Review Article

A Review on the Therapeutic management of COVID-19 associated with Thrombotic events and Coagulopathies.

Abstract:

Severe acute respiratory syndrome coronavirus two (SARS-CoV-2) is answerable for the coronavirus illness in 2019 (COVID-19) that chop-chop evolved from a virus in metropolis, Varied coagulopathies are rumored in association with COVID-19, together with disseminated intavasular action (DIC) sepsis-induced coagulopathy (SIC), native microthrombi, blood vessel occulation (VTE), blood vessels thrombotic complications and thrombo inflammation. There's a overplus of publications and conflicting information on hematologic and astringent derangements in COVID-19 with some information suggesting the link to illness progress, severity and/or mortality. There is also growing evidence of potentially usefull clinical biomarkers to predict COVID-19 progression and illness outcomes of these, a link between blood disease and COVID-19 severity or mortality was instructed. During this opinion report, we have a tendency to examine the revealed proof of hematological and astringent laboratory derangements in COVID-19 and also the reticular SARS-CoV-2 evoked inflammation, with a focused discussion on blood platelet count alterations.

Key words: Thrombotic actions, Coagulopathies, COVID-19, SARS-CoV-2, Blood platelet count.

Introduction:

Since March 11, 2020, the world Health Organization has declared the severe acute respiratory syndrome coronavirus two (SARS-CoV-2) caused by COVID-19 as a global pandemic. As of May 26, a total of 5495061 cases and 346232 fatalities had been reported in 188 countries or regions. Currently, there are approximately 1.3 million confirmed cases and over 82,000 deaths. The United States is the most powerful country in the world (1). The majority of COVID-19

patients experienced mild illness, but those who required hospitalization were at risk of developing deadly critical disease. A substantial frequency of acute vas events has been seen among these very ill individuals (2). SARS-CoV-2 and SARS-CoV have a similar cellular target and clinical symptoms, such as blood illness, extended coagulase time, and raised D-dimer levels (3). It means that, like SARS-CoV, SARS-CoV-2 is likely to be complex with coagulopathy, particularly disseminated intravascular action (DIC) or pre-DIC related to AN The patient with DIC has a prothrombotic character and a high risk of venous thromboembolism (VTE) (4). COVID-19 has previously been linked to blood vessel thrombotic events, as well as deep vein occlusion and embolism (PE) (5). Complications of VTE in individuals with COVID-19 are prevalent when they have a severe hypercoagulable condition, according to new evidence (6).VTE was found in 25% of ICU patients who did not receive thromboprophylaxis, with a 40% death rate (7). The prevalence of VTE in the cuietal research seemed to be higher than in other studies including patients admitted to ICUs for various illnesses (8). According to a meta-analysis, patients with VTE in the ICU had a slightly higher risk of in-hospital death (relative risk 1.31;95 percent Cl:0.99—1.74) (9). Patients with a considerably increased D-dimer or sepsis-induced coagulopathy benefited from anticoagulant medication, particularly low mass anticoagulant therapy, in a trial of 449 patients with severe COVID-19 (10). VTE is linked to infection in the meanwhile. COVID-19, as a unique infection, may increase the incidence of VTE by causing epithelial tissue damage, microvascular blockage, and occlusion, or by triggering response mechanisms (11). As a result, it appears that severe COVID-19 individuals are at a high risk of VTE and death, and their prognosis might be improved with pharmaceutical medical treatment. Patients with COVID-19, on the other hand, may have a prolonged activated partial-thromboplastin time (aPTT), which might suggest the presence of a plasma protein (12). In Bowles' research, 216 patients with severe SARS-CoV-2 were screened for action, 44 (20%) of whom had a prolonged aPTT, and the majority of those who had a prolonged aPTT were positive for lupus treatment (91%) with no evidence of damage (13). As a result, a prolonged aPTT should not be a barrier to the use of thrombo prophylactic medications in COVID-19 patients. These findings pose an important question: what is the current role of antiplatelet/anticoagulant medical care in the prevention and treatment of COVID-19 patients(14).

