Indian J Med Res 155, May & June 2022, pp 570–574
DOI: 10.4103/ijmr.ijmr_1180_21

Quick Response Code:

COVID-19 infection in patients with haematological disease - A tertiary centre experience from north India

Mukul Aggarwal[1], Mirza Saleem Amjad[1], Akash Khandelwal[1], Pradeep Kumar[1], Rishi Dhawan[1], Jasmita Dass[1], Kumar Vishwanathan Ganesh[1], Punit Khanna[2], Akhil Kant Singh[2], Kapil Dev Soni[3], Richa Agarwal[3], Mohan Bairwa[6], Arul Selvi[4], Seema Tyagi[1], Tulika Seth[1], Manoranjan Mahapatra[1], Naveet Wig[5] & Anjan Trikha[2]

Departments of [1]Hematology, [2]Anaesthesia, Pain Medicine & Critical Care, [3]Trauma Critical Care, [4]Laboratory Medicine, [5]Medicine & [6]Center for Community Medicine, All India Institute of Medical Sciences, New Delhi, India

Received April 24, 2021

This retrospective study was aimed to understand the clinical, laboratory, radiological parameters and the outcome of COVID-19 patients with underlying haematological disease. All patients with known haematological disease admitted with COVID-19-positive status from April to August 2020 in the COVID-19 facility of a tertiary care centre in north India, were included. Their medical records were analyzed for outcome and mortality risk factors. Fifty four patients, 37 males, were included in the study. Of these, 36 patients had haematological malignancy and 18 had benign disorder. Fever (95.5%), cough (59.2%) and dyspnoea (31.4%) were the most common symptoms. Nine patients had severe disease at diagnosis, mostly malignant disorders. Overall mortality rate was 37.0 per cent, with high mortality seen in patients with aplastic anaemia (50.0%), acute myeloid (46.7%) and lymphoblastic leukaemia (40.0%). On univariate analysis, Eastern Cooperative Oncology Group performance status >2 [odd ratio (OR) 11.6], COVID-19 severity (OR 8.2), dyspnoea (OR 5.7) and blood product transfusion (OR 6.4) were the predictors of mortality. However, the presence of moderate or severe COVID-19 (OR 16.6, confidence interval 3.8-72.8) was found significant on multivariate analysis. The results showed that patients with haematological malignancies and aplastic anaemia might be at increased risk of getting severe COVID-19 infection and mortality as compared to the general population.

Key words COVID-19 - haematological malignancies - risk factors

COVID-19 can present with variable clinical manifestations, from asymptomatic state to severe disease with 2-33 per cent mortality[1-3]. Older age and co-morbidities such as diabetes, hypertension and malignancy have been recognized as the risk factors for severe COVID-19 disease in the general population[3,4].

Patients with haematological malignancies are immunocompromised due to their underlying disease. The antineoplastic and immunomodulatory medication scan causes bone marrow suppression, leading to neutropenia and predisposition to opportunistic infections. Similarly, patients of immune thrombocytopenia (ITP) or autoimmune haemolytic

anaemia and aplastic anaemia (AA) are on steroids, rituximab, *etc*[4-6]. COVID-19 outcomes in patients with haematological cancer are dismal with mortality rates varying from 13 to 62 per cent[7,8]. Limited data are available for non-malignant haematological disorders[9-11].

This study was aimed to understand the clinical, laboratory, radiological parameters and the outcome of COVID-19 infection in patients with underlying haematological disease and how these characteristics influence outcomes in these patients. This was a retrospective observational single centre study on patients >18 yr old treated at a dedicated COVID-19 facility of All India Institute of Medical Sciences, New Delhi, a tertiary care centre in north India from April to August 2020. The study was approved by the Institutional Ethics Committee.

