journals. We just show the data provided in the latest update by Scopus. Please contact Scopus Support regarding this matter here:  
[https://service.elsevier.com/app/answers/detail/a\\_id/14883/kw/scimago/supporthub/scopus/](https://service.elsevier.com/app/answers/detail/a_id/14883/kw/scimago/supporthub/scopus/)  
Best Regards, SCImago Team



**Andy** 2 years ago

My journal has been accepted and the APC is paid. However, the editor is ignored it and didnt reply any email nor phone call. Can Scimago check this journal credibility?

Best regards

Andy

← reply



**Arief** 11 months ago

Editor tidak membalas email tapi bukti bayar di upload di OJS  
Tunggu saja dua bulanan. Nanti akan di minta koreksi final draft dan setelah itu nunggu terbit

Mereka tidak membalas email tapi memang langsung di tindak lanjuti prosesnya.



**Mirko Spiroski** 2 years ago

Dear Andy,

We sent you on 2020-11-13 09:57 AM a llete for Publication Fee and you did not answer to it  
Prof. Dr Mirko Spiroski



**Ivana** 2 years ago

Hi Andi,

I also experience the similiar thing with my submisson. I could not login and no email replies right after I paid for the publication fee. May I know about your progress at te moment?

Best regards,

Ivana



**Ivanova Gergana** 2 years ago

Journal is no more indexed in pubmed and PMC since one year?

Is this correct

← reply



**Hardi Chan** 2 years ago

The journal is no longer in Pubmed/ PMC, <https://www.ncbi.nlm.nih.gov/nlmcatalog?cmd=historysearch>



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Ivanova,  
Thank you for contacting us.  
SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.  
Unfortunately, we cannot help you with your request referring to the index status. We suggest you consult Scopus database (see the current status of the journal) or the mentioned database for further information. You can also check that information in the journal's website or contact directly with the editorial staff.  
Best Regards, SCImago Team



**Yousra Aly** 2 years ago

Good evening sir,

I am Yousra Aly . I am one of the authors of the article: A promising Probiotic irrigant: An in vitro study,published in open access Macedonian journal of medical sciences 2019 Feb 15; 7(3):407-411.

We found that within the article the revision date was written 1 Dec 2019 instead of 2018 as well as the acceptance date was written 2 Dec 2019 instead of 2018 , which is so confusing

Kindly; would you adjust it and send me a copy as soon as possible

Best regards  
Yousra Aly

← reply



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Yousra,  
thank you for contacting us.  
We are sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.  
Unfortunately, we cannot help you with your request, we suggest you contact the journal's editorial staff , so they could inform you more deeply.  
Best Regards, SCImago Team



**Andi Sadapotto** 2 years ago

Dear Prof. Dr Mirko Spiroski,  
Our article has been published in OAMJMS in Vol. 8 No. F , 2020, but it hasn't been appear in my scopus profile. How long to it appear in my scopus profile ?  
Thank you for your concern.

← reply



**Agus Supinganto** 2 years ago

I Agus Supinganto has submitted the Implementation Implementation of Health Examination for Elector Recruitment Processes in the West Nusa Tenggara Province, "Manuscript ID = OJS4586" and has paid the publication fee on April 1, 2020 and the transfer slip has been sent directly to you and uploaded on the website OAMJMS. I have received the email for proofreading but I can't go to the website for proofreading. when will the article be available online?

Be thankful.

Best regards,  
Agus Supinganto



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Agus,  
thank you for contacting us.  
Unfortunately, we cannot help you with your request, we suggest you contact the journal's editorial staff , so they could inform you more deeply.  
Best Regards, SCImago Team



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Andi,  
thank you very much for your comment, unfortunately we cannot help you with your request. We suggest you contact Scopus support: [https://service.elsevier.com/app/answers/detail/a\\_id/14883/kw/scimago/supporthub/scopus/](https://service.elsevier.com/app/answers/detail/a_id/14883/kw/scimago/supporthub/scopus/)  
Best Regards, SCImago Team



**Majdah** 2 years ago

We sent our manuscript and did submission, how many day take to publish our research if did fast track because some people did fast track and take long time to publish , and how can pay money to confirm if you are that will published early.

← reply



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Majdah,  
thank you for contacting us.  
We are sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.  
Unfortunately, we cannot help you with your request, we suggest you contact the journal's editorial staff , so they could inform you more deeply.  
Best Regards, SCImago Team



**Sura Khairialdeen Mohialdeen** 2 years ago

Dear Prof. Dr Mirko Spiroski,

I had submitted my revised manuscript titled: Inflammatory Markers in Pre-eclampsia to Open Access Macedonian Journal of Medical Sciences via the online submission system at 25/3/2020. I would be grateful if you could let me know whether there has been any further progress on my submission.

I resend the revised manuscript again here. thank you for all

Sura Khairialdeen Mohialdeen

← reply



**Sultan** 2 years ago

Just a follow-up, the journal is vanished and so do the Editor-in-Chief emails. They are no longer available.

Absolutely weird to happen in Science and research.

← reply



**Annisa** 2 years ago

i emailed scientific foundation spiroski yesterday and they said they are migrating website content to a new server



**Sneha Vaswani** 2 years ago

Prof. Dr Mirko Spiroski,

I Sneha Vaswani has submitted case report titled " Conservative management of the horizontal root fracture in the middle third using fiber post as an intraradicular splint." I have received acceptance letter for my manuscript (manuscript ID: OJS 4865) on 30 July 2020 and have paid the publication fee on 4th August 2020 and the transfer slip has been directly sent to you and uploaded on the OAMJMS website. I have received the email for proofreading but I couldnt login into website for proofreading. I would ask, when would the article be available online?

Waiting for your reply.

Thanking You.

Yours Sincerely,  
Sneha Vaswani

← reply



**Annisa** 2 years ago

Hi Ms Vaswani, did they just contact you recetly? Because i couldnt send email since they remove the website



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Sneha,

Thank you for contacting us. Please see comments below

Best Regards, SCImago Team

R

**ROHINI KARAD** 2 years ago

Dear Prof Dr. Mirko Spiroski,

My name is Dr. Rohini Karad. I have submitted the manuscript entitled "Confocal Laser Scanning Microscopic evaluation of sealer penetration in root canals of teeth with the butterfly and non butterfly effect: An in-vitro study.". The manuscript ID : OJS 5168. I havent recieved any update since i have submitted the paper. I have emailed you several times but did not get a response. Is there any alternative where i can contact ?

Waiting for your reply.

Kind regards.

← reply



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Rohini,

Thank you for contacting us. Please see comments below

Best Regards, SCImago Team

R

**Rawad Tarek** 2 years ago

Please I can't reach the website of the journal for author's guide to publish in your journal.

← reply



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Rawad,

Thank you for contacting us. Please see comments below

Best Regards, SCImago Team

R

**Raghad E. Naji** 2 years ago

Dear publisher

I'm thankful for the opportunity to send my research to your journal. Whoever, if i want to open an account in your journal so i can send my research but the trouble there is no instruction in your home page about opining an account.