Hematological/Hemostatic lap abnormalities in COVID-19

In COVID-19, hematological/hemostatic abnormalities are widespread, with more severe alterations noted in people having the illness (15). To examine patients with COVID-9, favaloro and lippi propose the following minimal hematologic testing panel based on documented coagulation abnormalities: full blood count, routine coagulation tests prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer (16). Patients with COVID-19 may experience lymphopenia, neutrophilia, thrombocytopenia, leukocytosis, and/or leukopenia in terms of blood cell count. Lympopenia is one of the most prevalent cell count abnormalities in COVID-19, and it may be a good predictor of prognosis. Guan et al. investigated 1099 COVID-19 patients and found that 83.2 percent had lymphocytopenia (17). Lympopenia was detected in the majority of COVID-19 patients in many different investigations. The researchers Huang et al. and Wang et al. discovered a link between lymphopenia and ICU hospitalisation (18). Fan et al. observed that lymphopenia (P0.001) and increased lactate dehydrogenase (LDH) (P0.005) were substantially linked with ICU admission on entry, which is consistent with prior investigations (18). Lympopenia, neutrophilia, low albumin, and increased LDH and C-reactive protein (CRP) were all found to be predictors of COVID-19 severity by Liu et al (19). In a retrospective review of fatal and recovered COVID-19 patients, Deng et al. discovered that those who died had substantially lower lymphocyte counts (P0.001) and lymphocyte to white blood cell ratios (P0.01) on admission and during hospitalisation than those who recovered (22). In individuals with severe COVID-19, thrombotic indicators such as D-dimer are frequently increased in addition to changes in blood cell count (23). Laboratory abnormalities such as leukocytosis, neutrophilia, and lymphopenia increased prothrombin time and elevated D-dimer were significant predictors of ICU admission, according to Huang et al (20). D-dimer and fibrin/fibrinogen levels were raised in all COVID-19 patients, according to Han et al., and D-dimer and FDP levels were greater in patients with severe infections than in those with milder illnesses (25). When comparing non-survivors to survivors, Tang et al. discovered considerably higher D-dimer and FDP levels, as well as significantly longer PT and aPTT (15). D-dimer levels of more than 1 g/ml (Zhou et al., P=0.0033) (26) or more than 2.0 g/ml (Zhang et al., P0.001) on admission were shown to be predictive of in-hospital mortality in several investigations (24). Elevations of cytokines such IL-1 and IL-6, in addition to D-dimer and neutrophilia, appear to be indicators of severe COVID-19 (27). Finally,

hypercoagulability was confirmed by thromboelastography and thromboelastometry in COVID-19 (23)

