Open Access

Editorial

Haematological Biomarkers in Covid-19 Infection

Nadeem Ikram

Department of Pathology
Rawalpindi Medical University

Address for Correspondence
Dr. Nadeem Ikram
Department of Pathology
Rawalpindi Medical University
drnadeemikram@gmail.com

Introduction

Despite the preventive infection measures, COVID-19 infection has taken on the proportions of pandemic around the globe. COVID-19 patients present with protean manifestations, from flu-like symptoms to pneumonia, multiple organ failure and death. Nearly 20% of patients, with COVID infection, become critically ill, with high mortality, ranging from 8% to 33%.[1-3] Excessive inflammation, platelet activation, endothelial dysfunction, hypercogulability, and sepsis, along with many others, are held responsible for patho-physiological events in COVID infection. In-turn, these translate into different findings, which predict the course and prognosis of the disease. In this regard, haematological findings are also of paramount importance.[4,5]

Due to high morbidity and mortality, an early diagnosis of COVID infection is essential. The definitive diagnosis of this disease is made by a positive PCR test for the COVID antigen. Limited resources, insufficient training of the men power, and many other confounding variables justify the identification of some inexpensive parameters which can reflect the presence of this disease. These, to a larger extent, can help manage the disease and can help differentiate severe from non-severe cases.[6] Standard guidelines for COVID-19 also give weightage to radiological, haematological, and biochemical parameters. Complete blood counts (CBC) are easily performed and inexpensive. Different parameters of CBC like, leucocyte count, absolute neutrophils and lymphocytes count and their ratios are of importance in this regard.[7-9]

Out of different pathogenetic mechanisms, underlying the severity of COVID infection, cytokine storm is now well established. Interleukin -6 (IL-6) is a key molecule in stimulating cytokine storm.[10] Criterias, clinical and diagnostic, are proposed to find out the risk of a cytokine storm. In lab tests, parameters reflecting inflammation, immune dysregulation, and hypercoagulability are of pivotal significance, in diagnosing cytokine storm. The majority of the patients, in cytokine storm, validate these criteria`s. [11]

Haemostatic changes, observed in COVID patients, are detrimental in deciding the course and outcome of the COVID disease. [2,12] Pulmonary complications and acute respiratory distress syndrome, seen in COVID, have a clear thrombo-embolic component.[2] Endothelial cell infection can induce endothelial damage and dysfunction/activation, which in turn, triggers coagulation cascade.[2,13-19]

Deranged hematological parameters and haemostatis are commonly observed in the progression of the COVID infection.[20,21] In this scenario speedy inexpensive laboratory testing can be helpful to provide clinicians with suitable information for rational medical resource allocation to reduce patient morbidity and mortality. [22] Because of its severity, it would be valuable to explore risk factors of severity and mortality in patients with COVID-19 disease. It can help in adopting timely measures and interventions, to enhance the cure rate.[23-25]

Studies showed that besides age, haematological parameters including, 1: Neutrophil lymphocyte ratio(NLR), D-dimer are significant predictors of disease severity and mortality.[17,26-30] Elevated D- dimer level is a risk factor for the development of Deep vein thrombosis (DVT) or pulmonary embolism and can predict both severity and mortality.[2,31,32] British Thoracic Society, based on risk stratification, suggested prophylactic low dose heparin in COVID patients with D-dimer more than

3000 ng/ml, while D-dimer more than 1000 ng/ml is an independent risk factor for the critical disease.[4,14,33]

SARS-CoV2 infects type–II pneumonocytes via angiotensin converting enzyme 2 (ACE 2) receptors. These, in –turn, triggers the phenomenon culminating in a characteristic Pulmonary Intravasular Coagulation (PIC).[34] Cytokine storm, increased expression of tissue factor on endothelium, and excessive recruitment of neutrophils and macrophages, all potentiate intrapulmonary activation of coagulation. Thrombosis observed is primarily intrapulmonary, but can proceed to systemic thrombosis in a subset of patients. This hypercoagulability may be attributed to endothelial dysfunction, elevated circulating platelet microparticles, neutrophil extracellular traps (NATs), and elevated inflammatory cytokines.[18,24,29,35,36] Resistance to fibrinolysis could be an additional underlying mechanism to the hypercoagulable state that predisposes to thrombosis.[37] Majority of the patients with COVID -19 infection show high levels of a pro-inflammatory cytokine, IL-6. IL-6 induces tissue factor gene expression in endothelial cells and moncytes, fibrinogen synthesis, and platelets production.[10]