All patients with known or suspected haematological disease diagnosed to have COVID-19-positive status, as confirmed by the real-time PCR for SARS-CoV-2 during the study period, were included. Epidemiological, clinical, radiological, laboratory, therapy and outcomes-related data were obtained from the medical records. Severity of COVID-19 at admission was graded according to the Government of India, Ministry of Health and Family Welfare definitions[12]. Several factors, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, primary diagnosis, disease nature, COVID-19 severity, blood transfusion, haemoglobin, neutrophil count (ANC) and treatment parameters, were analyzed as risk factors for mortality.

Descriptive statistics were presented as median and inter-quartile range (IQR) for the continuous variables and number and percentage for the categorical variables. Logistic regression was performed to find the risk of the standardized parameters. Given the small number of patients in the study, two regression models were used to find the predictors of mortality. In one model, all variables found significant in univariate regression analysis were included, and in another model only two variables with smallest *P* value in the univariate regression analysis were considered. All the analyses were performed using the SPSS version 24 software (IBM SPSS Inc., Chicago, Illinois, USA).

Fifty four patients were included in the study, of whom 37 were males and 29 patients were <40 yr of age. Thirty six patients had haematological malignancies while 18 had benign disorders. Forty four patients had active disease, eight were relapsed cases and two patients were in remission. Fifteen patients had acute myeloid leukaemia/myelodysplastic syndrome (AML/MDS), 10 had acute lymphoblastic leukaemia (ALL), three had multiple myeloma, two patients had chronic myeloid leukaemia, polycythaemia, chronic lymphocytic leukaemia (CLL) and AL amyloidosis each. Benign disorders included AA (n=12), venous thrombosis (n=2), others (bicytopaenia, chronic liver disease with hypersplenism, haemolytic anaemia and ITP, one each). ECOG performance status was >2 (poor) in two patients.

Fifty two patients (96%) were symptomatic, with fever (n=50, 95.5%) being the most common symptom. At admission, 32 patients were in mild category, 13 in moderate category and nine were in severe category. Dyspnoea at admission was present in 12.5 per cent (n=4) of mild cases, 76.9 per cent (n=10) in moderate and 33.3 per cent (n=3) in severe disease, respectively (Table). Ten patients had infiltrates involving >50 per cent of lung fields on chest X-ray, 30 patients had <50 per cent of lung fields involved. Severe COVID infection was present in three AA patients, two ALL and one patient each of AML/MDS, CLL, myeloma and bicytopaenia under evaluation. Overall, four patients with mild COVID and 11 with moderate COVID at presentation progressed to severe category. All nine patients with severe disease at admission required invasive ventilation.

All patients were managed as per available guidelines, at the discretion of treating physician. Eleven patients (20.4%) required only oxygen support and 21 (38.9%) patients required non-invasive or mechanical ventilation. Mean ICU and hospital stay was 6.3 and 11.4 days, respectively, after the diagnosis of COVID-19 infection. Overall, 20 patients (37.0%) expired. High mortality was seen in AA patients (50.0%) followed by AML/MDS (46.7%) and ALL (40.0%). Among patients with active disease, 14 patients expired, whereas five patients with relapsed disease expired. Fifteen of 22 patients with poor performance status expired, while five patients with good ECOG status expired.

Comparing the mortality across COVID severity, four patients with mild COVID (12.5%) and all patients with severe disease at diagnosis expired (P<0.001). Transfusion support was given to 33 patients, of whom 17 patients expired, as compared to three of 18 patients who did not need blood transfusions (P=0.010). There was only one survivor among patients who

Table. COVID-related symptoms, laboratory and treatment parameters (n=54)