Pls. would you help me ?

← reply



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Raghad,  
thank you for contacting us.

We are sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.

Unfortunately, we cannot help you with your request, we suggest you contact the journal's editorial staff , so they could inform you more deeply.

Best Regards, SCImago Team

S

**Sultan Alshahrani** 3 years ago

Their website is broken. No reply to my emails.

← reply

R

**Rindu** 2 years ago

I Can't access the journal, i've tried to send a email to chief editor but have not received an answer..i need confirmation, please scimagojr team, could you please to help me/us?



**Melanie Ortiz** 2 years ago

SCImago Team

Dear users,

Thank you for contacting us.

We inform you that all the information referring to the website of this Journal has been temporary erased on our website (you'll see "Information not localized") due to the fact that it is not available anymore. Unfortunately, we can not help you regarding the different questions related to the manuscripts sent to this journal. SJR is committed to help decision-making through scientometric indicators.

Best Regards,  
SCImago TEAM



**Aisyah Shofi** 2 years ago

I can't access website of OAMJS what should we do? there is no another contact of that journal except Prof Spiroski, either he never reply my message. Since last year it was Q2 and accredited with Scopus, I have no idea, is it predator journal? My manuscript was accepted last June, and until now there is such an information when the manuscript would be published.



**Iin Ernawati** 2 years ago

yes, their website can't be access. why, we need confirmation.. may be Scopus can forward or looking for information about this condition



**Melanie Ortiz** 2 years ago

SCImago Team

Dear Sultan,

Thank you for contacting us. We will revise the information related to the journal's website as soon as possible.

Best Regards, SCImago Team



**Researcher 1** 3 years ago

I received the acceptance letter almost one year ago and paid for fast track. Now, it has been 9 months and the manuscript stuck in the copyediting phase. No response at all from the editor in chief. Strangely enough, there is only one email to Dr. Spiroski that you only can contact. No one else could be in touch. I sent him too many emails and never replies back. Now, I am confused, how can I withdraw my paper, how would they reply to me, can they get my money back??? Will never try to publish there again.

← reply



**Andy Zulfiqqar** 3 years ago

hello prof. Spiroski. my name is Andy Zulfiqqar, we submitted 2 of manuscript on last December and accepted on February. therefore we completed the payment on the same day on both manuscript, one of manuscript was FAST-TRACT! and our payment already confirmed by your admin on 3rd day our payment. however, the editing programs has took 4 months, and we got declined email that declared that we can not full filled the payment. we already sent our confirmation both on system and by an email, we sent you follow up email. but it's already 2 weeks neither our phone call and email that replied both your account and your supporting contact staff. we urgently need your confirmation.

Best Regards

Andy Zulfiqqar

← reply



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Andy,

thank you for contacting us.

SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.

Unfortunately, we cannot help you with your request, we suggest you contact the journal's editorial staff, so they could inform you more deeply.

Best Regards, SCImago Team



**Wishahi** 3 years ago

Dear Prof Dr. Mirko Spiroski,

My name is Prof. Dr. Mohamed Wishahi. In November 2019, we submitted our manuscript entitled "Ultrastructure pattern of smooth muscles of ureteropelvic junction obstruction in adults: An evidence for surveillance rather than pyeloplasty: Ureteropelvic junction by in adults". The manuscript ID is OJS4005.

Our manuscript was accepted on 07.03.2020, due to COVID-19 pandemic we paid the publication fees on April 21, 2020 by SWIFT. I emailed you the transfer document On the same day. And bank statement showed that the money was transferred to FOUNDATION SPIROSKIRAJKO ZHINZIFOV NO 48, Consequently, on the journal website the status of our paper changed to "editing process and later Editor decision"

Surprisingly, on July 3, 2020, all the co-authors received an email that the decision was to decline the publication because we had not paid. Immediately, I re-sent my email of April 21, 2020 together with the transfer document. Since then I have not received any answer from your side. I have tried to call you several times on the telephone given in your email contact – but no response. Please, clarify the situation.  
Yours sincerely,  
Prof. Dr.med. Mohamed Wishahi

← reply



**Anas Munir** 3 years ago

Dear Sir,  
You might have been scammed. The journal has been covered by the Science Integrity Digest in the article titled: "A Dermatology journal issue that might make your skin crawl" on 29th July as a potential predatory journal, publishing papers without peer review and unsubstantiated evidence. It is not even a member of Committee of Publication Ethics (COPE) officially and the peer review process is extremely unclear. I suggest you to keep making contact with the "editors" in hope that they return your money either or publish your paper.  
Best of luck.



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Anas, thanks for the info! Best Regards, SCImago Team



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Prof. Dr.med. Mohamed Wishahi,  
thank you for contacting us.  
We are sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus. Unfortunately, we cannot help you with your request, we suggest you contact the journal's editorial staff, so they could inform you more deeply.  
Best Regards, SCImago Team



**Khairun Nisa Berawi** 3 years ago

Is the OAMJMS still scopus index for this year?  
thank you

← reply



**sri maya** 3 years ago

Dear Prof Dr. Mirko Spiroski,  
My name is dr. Sri Maya. I am a pediatrician in Indonesia. On 12th August 2019, I submitted my manuscript entitled "Growth, Development and Quality of Life in Children with Congenital Heart Disease". The manuscript ID is 4047.

My manuscript had been accepted and I was given 7 days to pay for the publication fees on March 2020. Unfortunately, I missed the deadline because I was in Tapanuli, a remote area in Sumatra island.

I apologise for this mistake due to the circumstances, I asked that you kindly allow me the opportunity to extend payment dateline now so that my article could be published in OAMJMS. I believe that many of our peers in the medical field could benefit from my article.

Please confirm that this arrangement can still be made so that I can process the required payment as soon as possible.

I've tried to reach you by email several times but haven't been replied until today. I look forward to hearing from you soon. Thank you very much for your assistance.

Sincerely yours,



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Sri Maya,  
thank you for contacting us.  
We are sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus. Unfortunately, we cannot help you with your request, we suggest you contact the journal's editorial staff , so they could inform you more deeply.  
Best Regards, SCImago Team



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Khairun, thank you very much for your comment. We suggest you consult the Scopus database directly. Keep in mind that the SJR is a static image (the update is made one time per year) of a database (Scopus) which is changing every day.  
Best Regards, SCImago Team



**mustaqim** 3 years ago

why Database connection failed!

← reply



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Mustaqim,

Could you please expand a little bit your comment? Best Regards, SCImago Team



**Researcher** 3 years ago

I'd like to know when the next issue will be published knowing that the last one was published in Junary-February??

Thank you.

← reply



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Sir/Madam,  
thank you for contacting us.  
Unfortunately, we cannot help you with your request, we suggest you visit the journal's homepage or contact the journal's editorial staff , so they could inform you more deeply.  
Best Regards, SCImago Team



**Sohel** 3 years ago

Dear Prof.Dr.Mirko Spiroski,  
I have found that there are many manuscripts published in your journal in OAMJMS in August but till now they have not found in PM/PMC. Now, is this journal excluded from the PM/PMC database? Please provide information regarding this issue.