Thrombocytopenia and COVID-19

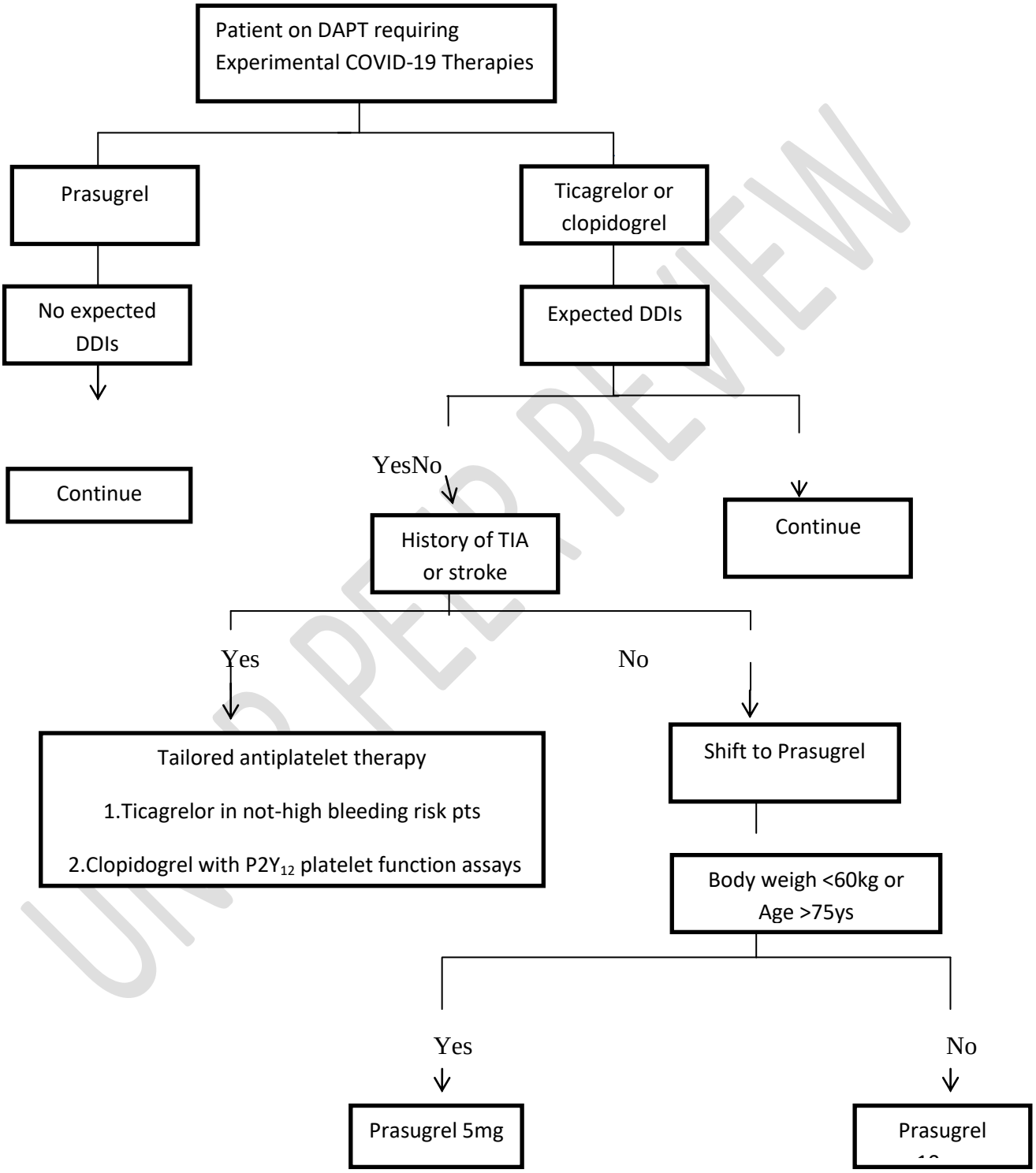
There is some indication of a link between thrombocytopenia and the severity of COVID-19. However, the data on whether thrombocytopenia can be utilised as a clinical biomarker for COVID-19 and, if so, whether it is linked with disease mortality is mixed. The platelet count was significantly lower in patients with more severe COVID-19 (weighted mean difference (WMD) -3119/L, 95 percent CL-35 to -29109/L), and an even lower platelet count was associated with mortality (WMD -48109/L, 95 percent CL-57 to -39109/L), according to a meta-analysis of nine studies involving 1779 patients with COVID-19. Patients with a low platelet count had a five-fold higher risk of severe COVID-19 (OR 5.1, 95 percent Cl-1.8-14.6), according to the researchers (28). The heterogeneity of the papers included in the meta-analysis, on the other hand, was substantial (28). Thrombocytopenia was observed to be more prevalent in individuals with severe COVID-19 than in those with less severe instances in several investigations (26). Thrombocytopenia (P=0.015) was found to be an independent risk factor for COVID-19 disease development (29). Several studies have found a relationship between thrombocytopenia and mortality in patients with COVID-19. There was a significant difference in platelet count between survivors and non-survivors in trials where mortality was the major outcome (26). Tang et colleagues discovered that platelet count was adversely connected with 28-day mortality in patients with severe COVID-19 (30). In a multi-center retrospective cohort research, Zhou et al found that non survivors (165.5109/L, IQR 107.0-229.0) had a substantially lower median platelet count (P0.0001) than survivors (220.0109/L, IQR 168.0-271.0). (26). Three further retrospective investigations verified this, one of which looked at 1476 patients (31). When compared to individuals without thrombocytopenia, thrombocytopenia upon admission was an independent risk factor for in-hospital death, with a nearly three-fold higher risk of mortality (P0.05) (32). Other research did not find a link between thrombocytopenia and COVID-19 severity or prognosis, despite the findings of the previously listed studies. According to Wang et