Parameter	Frequency (%)
Symptoms	
Fever	50 (92.5)
Dyspnoea	17 (31.5)
Cough	22 (40.7)
Diarrhoea	2 (4.5)
Sore throat	1 (2.0)
Asymptomatic	2 (3.7)
Haematological parameters	
Haemoglobin (median with IQR, in g/dl)	7 (3)
WBC count (median with IQR, in/ul)	5450 (11,350)
Platelet count (median with IQR, in/ul)	32,000 (79,000)
Absolute neutrophil count (median with IQR, in/ul)	1630 (5659)
PT (median with IQR, in sec)	15 (3.5)
APPT (median with IQR, in sec)	33 (9.1)
COVID-related laboratory parameters	
COVID-19 PCR	54/54 (100)
Deranged PT; median in sec (IQR)	3/31 (10.0); 15 (3.5)
Raised ferritin	9/10 (90.0)
Raised IL-6; median in pg/ml (IQR)	7/11 (63.7); 39.88 (97.9)
Raised CRP; median in mg/l (IQR)	8/10 (80.0); 13.36 (7.7)
Raised D dimer; median in mcg/ml (IQR)	16/19 (84.4); 1.59 (3.4)
COVID-related treatment	
Vitamin C, zinc and B-complex	52 (96.3)
Doxycycline	29 (53.7)
Hydroxychloroquine	21 (38.9)
Azithromycin	7 (12.9)
Ivermectin	11 (20.4)
Steroids	32 (59.2)
Remdesivir	4 (7.4)
Tocilizumab	3 (5.5)
Plasma therapy	0

COVID-related laboratory parameters were performed at the discretion of treating physician and were not available for all patients; Ferritin assay did not give values>1500 ng/ml; hence, its median and IQR not provided. COVID-19 PCR by AriaMx Real-time PCR system (Agilent technologies; Santa Clara; CA); using RT-PCR kits (BGI Genomics Co. Ltd.; China); interleukin-6 (IL-6 by access IL-6 assay; Access immunoassay systems; Beckman coulter; USA); CRP (CRP by CRP latex Beckman coulter AU analyzer; Beckman Coulter; USA); ferritin (Access IL-6 assay; Access immunoassay systems; Beckman coulter; USA). PT, prothrombin time; IL-6, interleukin 6; CRP, C-reactive protein; IQR, interquartile range; APTT, activated partial thromboplastin time

needed ventilator support, while half of patients who required oxygen support expired (P<0.001). Eleven of 17 patients with dyspnoea expired, and nine without dyspnoea died. Co-morbidities, such as diabetes and hypertension present in two patients each and one patient had mild pericardial effusion, were not associated with mortality.

On univariate analysis, ECOG performance status >2 [odd's ratio (OR) 11.6, 95% confidence interval (CI)

3.1-42.9, *P*<0.001], severity of COVID-19 (OR 8.2, 95% CI 1.8-37.0, *P*=0.006), blood product transfusion (OR 6.4, 95% CI 1.6-25.8, *P*=0.010) and dyspnoea (OR 5.7, 95% CI 1.6-19.8, *P*=0.006) were predictive of mortality. Low ANC (*P*=0.115) and active disease (*P*=0.102) showed a trend towards mortality. Age above 40 yr, sex, primary diagnosis, malignant nature of disease, disease activity and haemoglobin <6 g/dl were not significantly associated with mortality. On multivariate analysis, after adjusting for dyspnoea and ECOG, presence of moderate or severe COVID-19 (OR 16.6, CI 3.79-72.84, *P*<0.001) was significant while blood transfusions showed a trend (OR 5.2, CI 0.99-27.1, *P*=0.052).

The incidence of COVID-19 infection in patients with haematological disorders was similar to the general population[13,14]. In a systematic review on affected general population, most common symptoms were fever (78.8%) and cough (53.9%). Dyspnoea was seen in 18.99 per cent of total patients and 48.9 per cent patients with severe disease[15]. Among COVID-19 patients with haematological malignancies (n=451) in Italy, common symptoms were fever in 75 per cent patients and dyspnoea in 51 per cent patients[16]. The current study had higher proportion of febrile (92.5%) and dyspnoeic (31.5%) patients than general population. More patients with dyspnoea in the above Italian study could be due to higher cut-off of severe disease (SpO_2<93%), as compared to the current study (SpO_2 <90%). Another plausible explanation could be happy hypoxia effect in severe COVID-19 patients[17].