Regards,  
Sohel Rana

← reply



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Sohel,  
thank you for contacting us.  
We are sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus. Unfortunately, we cannot help you with your request, we suggest you to contact the journal's editorial staff , so they could inform you more deeply.  
Best Regards, SCImago Team



**Prof Radovenski** 3 years ago

When will appear the 2 issues from September in PMC!  
Is there a delay

← reply



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Radovenski,  
thank you for contacting us.  
Sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.  
Unfortunately, we cannot help you with your request, we suggest you to visit the journal's homepage or contact the journal's editorial staff , so they could inform you more deeply.  
Best Regards, SCImago Team

B

**B Ivanova** 3 years ago

Please, let us know why there is a delay in the indexation of the August issue of OAMJMS? This seems to be very strange? Is the pubmed indexation of the journal interrupted already or discontinued?

When YES- state this officially on the journal homepage?

Please, do not send me separate emails and answer public so that we all know what's going on

Kind regards

B Ivanova

← reply



**Melanie Ortiz** 3 years ago

SCImago Team

Dear Ivanova,

could you expand your comment? If you are referring to Scopus indexation, we suggest you to contact Scopus directly:

[https://service.elsevier.com/app/answers/detail/a\\_id/14883/kw/scimago/supporthub/scopus/](https://service.elsevier.com/app/answers/detail/a_id/14883/kw/scimago/supporthub/scopus/)

Best Regards, SCImago Team

S

**Susy** 4 years ago

Prof. Dr Mirko Spiroski,

I have received acceptance letter for my manuscript (manuscript ID: OJS 2824) and have paid the publication fee at the smne day 2 days ago and the transfer slip has been directly sent to you . I would ask, when would the article be available online? Thank you.

Regards:  
Susy

← reply

N

**Nahed soliman** 4 years ago

Dear Dr Mirko

You sent acceptance to me without revising the PDF proof .I need to know more about the publication fee. What is the difference between regular article fee and copy rights editing  
Thanks you

← reply

R

**Rodiah** 4 years ago

Dear SCImago team and Prof Mirko Spiroski

Hi..Iam Rodiah R Lubis, my article was published in OAMJS, May 18 2018, title "The Correlation Between Daily Lens Wear Duration and Dry Eye Syndrome". I've been waiting for my name listed in Author preview scopus for 6 months, but still can't find my article listed. Some of my friends whose articles were published in September in your journal have listed their articles in the author preview scopus. Why is my article that was published 4 months earlier still not listed in scopus. Is there anything else that I haven't fulfilled so that my name is listed

Thank you Sir/Madame and I will wait for your answer



Regards,  
Rodiah

← reply

**R** **rusdiana** 4 years ago

Dear Prof.Dr.Mirko Spiroski

Dear Sir, my article has been published in your journal at 25 September 2018. But it is not indexed in scopus. My experience in your journal it was very fast indexed in scopus. thank you Sir and I will wait for your answer.

← reply



**Elena Corera** 4 years ago

SCImago Team

Dear Rusdiana,

articles published in 2018 are not over yet (we are in September). 2018 indicators will not be available until June 2019. We cannot see what will happen in the future with this journal. SCImago receives the data from Scopus / Elsevier annually and does not have the authority to include, exclude or modify the data provided by Scopus.

Best Regards,  
SCImago Team

**R** **Rodiah R Lubis** 4 years ago

Hi, My name is Rodiah R Lubis, my article has been published in OAMJMS, May 18, 2018 with title: "The Correlation Between Daily Lens Wear Duration and Dry Eye Syndrome", but I still can't find my name listed in Scopus author preview yet, and it almost 6 months since the publication. Kindly informed me why it takes so long.

Thank you,  
Best regards,

Rodiah R Lubis

← reply



**Elena Corera** 4 years ago

SCImago Team

Dear Rodiah,

articles published in 2018 are not over yet. 2018 indicators will not be available until June 2019. We cannot see what will happen in the future with this journal. SCImago receives the data from Scopus / Elsevier annually and does not have the authority to include, exclude or modify the data provided by Scopus.

Best Regards,  
SCImago Team

**N** **Nevena Todorova** 4 years ago

I've noticed missing articles in Scopus. For example the article "Linguistic Validation and Cultural Adaptation of Bulgarian Version of Hospital Survey on Patient Safety Culture (HSOPSC)" is not indexed in Scopus database. What is the reason?

← reply



**Elena Corera** 4 years ago

SCImago Team

Dear Nevena,

thank you very much for your comment, unfortunately we cannot help you with your request. We suggest you consult the Scopus database directly. Remember that the SJR is a static image of a database (Scopus) which is changing every day.

Best regards,  
SCImago Team

**E** **Elham M.Youssef** 5 years ago

Hi, My name is Elham M. Youssef

I highly appreciate the time and effort for reviewing my manuscript. However, I have been sending several e-mails with the swift document of the publication fees the last couple of weeks but did not get any response.

I wonder if somebody help.

Manuscript number 1816-6534.

Entitled "Investigating of Moringa Oleifera Role on Gut Microbiota Composition and Inflammation Associated with Obesity Following High Fat Diet Feeding."  
Kind Regards.

← reply



**Prof. Dr Mirko Spiroski** 4 years ago

Dear Elham,

As you know, your paper is published and you can find it on the following links:

- <https://www.idpress.eu/mjms/article/view/oamjms.2018.313>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6108815/>
- <http://europepmc.org/articles/PMC6108815/>
- <https://www.ncbi.nlm.nih.gov/pubmed/30159057>

and will be visible very soon in many other databases.

Best regards,  
Prof. Dr Mirko Spiroski  
Editor-in-Chief  
OAMJMS



**Elena Corera** 5 years ago

SCImago Team

Dear Elham, we suggest you contact the journal directly. Best Regards, SCImago Team

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**Published:** 2020-01-02

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(Author)

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Rasha Ibrahim, Georgios P. Chatzis, Mohamed A. Korayem, Mahmoud K. Mansour (Author)

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# Possible Mechanism and Current Recommendation of Thromboembolism in COVID-19

Dita Aulia Rachmi, Eka Prasetya Budi Mulia, Johannes Nugroho\*

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## Abstract

The coronavirus disease (COVID-19) has become a global pandemic with a high mortality rate. There has been emerging evidence regarding the presence of thrombosis in patients with severe COVID-19 infection. In addition, prognosis of COVID patients, once they are complicated with DVT or fatal pulmonary emboli, will also significantly decline. Hence, understanding the pathomechanism and prompt treatment of thromboembolism is important in improving the outcome in COVID-19 patients. Prophylaxis anticoagulant was proposed for all hospitalized COVID-19 patients. The aim of this article is to review the current literature regarding pathomechanism, risk assessment, diagnosis, and management of VTE.