al., there was no significant difference in median platelet count between COVID-19 ICU patients and non-ICU patients (33). Young et al. identified similar platelet counts in patients who needed supplementary oxygen and those who did not, but no statistical comparison was made (34).A significant difference in platelet count between survivors and non-survivors with COVID-19 complicated by acute respiratory distress syndrome (ARDS) was not found by Wu et al (21). In line with these findings, Fan et al. discovered no link between platelet count and ICU admissions at admission or throughout hospitalisation (18), and therefore were proposed as a clinical biomarker of the condition. A substantial link was found between cell free DNA, acute phase reactants (C-reactive protein, D-dimer, and LDH), and absolute neutrophil count, all of which have been found to be high in severe COVID-19 cases (27). MPO-DNA was linked to absolute neutrophil count, but Cit-H3 was linked to platelet count (27). COVID-19-related thrombosis may be connected to NETs by direct activation of the intrinsic coagulation pathway, disabling natural coagulation inhibitors, and/or direct contact with platelets (27). The presence of neutrophilic infiltration in autopsy samples from COVID-19-infected lungs adds to the possibility of increased NETs (35). Literature links NET creation to pulmonary illnesses, thrombosis, and cytokine strom, indicating that NET formation may be a driver of poor prognosis in COVID-19 patients (35). On the other hand, it's possible that NETs are just a result of acute inflammation rather than a key player in COVID-19 pathogenesis (27). Platelet activation is triggered by SARS-CoV-2 stimulation of the inflammatory and coagulation pathways. Platelet leukocyte complexes are formed when active platelets bind neutrophils, potentially increasing NET development (35). The specific mechanism of COVID-19-induced inflammation is still unknown; however, it is likely complex. Immune suppressants such as steroids, immunoglobulin, selective cytokine blocking (such tocilizumab, which has been authorised in China), and JAK inhibition may be beneficial for individuals with signs of excessive inflammation (36).

Mechanism of thrombocytopenia/thrombocytosis in COVID-19

Several plausible pathways for clarifying blood illness in COVID-19 have been proposed, however the exact processes remain unknown. Reduced protoplasm destruction and removal of existing platelets are the three basic processes that cause blood disorder. SARS-CoV-2 may cause a protein storm, as previously described, or infect/kill bone marrow cells directly via

CD13/CD66a, halting hematopoiesis (37). As long as white blood cell counts (apart from lymphopenia) in COVID-19 remain essentially unaffected, the bone marrow mechanism appears to be a lesser amount, making the protein storm method a lot more feasible for decreased protoplasm production (37). SARS-CoV-2 iatrogenic auto antibodies or immune complexes that concentrate on platelets cause platelet clearance by the system, resulting in blood disease canal (37). Furthermore, SARS-CoV-2 iatrogenic respiratory organ injury, which is associated with protoplasm unharness from megakaryocytes (39), as well as epithelial cell damage, which causes inflammation and protoplasm activation, will all contribute to the development of blood illness (37). Many recent claims of increased protoplasm count in COVID-19 have been based on study that focused on a decline rather than a gain in protoplasm count (38). Patients with significantly higher protoplasm count peaks (P=0.047) and protoplasm-to-lymphocyte ratios (PLRs) at platelet peak (P=0.001) during therapy had longer average hospitalization durations, according to a retrospective review of thirty patients hospitalized with COVID-19 (40). Similarly, non-survivors of COVID-19 had the next median or average protoplasm estimate entrance on than survivors, according to two different research (41). We believe that an elevated protoplasm count is a nursing indicator of (42) protein storm (cytokines such as TPO, IL-3, IL-6, IL-9, IL-11, and somatic cell issue will stimulate megakaryocyte assembly, and IL-6 will directly stimulate thrombopoiesis, resulting in increased protoplasm synthesis by extension) (40). Endothelial damage causes Vwf unharness, which can act with megakaryocytes via the GPIbvWF signal to increase protoplasm formation (39), and/or thrombopoietin unharness stimulates respiratory organ megakaryocytes to provide platelets (38). Given the critical role platelets play in thrombo inflammation and host defense, it's worth seeing if antiplatelet drugs, notably ticagrelor, which also has anti-inflammatory characteristics (43), might prevent platelet-mediated problems seen in COVID-19.