Severe COVID-19 infection was seen in 25 per cent oncology patients and 36-52 per cent haemato-oncology patients[14,16,18]. In the general population, severe disease was present in 15.74-23 per cent patients with mortality rate of 5.6 per cent[3,15,19]. In the current study, 37 per cent patients had critical disease. Six of 18 (33.3%) died in the benign disease category (all AA patients) and 14 of 36 (38.9%) died in the malignant category. The mortality figures were similar in smaller oncology cohorts ranging from 32 to 61 per cent[7,14,16,20]. In a multicentre study from India, severe infection was present in 25 per cent patients and mortality rate was 20 per cent[21]. Patients with haematological malignancies have higher fatality (41%), as compared to 17 per cent in solid tumours (HR 3.3, *P*=0.0009) and a trend towards lower severe event-free survival (30 *vs.* 61.4%), longer hospital stays (21 *vs.* 13 days) and longer time to clinical improvement (18.5 *vs.* 11.5 days) as compared to solid cancer patients[18,22].

Risk factors for mortality among malignancy patients are heterogeneous. Yang *et al*[18], identified male sex and receiving chemotherapy four weeks prior as risk factors; while Lee *et al*[23] identified older age, male sex and co-morbidities as risk factors. Passamonti *et al*[16] found older age, progressive disease, AML, non-Hodgkin lymphoma or myeloma and severe COVID-19 at admission to be associated with worse survival, while Borah *et al*[21] reported age >60 yr and severe infection to be associated with higher mortality. Proportion of severe disease in haemoglobinopathies was similar to the general population[24].

Several international registries such as sickle cell registry, American Society of Haematology (ASH) research collaborative and Centre for International Blood and Marrow Transplant Research (CIBMTR) registry have been set up to track the progress of haematological patients with COVID-19 infection[25-27]. Mortality rates have varied from 2.7 per cent in sickle cell patients to 16.5 per cent in ASH collaborative and 14.2 per cent in CIBMTR registry. Mortality was higher in patients above 70 yr of age (27.7%) and those with relapsed disease (31.2%)[26].

Mortality in benign disorders was predominantly among AA patients. Risk due to comorbidities was perhaps overshadowed by underlying haematological disorder. Due to retrospective nature of the present study, laboratory parameters (especially COVID-19–related inflammatory markers) were not available for all patients. This as well as small sample size and single centre nature were the major limitations of the study.

To conclude, the current study showed that patients with haematological malignancies and aplastic anaemia were at increased risk of getting severe COVID-19 infection and higher mortality as compared to the general population. Larger prospective studies can provide guidance on multiple aspects of COVID-19 patients with underlying haematological disorders.

***Acknowledgment*:** Authors acknowledge the contributions of all healthcare workers including our residents and faculty members who were actively involved in the management of these cases.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; *395* : 497-506.