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## Introduction

The coronavirus disease (COVID-19) has become a global pandemic. Since December 2019, the total number worldwide of confirmed cases is 2,356,414 with mortality rate 6.8% involving 213 countries all over the world (WHO data April 21, 2020) [1]. The first two COVID-19 patients in Indonesia were reported on March 2, 2020. As per April 21, 2020, the total cases of COVID-19 reached 6760 positive cases, of which 590 had died. The mortality rate in Indonesia was as much as 8.7%, and it was the highest rate in Southeast Asia [2].

Study of epidemiology and clinical characteristics of COVID-19 patients have started to unfold. On the other hand, the mortality risk factors and the exact clinical course of disease, including shedding of the coronavirus, have not been well described. The clinical spectrum of COVID-19 ranges from mild to critically ill cases. The clinical spectrum of COVID-19 consists of mild to critical illness. The previous studies revealed that old age, increased SOFA scores, greater d-dimers level more than 1000 ng/mL, and those who have pre-existing comorbidities are more likely to have a poor prognosis [3], [4]. Patient with COVID-19 who fell into severe or critical condition is exposed to venous thromboembolism

potential risk factors such as infection, immobilization, respiratory failure, hypoxia, mechanical ventilation, and use of central venous catheter (CVC) [5].

Three cases in China showed antiphospholipid autoimmune response in patients with COVID-19. These findings give rise to coagulopathy roles in extensive thromboembolism in patients with COVID-19 [6]. The prognosis of COVID patients, once they are complicated with DVT or fatal pulmonary emboli, will significantly decline [5], [7], [8].

This article was aimed to summarize the current literature of mechanism and recommendation in thromboembolism related COVID-19 patients.

## Epidemiology

Venous thromboembolic events (VTE) discussed in this article include deep vein thrombosis (DVT) and pulmonary embolism (PE). Epidemiology data regarding these events in COVID-19 were still very limited. The prevalence of VTE, particularly in critically ill/severe patients suffering from COVID-19, was reported as much as 25–27%. A study from three Dutch hospitals showed a 27% incidence of VTE, including PE and DVT [5]. Another data from China hospital

revealed 25% (25/81) patients with severe COVID-19 pneumonia developed lower extremity venous thrombosis [8]. In a study by Xie *et al.* in Tongji Hospitals, 40% (10/25) COVID-19 pneumonia confirmed patients who underwent computed tomography pulmonary angiography scans (CTPA) were found to be acute PE positive [9].

### **Pathomechanism**

COVID-19 may put the patient susceptible to both arterial and venous thromboembolism due to hypoxia, immobilization, disseminated intravascular coagulation (DIC), and excessive inflammation [5]. Systemic pro-inflammatory cytokine responses, including interleukin-1 and interleukin-6, are mediators of atherosclerosis, directly contributing to plaque rupture through local inflammation and hemodynamic changes. These responses also induce procoagulant factors, which predispose to ischemia and thrombosis [4]. Patient with COVID-19 who fell into severe or critical condition is also exposed to other potential risk factors for VTE such as mechanical ventilation, respiratory failure, and use of CVC [5].

Cell entry is an important component for cross-species transmission, particularly for beta-coronavirus. Spikes, surface glycoproteins encoded by all coronaviruses which bind to host cell receptors, mediate the entry of viruses. For beta-coronaviruses, the receptor-binding domain, a single region of spike protein, mediates interactions with receptors of host cell. After binding to the receptor, protease of the adjacent host cuts the spike, which liberates fusion peptides in spike, facilitating the entry of the virus. Familiar host receptors for beta-coronavirus include dipeptidyl peptidase-4 for MERS-CoV and angiotensin-converting enzyme 2 (ACE2) for SARS-CoV. In addition, ACE2, which is also the receptor for SARS-CoV-2, is expressed on myocytes and vascular endothelial cells. The dysfunction of vascular endothelial cells is one of the mechanisms of thrombus formation [10].

Endothelial cell dysfunction caused by infection results in excess thrombin production and cessation of fibrinolysis, which indicates a state of hypercoagulability in patients with infections such as COVID-19. In addition, hypoxia found in severe COVID-19 can induce thrombosis by increasing not only viscosity of blood but also signaling pathways that depend on transcription factors induced by hypoxia [11].

Study by Chen *et al.* revealed index of biochemical examination of 99 patients with COVID-19 pneumonia, and also reported an abnormal biochemical indexes phenomenon related to patients' hemoglobin. This report shows that the number of neutrophils and hemoglobin in most patients decreased, while the rate of erythrocyte sedimentation, serum ferritin, albumin, C-reactive protein, and lactate dehydrogenase in many patients increased significantly [12].

Whenzong and Hualan hypothesize a possible involvement of hemoglobin in the pathogenesis of COVID-19 [13]. When hemoglobin decreases, and heme increases, the body will accumulate too much dangerous iron ions, which will induce inflammation and increase albumin and C-reactive protein. Cells react to stress due to inflammation, creating large amounts of serum ferritin to bind to free iron to reduce destruction [13]. The previous study stated that iron ion might cause endothelial dysfunction, including vascular endothelial. A study by Zhu concludes that intravascular nanoparticles of iron oxide may provoke inflammation and dysfunction of endothelial cells [14]. However, that proposed pathogenesis of hemoglobin in COVID-19 by Whenzong and Hualan has received critical commentary by Read *et al.* due to the lack of experimental evidence to support any of their conclusions and their claiming the therapeutic effect of drugs that are only just entering clinical trials [15].

The presence of antiphospholipid (aPL) antibodies might also eventually cause thrombosis. Anticardiolipin IgA antibodies, as well as anti- $\beta$ 2-glycoprotein I IgA and IgG antibodies, were found in COVID-19 patients [6]. Antiphospholipid antibodies target phospholipid protein abnormally, and the presence of these antibodies is important in antiphospholipid syndrome diagnosis. Still, these antibodies can also increase temporarily in patients with critical diseases and various infections. In critical patients such as thrombotic microangiopathy, heparin-induced thrombocytopenia, and disseminated intravascular coagulation, the appearance of these antibodies may rarely cause thrombotic events that are difficult to distinguish from other causes of multifocal thrombosis [6]. The main antigenic target of the aPL antibody is known as  $\beta$ 2-glycoprotein I ( $\beta$ 2GPI), mediating the binding of aPL antibodies to target cells, including monocyte, endothelial cells, trophoblast, and platelet, which lead to pro-inflammatory and prothrombotic changes that subsequently result in thrombosis [16].

The net results of those mechanisms may induce the development of subclinical thrombosis in patients suffering from COVID-19. Increased D-dimer, a sign of excessive coagulation activation and hyperfibrinolysis, may explain the result of those pathomechanisms. D-dimer is often used to identify active thrombus with high sensitivity but low specificity. Patients with COVID-19 have an increase of the D-dimer level. After undergoing therapeutic anticoagulation, D-dimer level decreases continuously, which means D-dimer can predict not only thrombosis but also monitor anticoagulant's effectiveness [7]. Another evidence, histopathology study on lung biopsy of critical patients with COVID-19, revealed the presence of occlusion and microthrombosis formation in pulmonary small vessels [17].