Markedly increased D-dimers, increased fibrinogen, unusual anaemia and haemolysis, unpronounced PT/APTT prothrombin time or activated partial thromboplastin time, mild thrombocytopenia, uncommon bleeding, marked pulmonary involvement and evident thrombosis are characteristic findings in COVID coagulopathy. As compared to it, DIC is characterized by a moderate increase in D-dimers, decreased fibronegen, evident anaemia and haemolysis, pronounced prolongation of PT/APTT, severe thrombocytopenia, unusual thrombosis, prominent bleeding and mild pulmonary involvement.[12,28,39-41]

High NLR with lymphopenia suggests aggravated infection and is difficult to control.[23] Lower count of lymphocytes and a higher count of neutrophils, with high neutrophils -to- lymphocytes ratio (NLR) in the severely infected COVID-19 patients compared with the mildly infected group are registered in may studies.[42-47]Age more than 50 years with an NLR of more than 3.13 predicts course towards a critical illness.[43,48] In COVID -sepsis, neutrophils are hyper-activated along with depletion of CD4 lymphocytes, as a result of apoptosis.[40,49] Patients who died from COVID -19 are reported to have significantly lower lymphocytes count. This reflects exhausted adaptive immune system.[50-54]

Monitoring haematological and coagulation parameters might provide a reliable and convenient method for classifying and predicting the severity and outcomes of patients with COVID-19. High NLR and elevated D-dimer levels can be considered as independent risk factors in assessing the severity of COVID -19 disease.

References

1. Liao D, Zhou F, Xu M, Wang H, Xia J. Haematological characteristics and risk factors in the classification and prognostic evaluation of COVID-19. Lancet, 2020;10.1016/82352-3026(20).30217-19
2. Aggarwal M, Dass J, Mahapatra M. Haemostatic abnormalities in COVID- 19: An update. Indian Hematol Blood Transfus, 2020 ; 36(4): 616–626.
3. Guan W, Ni Z, Hu Y, Liang WH. Clinical characteristics of Corona virus disease 2019 in China. N Eng J Med, 2020; 382:1708-20
4. Bikedli B, MAdhavan MV, Jimenaz D, Chuich T. COVID-19 and thrombotic or thrombo-embolic disease. J Am Coll Cardiol, 2020; 20:35008-017
5. Lagnhas-Rangel FA. Neutrophil to lymphocyte ratio and lymphocyte to –C-reactive protein ratio in patients with severe corona virus disease. Journal of Med Virol, 2020;92:733-36
6. Ghahramanni S, Tabrizi R, Lankarani KB, Kashani MA, Rezaei S. Laboratory features of severe versus non-severe COVID- 19 patients in Asian population. Eur j Med Res, 2020;25:30-39.
7. Usul E, Sau I, Bekgoz B, Sahin A. The role of hematological parameters in COVID-19 patients in the emergency room. Biomark Med,2020;10.2217/bmm-0317
8. Khartabil TA, Russchert H, vanderVen A, Rijke B. Diagnostic and prognostic value of hemocaytaometro – markers in COVID-19 patients. Critical Reviews in Clinicla Lab Sciences, 2020 57(6)415-31
9. Weikove R, Quilten Z, Adler J. Haemotology and oncology COVID-19 interim guidance version 3.0.Hematol Soc Aust New Zeal, 2020; https://www.hsanz.org.an
10. Ranucci M, Ballota A, Dedda U, Bayshnikova E, Poli M. The pro-coagulant pattern of patients with COVID-10 acute respiratory distress syndrome. J Thrombhaemost, 2020; 18: 1747-51
11. Caricchio R, Gallucci M, Dass C. Preliminary predictive criteria for COVID-19 cytokine storm. Ann Rheum Dis, 2020; doi:10-1136/ 218323
12. Tang N, Li D,Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in novel corona virus pneumonia. Journal of Thrombosis and Hhaemostasis, 2020. 18(4): 844-47
13. Kiok FA, Kruip MJ, vander Meer NJM. Incidence of thrombosis in patients with severe SARS-CoV-2 infection:a multicenter prospective cohort study. Intensive Care med,2020;46:1089-94
14. Khidar L, Gendron N, Gondot G, Chocron R. Curative anticoagulation prevents endothelial lesions in COVID-19 pateints. J Thrombhaemost, 2020;18:2391-99