Conclusion:

COVID-19 is a pace spreading and infecting millions round the world. Despite the embarrassment of publications, many a conflicting and lots of pathological aspects of this sickness stay unclear. Blood disease has been well characterized in COVID-19. Different derangements in haematological tests are documented further more, albeitlessy systemically. Cytokines and acute section reactants like protein, fibrinogen, serum globulin and D-dimer want that require to be uncovered regarding COVID-19 and extra analysis on this virus is in direct need. The actual fact remains that SARS-CoV-2 target respiratory organ tissue and there's some proof that a protein storm or a minimum of important inflammation is induced. Supported platelets distinguished role in haemostasia, inflammation and immune defense, careful to changes in serial protoplasm count could offer useful insight into a patients clinical standing and sickness outcomes. COVID-19 induced blood disorder seems to be gentle and the injury manifestations.

Reference

1.CORONAVIRUS RESOURCE CENTER of Johns Hopkins https:// coronavirus.jhu.edu/map.html May 5, 2020.

2.Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506

3.Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.

4.Yu X, Sun X, Cui P, et al. Epidemiological and clinical characteristics of 333 confirmed cases with coronavirus disease 2019 in Shanghai, China. TransboundEmerg Dis 2020;67:1697–707.

5.LangZW,ZhangLJ,ZhangSJ,etal.Aclinicopathologicalstudyofthree cases of severe acute respiratory syndrome (SARS). Pathology 2003; 35:526–31.

6.Danzi GB, Loffi M, Galeazzi G, et al. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J 2020;41: 1858.

7.HelmsJ,TacquardC,SeveracF,etal.Highriskofthrombosisinpatients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46:1089–98.

8. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J ThrombHaemost 2020;18:1421–4.

9.Malato A, Dentali F, Siragusa S, et al. The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes. Blood Transfus 2015;13:559–68.

10.TangN,BaiH,ChenX,etal.Anticoagulanttreatmentisassociatedwith decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J ThrombHaemost 2020;18:1094–9.

11. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38.

12. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J ThrombHaemost 2020;18:844–7.

13. Bowles L, Platton S, Yartey N, et al. Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19. N Engl J Med 2020; 383:288–90.

14.Kollias A, Kyriakoulis KG, Dimakakos E, et al. Thromboembolic risk andanticoagulanttherapyinCOVID-19patients:emergingevidenceand call for action. Br J Haematol 2020;189:846–7.

15. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J ThrombHaemost 2020;18:844–847. doi:10.1111/jth.14768

16.Favaloro EJ, Lippi G. Recommendations for minimal laboratory testing panels in patients with COVID-19: potential for prognostic monitoring. SeminThrombHemost 2020;46(3):379–382. doi:10.1055/s-0040-1709498

17. Guan W, Ni Z, Hu Y, Liang W-H, Ou C-Q, He J-X, Liu L, Shan H, Lei C-L, Hui DSC, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–1720. doi:10.1056/NEJMoa2002032

18. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, Mucheli SS, Kuperan P, Ong KH, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020 Mar; ajh.25774. doi:10.1002/ajh.25774.

19.LiuY,YangY,ZhangC,HuangF,WangF,YuanJ,WangZ,LiJ,LiJ, Feng C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63(3):364–374. doi:10.1007/s11427-020-1643-8

20. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395 (10223):497–506. doi:10.1016/S0140-6736(20)30183-5

21. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020. doi:10.1001/jamainternmed.2020.0994

22. Deng Y, Liu W, Liu K, Fang -Y-Y, Shang J, zhou L, Wang K, Leng F, Wei S, Chen L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl) 2020 Mar. doi:10.1097/CM9.0000000000000824.