### Risk assessment and diagnosis

It is important to identify which patients with COVID-19 are at increased risk of VTE. Current clinical recommendation state that thromboprophylaxis should be given to all acute patient with high risk of VTE. Modified IMPROVE-VTE risk score is a scoring system that combines D-Dimer level with other VTE clinical predictors to identify patients with high-risk VTE who are eligible for thromboprophylaxis medication (Table 1). Marker for higher VTE risk is a total score of 4 or 2–3 with D-dimer level at the time of screening is more than twice the upper limit of normal range [18].

**Table 1: Modified IMPROVE VTE risk score**

VTE risk factor	VTE risk score
Previous VTE	3
Known thrombophilia <sup>a</sup>	2
Current lower limb paralysis or paresis <sup>b</sup>	2
History of cancer <sup>c</sup>	2
ICU/CCU stay	1
Complete immobilization <sup>d</sup> ≥ 1 day	1
Age ≥ 60 years	1

CCU: Cardiac care unit, ICU: Intensive care unit, IMPROVE: International Medical Prevention Registry on Venous Thromboembolism, NIH: National Institutes of Health, VTE: Venous thromboembolism. <sup>a</sup>A congenital or acquired condition that causes the risk of excessive thrombosis (e.g., factor C or S deficiency, lupus anticoagulant, Leiden Factor V). <sup>b</sup>Feet falls into bed 5 s but has an effort against gravity (taken from the NIH stroke scale). <sup>c</sup>Cancer (not including non-melanoma skin cancer) at any time in the past 5 years (cancer must be in remission to meet eligibility criteria). <sup>d</sup>Immobilization is limited to beds or chairs with or without bathroom privileges.

### Risk of pulmonary embolism

The clinical manifestation of acute PE is not specific. Symptoms include chest pain, dyspnea, hemoptysis, and syncope. COVID-19 may exhibit symptoms that bear a misleading resemblance to acute PE. This generates a diagnostic challenge for clinician treating patient with COVID-19. Identifying the presence of risk factors of VTE is vital to determine disease clinical probability. Revised Geneva Rule and Wells Score are often used as prediction rules. They combine symptoms, clinical findings, and risk factors to classify patients with suspected PE into specific category, separating them from the others. Acute thrombosis will activate coagulation and fibrinolysis, leading to increase serum D-dimer. D-dimer has high negative predictive value in diagnosing acute PE. If D-dimer level is normal, then the diagnosis of acute PE is unlikely. Meanwhile, the positive predictive value of high D-dimer is low. Making it less meaningful to confirm the presence of acute PE [19].

Several studies reported that increased D-dimer levels (>1000 ng/mL) are a potential predictor for mortality. D-dimer level has low specificity value, making it unfavorable as a screening tool. Relying D-Dimer as screening tool might cause overutilization of CTPA if applied in patients with acute kidney injury [20].

Prompt diagnosis of PE for patient presenting with respiratory distress, desaturation, and hypotension is crucial to improve the clinical outcomes. Despite the lack of evidence, assessment of serial D-dimer alongside imaging modalities such as bedside echocardiography or Doppler ultrasound will provide

valuable information to determine the presence of PE in patients with COVID-19 infection [21]. A recent study examining 25 patients suspected of PE showed that D-dimer levels in patients with confirmed PE had values higher than 7000 ng/mL, significantly higher than those without PE [9], [21].

### Risk of deep vein thrombosis

The initial step in the diagnostic algorithm of DVT suspicion is using two levels modified wells score. It will classify DVT suspected patients into two categories (DVT unlikely or likely). For DVT-unlikely, D-dimer examination is established. Normal D-dimer renders DVT unlikely. In patients with DVT-likely, D-Dimer testing is not required, but imaging is required. If not contraindicated, anticoagulation therapy must be started in patients with DVT-likely until imaging. First-line imaging modality of DVT is venous ultrasonography [22].

### Elevated serum D-dimer level

Study by Cui, *et al.* revealed that one-fourth of COVID-19 patients developed VTE. VTE was strongly correlated with elevated serum D-dimer level, as shown in Table 2. The authors subsequently tested several D-dimer cutoff value to predict VTE occurrence (Table 3). The best cutoff of D-Dimer value was 1500 ng/ml (85% sensitivity and 89% specificity). This supports the concept of empiric anticoagulation for patients with markedly elevated D-dimers (particularly in situations where frequent CT angiography and Doppler Ultrasound is impossible due to logistic restraints) [8].

**Table 2: Characteristics between the VTE and non-VTE groups (n = 81)**

Characteristics	Normal range	VTE (n = 20)	Non-VTE (n = 61)	p-value
Age (years)	-	68.4 ± 9.1	57.1 ± 14.3	0.001
Leukocytes (×10 <sup>9</sup> /L)	3.5–9.5	7.8 ± 3.1	6.6 ± 2.6	0.120
Lymphocytes (×10 <sup>9</sup> /L)	1.1–3.2	0.8 ± 0.4	1.3 ± 0.6	<0.001
Platelets (×10 <sup>9</sup> /L)	125.0–350.0	246.6 ± 110.6	248.8 ± 111.7	0.938
Hemoglobin (g/L)	115.0–150.0	123.2 ± 16.5	125.3 ± 16.7	0.633
APTT (s)	27.0–45.0	39.9 ± 6.4	35.6 ± 4.5	0.001
Prothrombin time (s)	11.0–16.0	15.4 ± 1.0	15.6 ± 1.0	0.465
D-dimer (ug/mL)	0.0–0.5	5.2 ± 3.0	0.8 ± 1.2	<0.001

Due to current limited studies, initiating full dose of anticoagulation based on D-dimer value will remain controversial. For now, these decisions may be judged on a patient-by-patient basis, considering both risks of thrombosis and hemorrhage. Among patients without risk factors for hemorrhage, empiric anticoagulation may be reasonable for patients with D-dimer levels above ~1500 ng/ml [8].

**Table 3: Sensitivity, specificity, positive predictive value, and negative predictive value of different D-dimer cutoff levels for predicting VTE in COVID-19 patients**

Cutoff (ug/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1.0	85.0	77.0	54.8	94.0
1.5	85.0	88.5	70.8	94.7
2.0	80.0	90.2	72.7	93.2
2.5	70.0	93.4	77.8	90.5
3.0	70.0	96.7	87.5	90.8
3.5	65.0	96.7	86.7	89.4

PPV: Positive predictive value, NPV: Negative predictive value

In conclusion, modified IMPROVE-VTE risk score and serum D-Dimer level are valuable tools to help identify COVID-19 patients at increased risk of VTE. Increased D-Dimer level above 1500 ng/ml has the best sensitivity and specificity value for predicting the VTE events in COVID-19 patients. The diagnosis of PE and DVT require imaging modality such as bedside echocardiography or Doppler ultrasound.