2. World Health Organization (WHO). Coronavirus Disease (COVID-19) Outbreak. Available from: *https://www.who.int*, accessed on February 21, 2021.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; *382* : 1708-20.
4. Ludwig H, Delforge M, Facon T, Einsele H, Gay F, Moreau P, *et al.* Prevention and management of adverse events of novel agents in multiple myeloma: A consensus of the European Myeloma Network. *Leukemia* 2018; *32* : 1542-60.
5. Maschmeyer G, De Greef J, Mellinghoff SC, Nosari A, Thiebaut-Bertrand A, Bergeron A, *et al.* Infections associated with immunotherapeutic and molecular targeted agents in hematology and oncology. A position paper by the European Conference on Infections in Leukemia (ECIL). *Leukemia* 2019; *33* : 844-62.
6. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, *et al.* Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. *J Clin Oncol* 2018; *36* : 3043-54.
7. He W, Chen L, Chen L, Yuan G, Fang Y, Chen W, *et al.* COVID-19 in persons with haematological cancers. *Leukemia* 2020; *34* : 1637-45.
8. Martín-Moro F, Marquet J, Piris M, Michael BM, Sáez AJ, Corona M, *et al.* Survival study of hospitalised patients with concurrent COVID-19 and haematological malignancies. *Br J Haematol* 2020; *190* : e16-20.
9. Arlet JB, de Luna G, Khimoud D, Odièvre MH, de Montalembert M, Joseph L, *et al.* Prognosis of patients with sickle cell disease and COVID-19: A French experience. *Lancet Haematol* 2020; *7* : e632-4.
10. McCloskey KA, Meenan J, Hall R, Tsitsikas DA. COVID-19 infection and sickle cell disease: A UK centre experience. *Br J Haematol* 2020; *190* : e57-8.
11. Hussain FA, Njoku FU, Saraf SL, Molokie RE, Gordeuk VR, Han J. COVID-19 infection in patients with sickle cell disease. *Br J Haematol* 2020; *189* : 851-2.
12. Ministry of Health and Family Welfare. *Clinical management protocol for COVID-19*. Available from: *https://www.mohfw.gov.in/pdf/UpdatedDetailedClinicalManagementProtocolforCOVID19adultsdated24052021.pdf*, accessed on May 30, 2021.
13. Girmenia C, Gentile G, Micozzi A, Petrucci L, Malaspina F, Di Prima A, *et al.* COVID-19 in patients with hematologic disorders undergoing therapy: Perspective of a Large Referral Hematology Center in Rome. *Acta Haematol* 2020; *143* : 574-82.
14. Malard F, Genthon A, Brissot E, van de Wyngaert Z, Marjanovic Z, Ikhlef S, *et al.* COVID-19 outcomes in patients with hematologic disease. *Bone Marrow Transplant* 2020; *55* : 2180-4.
15. Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F, *et al.* Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. *J Med Virol* 2021; *93* : 1449-58.
16. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, *et al.* Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: A retrospective, multicentre, cohort study. *Lancet Haematol* 2020; *7* : e737-45.
17. González-Duarte A, Norcliffe-Kaufmann L. Is 'happy hypoxia' in COVID-19 a disorder of autonomic interoception? A hypothesis. *Clin Auton Res* 2020; *30* : 331-3.
18. Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K, *et al.* Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: A multicentre, retrospective, cohort study. *Lancet Oncol* 2020; *21* : 904-13.
19. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA* 2020; *323* : 2052-9.
20. Saini KS, Tagliamento M, Lambertini M, McNally R, Romano M, Leone M, *et al.* Mortality in patients with cancer and coronavirus disease 2019: A systematic review and pooled analysis of 52 studies. *Eur J Cancer* 2020; *139* : 43-50.
21. Borah P, Mirgh S, Sharma SK, Bansal S, Dixit A, Dolai TK, *et al.* Effect of age, comorbidity and remission status on outcome of COVID-19 in patients with hematological malignancies. *Blood Cells Mol Dis* 2021; *87* : 102525.
22. Shoumariyeh K, Biavasco F, Ihorst G, Rieg S, Nieters A, Kern WV, *et al.* Covid-19 in patients with hematological and solid cancers at a Comprehensive Cancer Center in Germany. *Cancer Med* 2020; *9* : 8412-22.
23. Lee LYW, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA, *et al.* COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: A prospective cohort study. *Lancet* 2020; *395* : 1919-26.
24. de Sanctis V, Canatan D, Corrons JLV, Karimi M, Daar S, Kattamis C, *et al.* Preliminary data on COVID-19 in patients with hemoglobinopathies: A Multicentre ICET-A Study. *Mediterr J Hematol Infect Dis* 2020; *12* : e2020046.
25. Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion. *Updates & data*. Available from: *https://covidsicklecell.org/updates-data*, accessed on February 21, 2021.
26. American Society of Hematology Research Collaborative. *COVID-19 registry data summaries*. Available from: *https://www.ashresearchcollaborative.org/s/covid-19-registry-data-summaries*, accessed on February 21, 2021.
27. Center for International Blood & Marrow Transplant Research. *COVID-19 reported data*. Available from: *https://www.cibmtr.org/Covid19/Pages/Covid-Reports.aspx*, accessed on February 21, 2021.

For correspondence: Dr Manoranjan Mahapatra, Department of Hematology, All India Institute of Medical Sciences, New Delhi 110 029, India
e-mail: mrmahapatra@hotmail.com