23.Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A, et al. Hypercoagulability of COVID-19 patients in intensive care unit. A report of thromboelastography findings and other parameters of hemostasis. J ThrombHaemost 2020 Apr;jth.14850. doi:10.1111/ jth.14850

24. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z, et al. Ddimer levels on admission to predict in-hospital mortality in patients with Covid-19. J ThrombHaemost 2020 Apr;jth.14859. doi:10.1111/jth.14859

25, Han H, Yang L, Liu R, Liu F, Wu K-L, Li J, Liu X-H, Zhu C-L, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. ClinChem Lab Med 2020 Mar. doi:10.1515/cclm-2020-0188 18.

26. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–1062. doi:10.1016/ S0140-6736(20)30566-3 12.

27.Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, Blair CN, Weber A, Barnes BJ, Egeblad M, et al. Neutrophil extracellular traps in COVID-19. JCI Insight 2020 Apr. doi:10.1172/jci. insight.138999.

28. Lippi G, Plebani M, Michael Henry B. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. ClinChimActa 2020 Mar. doi:10.1016/j. cca.2020.03.022.

29. Bi X, SU Z, Yan H, Du J, Wang J, Chen L, Peng M, Chen S, Shen B, Li J, et al. Prediction of severe illness due to COVID-19 based on an analysis of initial fibrinogen to albumin ratio and platelet count. Platelets 2020 May;1–6. doi:10.1080/ 09537104.2020.1760230.

30. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J ThrombHaemost 2020;18(5):1094–1099. doi:10.1111/jth.14817.

31. Yang X, Yang Q, Wang Y, Wu, Y, Xu, J, Yu, Y, Shang, Y. Thrombocytopenia and its association with mortality in patients with COVID-19. J ThrombHaemost 2020 Apr. doi:10.1111/jth.14848.

32. Liu Y, Sun W, Guo Y, Chen, L, Zhang, L, Zhao, S, Long, D, Yu, L. Association between platelet parameters and mortality in coronavirus disease 2019: retrospective cohort study. Platelets.2020. doi:10.1080/09537104.2020.1754383.

33. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected

pneumonia in Wuhan, China. JAMA J Am Med Assoc 2020;323(11):1061–1069. doi:10.1001/jama.2020.1585.

34. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng O-T, Marimuthu K, Ang LW, Mak TM, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA J Am Med Assoc 2020 Apr;323:1488. doi:10.1001/jama.2020.3204.

35.BarnesBJ,AdroverJM,Baxter-StoltzfusA,BorczukA,Cools-Lartigue J, Crawford JM, Daßler-Plenker J, Guerci P, Huynh C, Knight JS, et al. TargetingpotentialdriversofCOVID-19:neutrophilextracellular traps. J Exp Med2020;217(6). doi:10.1084/jem.20200652.

36. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–1034. doi:10.1016/S0140-6736(20)30628-0.

37.Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients.AnnHematol2020Apr;1–4.doi:10.1007/s00277-020-04019-0.

38.Thachil J. What do monitoring platelet counts in COVID-19 teach us? J ThrombHaemost 2020 Apr;jth.14879. doi:10.1111/jth.14879.

39.Lefrançais E, Ortiz-Muñoz G, Caudrillier A, Mallavia B, Liu F, Sayah DM, Thornton EE, Headley MB, David T, Coughlin SR, et al. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. Nature 2017;544(7648):105–109. doi:10.1038/nature21706.

40.Qu R, Ling Y, Zhang YHZ, Wei L-Y, Chen X, Li X, Liu X-Y, Liu H-M, Guo Z, Ren H, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol 2020. doi:10.1002/jmv.25767.

41. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–481. doi:10.1016/S2213-2600(20)30079-5.

42. WHO COVID-19 Dashboard. [cited 2020 Apr 30]. Available from: https://covid19.who.int/
2. Connors JM, Levy JH.

43. Sexton TR, Zhang G, Macaulay TE, Callahan LA, Charnigo R, Vsevolozhskaya OA, Li Z, Smyth S, et al. Ticagrelor reduces thromboinflammatory markers in patients with pneumonia. JACC Basic to TranslSci 2018;3(4):435–449. doi:10.1016/j.jacbts.2018.05.005.