## Management

### Anticoagulant

Most patients with COVID-19 may have excessive activation of coagulation and will consequently have microthrombi [17]. Hence, several interim guidelines and health-care center protocols agreed that all hospitalized COVID-19 patients must all be in some form of anticoagulation, whether it is confirmed VTE or not [23], [24], [25], [26], [27].

Heparin, including LMWH or its synthetic form, is commonly used as an anticoagulant to prevent DIC and VTE in patients with infection due to its anti-inflammatory effects. As well as preventing thrombosis, heparin has its property to lower cytokine levels and prevents cytokine storm in patients with COVID-19 [23], [28], [29]. American Society of Hematology (ASH) recommends LMWH or Fondaparinux over UFH for all hospitalized patients unless increased bleeding risk is present. While in patients with heparin-induced thrombocytopenia history, it is recommended to use fondaparinux. If anticoagulants are not available or contraindicated, then mechanical thromboprophylaxis is advised (e.g., pneumatic compression device) [24], [30].

A retrospective analysis by Tang *et al.* comparing 28-day mortality between heparin users and non-users of 449 consecutive patients with severe COVID-19 was done in China. Ninety-nine patients had received heparin for 7 days or longer. They found no significant difference in 28-day mortality between heparin users and non-users (30.3% vs. 29.7%  $p = 0.910$ ). However, in patients with sepsis-induced coagulopathy (SIC) score  $\geq 4$  (Table 4), mortality was significantly reduced by anticoagulant medication ( $p = 0.029$ ). In patients with D-dimers  $>3000$  ng/mL (6 times of the normal upper limit), anticoagulation results in a 20% mortality reduction ( $p = 0.017$ ) [11].

**Table 4: ISTH SIC scoring system [11]**

Item	Score	Range
Platelet count ( $\times 10^9/L$ )	1	100–150
	2	$<100$
PT-INR	1	1.2–1.4
	2	$>1.4$
SOFA score	1	1
	2	$\geq 2$
Total score for SIC	4	

INR: International normalized ratio, ISTH: The International Society on Thrombosis and Hemostasis, SIC: Sepsis-induced coagulopathy, SOFA: Sequential organ failure assessment

### The International Society of Thrombosis and Hemostasis (ISTH)

The interim guidance delivers risk stratification of coagulopathy at admission for patients with COVID-19 and coagulopathy management (Figure 1) [23]. Their recommendations including:

1. Patients with high D-dimers (e.g., arbitrarily defined as 3–4 times increase) will need to be hospitalized.
2. Monitoring the reduction in fibrinogen levels later in the course of the disease (e.g., days 10–14) can help in determining whether the patient has progressed to DIC.
3. LMWH should be considered in all patients (including those who are not critical) who need to be hospitalized for COVID-19, if there are no contraindications:
  - Active hemorrhage
  - Platelet count  $<25 \times 10^9/L$
  - Monitoring recommended for severe renal impairment
  - Abnormal PT or aPTT is not a contraindication
4. LMWH might carry anti-inflammatory properties that provide added benefits in COVID-19 infection.

### Prophylactic anticoagulant

Brigham and Women's Hospital guideline recommendation of standard prophylactic anticoagulation for thrombotic disease management in all hospitalized COVID-19 is as follows [27]:

1. If GFR  $>30$  mL/min: Enoxaparin 40 mg subcutaneous (SC) daily
2. If GFR  $<30$  mL/min or acute kidney injury: Unfractionated heparin (UFH) 5000 units SC q8hr
3. Hold if platelets  $<30,000$  or bleeding, start thromboembolic deterrent stockings, and sequential compression devices.

Klok *et al.* reported that in spite of prophylaxis anticoagulant administration, 27% of patients had later developed VTE, and 4% had an incidence of arterial thromboembolism (which may be underestimated, due to the lack of systematic screening for this event and the interrupted observation period in some patients). As a result, they recommend doubling the conventional dose of heparin prophylaxis (e.g., Enoxaparin 40 mg twice a day, rather than once a day) [5]. Prophylactic doses higher than standard doses can also be considered in patients with elevated D-dimers (e.g., 500–1500 ng/mL) [31]:

GFR  $> 30$  mL/min: Enoxaparin 0.5 mg/kg q12hr. Check anti-Xa level 4 h after the third dose, with a target level of 0.5–0.8 IU/ml.

1. GFR  $< 30$  mL/min: UFH 7500 units q8hr (consider dose adjustment for atypical weight patients).

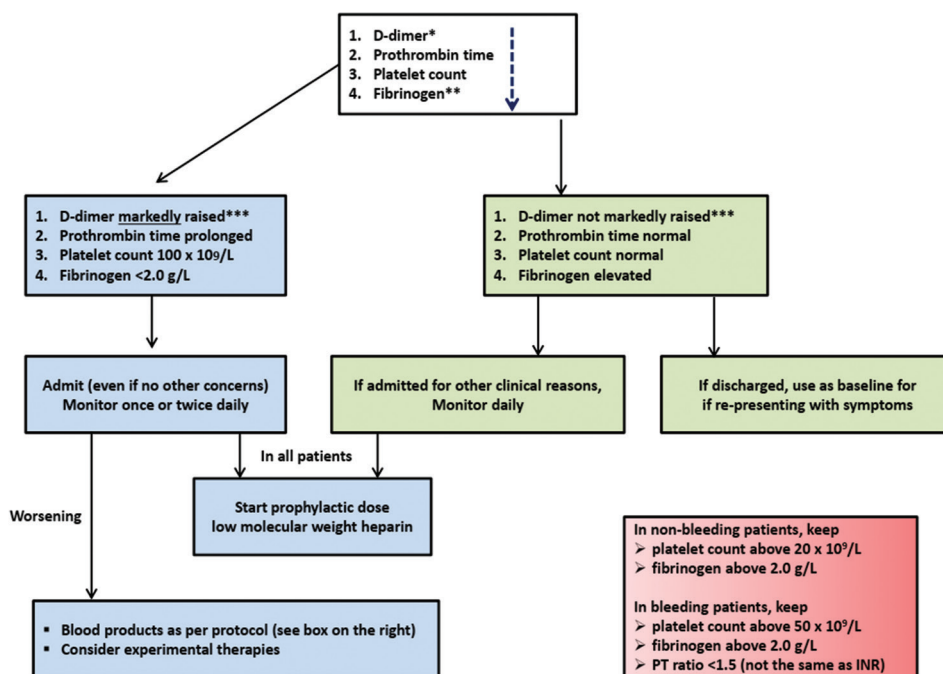


Figure 1: Algorithm of coagulopathy management in COVID-19 build on simple laboratory parameters. \*The list of parameters is written in descending order of importance. \*\*Taking a fibrinogen test may not be available in some laboratories, but monitoring levels can be helpful after hospitalization. \*\*\*Even though the specific cutoff cannot be defined, an increase in D-dimer 3-4-fold can be considered significant. One of the values in this table can be considered significant [23]