15. BosoloA,Spiezia L, Correale C, Sella N, Pesenti E. Different hyerpcoagualable profiles in patients with COVID-19. Thrombhaemost, 2020;120:1474-77

16. Chen N, Zhou M, Dong X, Qu J. Epidemiological and clinical characteristics of 99 cases of 2019 novel corona virus pneumonia. Lancet, 2020;395(2020):507-13.

17. Zhang L, Yan X, Fan Q, Liu H. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J ThrombHaemost, 2020; 10: 14859-62

18. Panigade M, Bottino N, Tagliabue P, Grasselli G. Hypercoagulability of COVID-19 patients in intensive care units. J ThrombHaemost, 2020; 111:14850-54

19. Helms J,Tacquard C, Severac F. High risk of thrombosis in patients with severe SARS-CoV-2 infection : a multicenter prospective cohort study. Intensive Care Med,2020;46:1089-98.

20. Pimental GD. Vega DM, laviano A. High neutrophil-to-lymphocyte ratio as a prognostic marker in COVID-19 patients in Asian population. Eur J Med Res, 2020;25; 30-39

21. Huang J, Cheng A, Lin S. Individulized prediction monograms for disease progression in mild COVID-19. J med Virol, 2020; DOI:10,1002/jmv.25969

22. Hu L, Chan S, Fu Y. Risk factors associated with clinical outcomes in 323 COVID-19 patients. Clin Infect Dis 2020; DOI:10.1101/ 03.25.20037721

23. Ye W, Chen G, Li X, Lau X, Ji C. Dynamic changes of D-dimer and neutrophil –lymphocyte ratio as prognostic biomarkers in COVID-19. Respiratory Research ,2020; 21: 169-75

24. Fan BE, Chia YW, Sum CL, Kuperan P. Global haemostatic tests in diagnosis and management of COVID-19 associated coagulopathy. Journal of Thrombosis and Thrombolysis 2020; 50: 292-97

25. Zhou F, Yu T, DuR. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China. Lancet, 2020; 395(10229): 1054-62

26. Di Minno MND, Calcaterra I, Lupoli R, Storino A, Spedicato GA. Hemostatic changes in patients with COVID-19: a meta-analysis with meta-regressions. Journal of clinical medicine, 2020. 9(7): p. 2244.

27. Huang C, Wang Y, LiPX, Ren PL. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet, 2020. 395(10223): 497-506.

28. Yao Y,Cao J, Wang Q1, Shi Q, Liu K, Luo Z, Chen X D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. Journal of intensive care, 2020. 8(1): 1-11.

29. Zuo Y, Talavartnis S, Shi H. Neutrophil extracellular traps in COVID-19. JC Insight, 2020; 5(11): 138999

30. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between SARS-CoV2 and non-SARS-CoV2. Journal of Thrombosis and Thrombolysis, 2020;10.1007/s11239-020-02105-08

31. Zhang B, Zhou X, Qiu y. Clinical characeteristics of 82 death cases with COVID-19. Med Rxiv, 2020; DOI:10;1101/2020.02.26.20028191

32. Lodigiani C, Iapichino G, Carenzo L. Venous and arterial thrombo-embolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res, 2020;191:9-14