### Therapeutic anticoagulant

Therapeutic anticoagulation with heparin has been proposed for patients with D-dimers level greater than 2000 ng/ml, but this has not been proven [11], [32]. At present, therapeutic anticoagulation was limited to COVID-19 patients with documented acute VTE, and pre-hospital management with therapeutic anticoagulation (such as for recurrent VTE, certain mechanical heart valves, and atrial fibrillation). In general, the recommendation for VTE therapeutic as follows [23], [25], [26], [27], [33]:

1. If the patient uses direct oral anticoagulant (DOAC) or warfarin for Afib or VTE, switch to the full dose of anticoagulant (LMWH or UFH, according to indications based on kidney function or clinical conditions; LMWH is preferred over UFH to reduce blood drawing in monitoring PTT because of more possible interactions with COVID 19).
2. If the patient has confirmed acute PE or DVT or is undergoing anticoagulant therapy before being hospitalized and is now converted to parenteral, the following guidelines are recommended:
  - a. LMWH is preferred to minimize blood drawing and has superior efficacy in critical care population [26].
  - b. Patients who need to use UFH (not LMWH) should be monitored with anti-Xa levels (in contrast to PTT given that the increases in COVID-19 patients who are severe and can make PTT unreliable) [26].
3. Consult with a hematologist to discuss specific guidelines if coagulopathy in the patient

appears to be deteriorating or to discuss an escalated or modified treatment approach, as some hematologic disorder such as thrombocytopenia increased risk of severity and mortality in COVID-19 [34].

4. Farkas proposed a possible approach to empiric anticoagulation with a limit of D-dimer above 1000–2000 ng/ml, fibrinogen level, thromboelastography (TEG) as guidance, as shown in Figure 2. This author states that this approach has not yet been supported by any high-level evidence, and the decision to provide anticoagulants should preferably be individualized, so this is only intended as an approach scheme in the management of patients. In the case of very advanced stages, severe disease may be characterized by low fibrinogen levels, which can produce hemorrhagic clinics, where anticoagulation can theoretically be dangerous in that condition [31].

Yale-New Haven Hospital (YNHH) and Massachusetts General Hospital (MGH) issued a local protocol of anticoagulation dosing guidelines including LMWH, heparin, fondaparinux, and DOAC (apixaban, rivaroxaban, and dabigatran) in prophylaxis and therapeutic management of VTE, as shown in Table 5.

### Direct oral anticoagulant (DOAC)

Because of possible drug interactions between DOAC and combinations of antiviral (especially

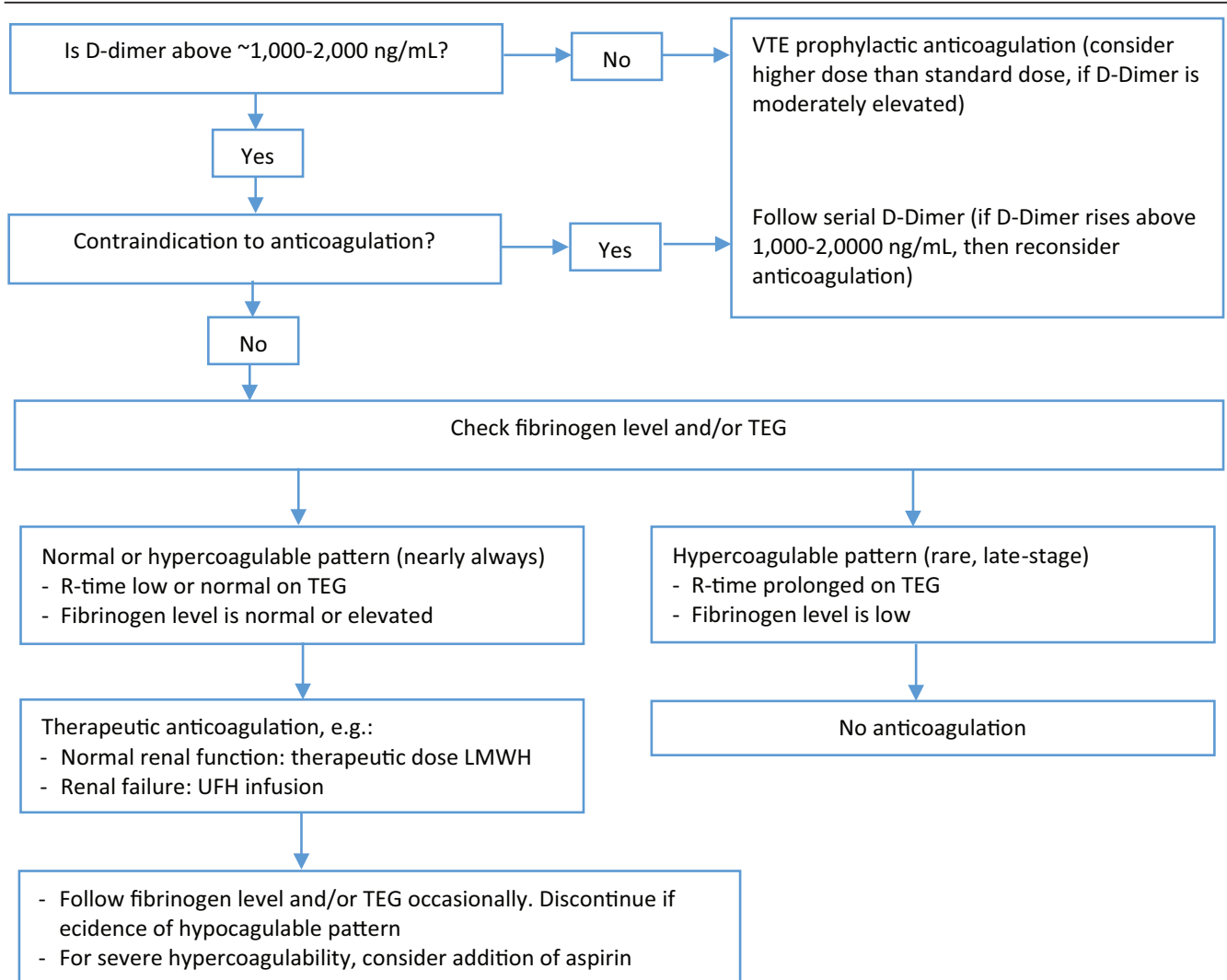


Figure 2: Possible approach to empiric anticoagulation in COVID-19 (adapted from Farkas, 2020) [31]. LMWH: Low molecular weight heparin, TEG: Thromboelastography, UFH: Unfractionated heparin.

anti-HIV protease inhibitors such as ritonavir) and antibacterial (such as azithromycin), LMWH or UFH should be preferred over DOAC. Such antiviral and antibacterial therapy interferes with the CYP3A4 and/or P-GP pathways, which can increase the risk of bleeding or reduce the antithrombotic effect in the case of DOAC use [19].

### Fibrinolytic

At present, there are not enough data suggesting the use of more advanced therapies such as tissue plasminogen activator/tPA or to increase the dose of prophylactic anticoagulation in VTE associated with critically ill COVID-19 patients. There is evidence in animals and humans that fibrinolytic in acute lung injury and acute respiratory distress syndrome (ARDS) improves survival. This evidence also shows fibrin deposition in pulmonary microvasculature as the main cause of ARDS and is expected to be found in ARDS patients and a concurrent diagnosis of DIC seen in laboratory parameters, as observed in more

than 70% of patients who died from COVID-19 [35]. Wang *et al.* reported three cases of intravenous tPA off-label (Alteplase) in COVID-19 patients with ARDS and respiratory failure. In all cases, patients showed an initial increase in the P/F ratio. However, the observed increase was temporary and disappeared over time in all three patients after completing their tPA infusion. They also mentioned that larger bolus tPA doses (50 mg or 100 mg bolus) without retaining anticoagulants are worth further considering and research to prevent the recurrence of suspected thrombosis of pulmonary microvascular that underlies ARDS in COVID-19 [35].

In conclusion, it is reasonable to give anticoagulant for prophylaxis treatment to all admitted patient with COVID-19. Heparin is the preferred anticoagulant for patients with COVID-19 because of its anti-inflammation property. Therapeutic anticoagulant should be given to patient with confirmed VTE or has high suspicion of developing VTE. The decision to give anticoagulation should be judged on patient-by-patient basis, considering both risks of thrombosis and hemorrhage.

**Table 5: Prophylactic and therapeutic dosing of anticoagulation in VTE management**

D-dimer	Brigham and Women's Hospital (BWH)	Yale-New Haven Hospital (YNNH)	Massachusetts General Hospital (MGH)
<500 ng/mL: Prophylactic dose	GFR > 30 ml/min: Enoxaparin 40 mg SC q24h GFR < 30 ml/min: UFH 5000 units SC q8h	BMI < 40 kg/m <sup>2</sup> GFR ≥ 30: Enoxaparin 40 mg SC q24h GFR < 30: Enoxaparin 30 mg SC q24h UFH 5000 units SC q12h BMI ≥ 40 kg/m <sup>2</sup> GFR ≥ 30: Enoxaparin 40 mg SC q12h GFR < 30: Enoxaparin 40 mg SC q24h Heparin 7500 units SC q12h	Standard dose UFH: 5000 units SC q12h Enoxaparin: 40 mg SC q24h Fondaparinux: 2.5 mg SC q24h Apixaban: 2.5 mg PO q12h Rivaroxaban: 10 mg PO q24h Dabigatran: 110 mg followed by 220 mg q24h BMI ≥ 40 kg/m <sup>2</sup> UFH: 5000 units SC q8h Enoxaparin: GFR ≥ 30: 40 mg SC q12h GFR < 30: 40 mg SC q24h
≥500 ng/mL: Intermediate prophylactic dose	Recommended higher prophylactic dose by Klok <i>et al.</i> and Farkas. GFR > 30 ml/min: Enoxaparin 0.5 mg/kg q12h. Check an Xa level four hours after the third dose, targeting a level of ~0.5–0.8 IU/ml. GFR < 30 ml/min: UFH 7,500 units q8hr (consider dose adjustment for atypical weight patients).	BMI < 40 kg/m <sup>2</sup> GFR ≥ 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban GFR < 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban UFH 7500 units SC q12h BMI ≥ 40 kg/m <sup>2</sup> GFR ≥ 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban GFR < 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban UFH 7500 units SC q12h Apixaban: 5 mg PO q12h regardless of renal function BMI < 40 kg/m <sup>2</sup> GFR ≥ 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban GFR < 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban Therapeutic UFH BMI ≥ 40 kg/m <sup>2</sup> GFR ≥ 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban GFR < 30: Enoxaparin 1 mg/kg SC q24h Apixaban Therapeutic UFH Apixaban: 10 mg PO q12h × 7 days followed by 5 mg PO q12h	n/a
Confirmed VTE or high clinical suspicion: Therapeutic dose	n/a	Standard dose: UFH: 80 unit/kg bolus + 18 units/kg/hr infusion Enoxaparin: 1 mg/kg SC q12h Fondaparinux: <50 kg: 5 mg SC q24h 50–100 kg: 7.5 mg 124h >100 kg: 10 mg q24h BMI ≥ 40 kg/m <sup>2</sup> Enoxaparin: GFR ≥ 30: 0.75 mg/kg q12h GFR < 30: 0.75 mg/kg q24h	n/a

n/a: Not available, BMI: Body mass index, GFR: Glomerular filtration rate, SC: Subcutaneously, UFH: Unfractionated heparin, VTE: Venous thromboembolism

## Prognosis

Several studies proved the role of increased D-dimers as a predictor of mortality. Higher levels of D-dimer and fibrin degradation products showed to have associated with multi-organ dysfunction syndrome and worse prognosis [4], [7]. Huang *et al.* showed that the level of D-dimer at admission was higher in patients who needed critical care support (median [range] D-dimer level 2400 ng/mL [600–14.400]) compared to patients who did not need it (median [range] D-dimer level 0.5 ng/mL [300–800],  $p=0.0042$ ) [29]. Tang *et al.* reported DIC development on the 4<sup>th</sup> day in 71.4% of patients who did not survive compared to only one patient (0.6%) who survived. They also reported increased D-dimer and PT levels with decreased levels of fibrinogen in those who did not survive on 10<sup>th</sup> and 14<sup>th</sup> days significantly [7].

Sepsis patients are more likely to develop multi-organ failure in the presence of coagulopathy. Giving these patients medication which inhibits thrombin formation will likely aid in reducing mortality [23]. Study by Tang *et al.* proposed that monitoring D-dimers, PT,

fibrinogen, and platelet counts can help to determine prognosis in patients with COVID-19. Aggressive critical care support is proposed if these parameters worsen.

Thrombocytopenia at presentation is considered to be a prognostic factor for mortality (OR, 5.1; 95% CI, 1.8–14.6), as stated by Lippi *et al.* [34]. Thus, this study suggests the clinician provide adequate blood product and consider giving more “experimental” therapies as the data regarding therapies in COVID-19 are still limited [7], [23].

## Conclusion

Patients suffering from COVID-19 are at high risk of developing thrombosis, including VTE. Excessive inflammation, hypoxia, immobilization, aPL antibody, and diffuse intravascular coagulation contributes to development of VTE. There has been upcoming evidence regarding the presence of thrombosis in patients with severe COVID-19 infection. Prophylaxis anticoagulant

was proposed for all hospitalized COVID-19 patients. However, until additional data are available, when to initiate full therapeutic anticoagulation will remain controversial. For now, these decisions may be judged on a patient-by-patient basis, considering both risks of thrombosis and hemorrhage. Anti-inflammatory effect of LMWH may provide additional benefit in COVID-19 patients.

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