33. Zhou F,YuT, DuR, Fan G, Liu Y. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet, 2020;395: 1054–62

34. Thachil J, Srivastva A. SARS-2 corona virus –associated hemostatic lung abnormality in COVID-19: isit pulmonary thrombosis or pulmonary embolism. Semin ThrombHemost, 2020; 10: 2155-59

35. Blasi A,Meinjenfeldt FA, Adelmeijer J, Calvo A. In-vitro hypercoagulability and in vivo activation of coagulation and fibrinolysis in COVD-19 patients.J Thromb haemost, 2020;18(10):https://doi.org/10.1111/jth.15043

36. Adam EH, Zacherowski K, Miesbach W. A comprehensive assessment of coagulation profile in critically ill COVID-19 pateints. Thrombosis Research, 2020; 194: 42-44

37. Weiss E, RonxO, Mayer JD, Burtz CP, Bondaond L. Fibrinolysis resistance: A potential mechanism underlying COVID-19 coagulopathy. Thromb Haemost,2020;120:1343-45

38. Yang X,Yang Q, Wang Y, Wu Y. Thrombocytopenia and its association with morality in patients with COVID-19 .J ThrombHaemost, 2020; 10: 14848-52

39. XuP.Zhou Q, XuJ. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol, 2020;99;1205-08

40. SpieziaL,Boscolo A, Poletto F, Ceruti L. COVDI-19 related severe hypercoagulability in patients admitted to intensive care unit from acute respiratory failure . ThrombHaemost, 2020;120:998-1000

41. Savioli F. Coagulation profile in severe COVID- 19 patients: What do we know sofar? Rev Bras ter Intensiva,2020;32(2): 197-99

42. Fu J, Kong J, Wang W, Wu M, Yao L, Wang Z.The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19. Thrombosis Research, 2020; 192: 3–8

43. Lin Y, Du X, Chen J, Jin Y, Peng L, Wang HX. Neutrophil – to – lymphocyte ratio as an independent risk factor for mortality in COVID-19. Journal of Infection,2020;81:e6-e12

44. Qin C, Zhou L , Hu Z , Zhang S, Yang S, Tao Y.Qin Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clinical Infectious Diseases, 2020;71(15):762-68

45. Bai, Y., Yao L,Wei T, Presumed asymptomatic carrier transmission of COVID-19. JAMA, 2020. 323(14): p. 1406-1407.

46. Alfaraj SH, Al-tawfiq JA, Assiri AY, AlzahraniNA. Clinical predictors of mortality of Middle East Respiratroy Syndrome corona virus infection – A cohort study. Travel Med Infect Dis,2019;29:48-50

47. Lin J, Lin Y, Xiang P. Neutrophil –to-lymphocyte ratio predicts critical illness patients with 2019 corona virus disease. J Transl Med, 2020;18(1)206- 09;https://doi.org/10.1186/s12967-020-02374-0

48. Yang AP, Liu JP, Tao W, LiH. The diagnostic and predictive role of NLR, d-NLR and PLR I COVID-19 patients. International Immuno-Pharmacology ,2020;84:106504

49. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med,2020; DOI: 10.1515/ cclm-2020-0198

50. Heinz BM. COVID-19 and lymphopenia; a word of caution. Lancet Respir Med, 2020;8:e24

51. Kong M,Zhang H, Cao X, Mao X, LuZ. Higher level of neutrophil –to-lypmohcyte is associated with severe COVID-19 . Epidemiology and Infection, 2020;148:e139;1-6

52. Bermejo – Martin JF,Almansa R, Menendez R,Kelvin DJ. Lymphopenic community acquired pneumonia as signature of severe COVID-19 infection. J Infect, 2020;80(5):23-27

53. Ghahramanni S, Tabrizi R, Lankarani KB, Kashani MA, Rezaei S. Laboratory features of severe versus non-severe COVID- 19 patients in Asian population. Eur j Med Res, 2020;25:30-39.

54. Wang Y, Lu X, Chen H. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med, 202; DOI:10.1164/rccm.202003-0736LE