Indian J Hematol Blood Transfus (Jan-Mar 2021) 37(1):181–185
https://doi.org/10.1007/s12288-020-01318-4

CORRESPONDENCE

COVID-19 in Adult Patients with Hematological Disease: Analysis of Clinical Characteristics and Outcomes

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Received: 15 June 2020 / Accepted: 1 July 2020 / Published online: 7 July 2020

Dear Editor,

Cancer has been shown to be associated with higher risk of COVID-19 complications [1]. However, data on patients with COVID-19 and an underlying hematological disease as well as on specific risks factors in this particularly immunocompromised population are scarce [2–5]. We conducted a retrospective study in a tertiary center of 1000 beds with a hematology reference center. Our ethics committee approved the study (N° CEHF 2020/06AVR/201). Between March 13 and May 15, 2020 a total of 375 consecutive patients were hospitalized with COVID-19 and among them 13 (3.4%) met the inclusion criteria of having an underlying hematological disease. Demographics, clinical characteristics and laboratory findings are summarized in Table 1. The median age was 70 years (IQR 59–79) and 77% of patients were male. COVID-19 pneumonia was the admitting diagnosis for the majority of patients (n = 10, 77%) and a delayed secondary diagnosis in 3 patients (23%) with one of them being highly suspect for nosocomial infection. Diagnosis was based on the association of positive RT-PCR and CT-scan in 11 patients (85%) and on compatible CT-scan only in the two remaining. Median duration of symptoms (after exclusion of patients presenting with symptom-overlapping acute conditions) was 8 days (IQR 3–10). The most common reported symptoms were fever (n = 12, 92%), shortness of breath (n = 8, 62%) and cough (n = 5, 39%). Lymphopenia was present in 5 patients (39%) and neutropenia (grade 3 or more) in 2 patients. Therapy directed against COVID-19 included hydroxychloroquine for 10 patients (77%) with addition of methylprednisolone in 2 patients, azithromycin in 1 patient, and lopinavir/ritonavir in 1 patient.

The underlying hematological diseases (Table 1) were distributed as following: 4 chronic lymphocytic leukemia's (31%), 4 plasma cell dyscrasia's (31%), 2 acute myeloid leukemia's (15%) with one of them being secondary to primary myelofibrosis and the other one being a phenotype shift from early T cell precursor acute lymphoblastic leukemia, 2 non-Hodgkin lymphoma's (15%) and 1 non-malignant condition which was a chronic hypogammaglobinemia of unknown origin. Two patients were stem cell transplant receptors (1 autologous and 1 allogeneic). Four malignant hematological diseases (33%) were newly diagnosed or in first line treatment, 3 were in remission or in a watch and wait strategy without ever having had any treatment, 2 were stable without remission and 3 were relapsed or refractory. Patients received a median of 1 (range 0–5) treatment lines.

Two patients were admitted to the intensive care unit (ICU) at presentation: one received high flow oxygen therapy and the other one invasive mechanical ventilation. Five more patients (39%) presented worsening respiratory state later during hospitalization and were medically eligible for an admission to the ICU but, owing to age and comorbidities, palliative care was provided instead. Four patients (31%) had a documented bacterial co-infection (Three urinary tract infections caused by *Escherichia coli* [2],and *Enterococcus faecalis* [1] and one septicemia

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Table 1 Characteristics of 13 patients with hematological disease and COVID-19

	All n = 13	Survivors n = 7	Non-survivors n = 6	*P* value
Demographics and underlying hematological disease				
Age, median (IQR), years	70 (59–79)	60 (45–79)	80 (70–83)	**0.043**
Sex				
Male	10 (77)	7 (100)	3 (50)	0.070
Female	3 (23)	0 (0)	3 (50)	
Ethnicity				
Caucasian	10 (77)	5 (71)	5 (83)	1.000
Sub-Saharan African	3 (23)	2 (29)	1 (17)	
Body mass index, kg/m^2				
Median (IQR)	24.9 (23.2–27.9)	25.6 (23.1–28.7)	24.3 (23.4–26)	0.945
18.5–24.9	7 (54)	3 (43)	4 (67)	0.266
25.0–29.9	5 (39)	4 (57)	1 (17)	
$\geq$ 30	1 (8)	0 (0)	1 (17)	
Chronic comorbidities				
Pulmonary	3 (23)	1 (14)	2 (33)	0.559
Cardiac or cerebrovascular	4 (31)	1 (14)	3 (50)	0.266
Diabetes	1 (8)	0 (0)	1 (17)	0.462
Renal	3 (23)	1 (14)	2 (33)	0.559
High blood pressure	2 (15)	1 (14)	1 (17)	1.000
Obesity	1 (8)	0 (0)	1 (17)	0.462
Number of comorbidities (among above-mentioned)				
0	5 (39)	4 (57)	1 (17)	0.394
1	4 (31)	2 (29)	2 (33)	
2	2 (15)	1 (14)	1 (17)	
$\geq$ 3	2 (15)	0 (0)	2 (33)	
ECOG performance status before COVID-19				
$<$ 2	9 (69)	6 (86)	3 (50)	0.266
$\geq$ 2	4 (31)	1 (14)	3 (50)	
Category of hematological disease				
Acute leukemia	2 (15)	1 (14)	1 (17)	0.646
Chronic lymphocytic leukemia	4 (31)	3 (43)	1 (17)	
Non-Hodgkin lymphoma	2 (15)	0 (0)	2 (33)	
Plasma cell dyscrasia	4 (31)	2 (29)	2 (33)	
Non-malignant	1 (8)	1 (14)	0 (0)	
Stem cell transplant receptor				
No	11 (85)	6 (86)	5 (83)	1.000
Allogeneic	1 (8)	1 (14)	0 (0)	
Autologous	1 (8)	0 (0)	1 (17)	
Status of malignant hematological disease (n = 12)				
New diagnosis or first line treatment	4/12 (33)	3/6 (50)	1/6 (17)	0.766
Remission or watch and wait	3/12 (25)	1/6 (17)	2/6 (33)	
Stable (no remission)	2/12 (17)	1/6 (17)	1/6 (17)	
Relapsed or refractory	3/12 (25)	1/6 (17)	2/6 (33)	
Most recent hematologic malignancy treatment (n = 12)				
Ongoing or $<$ 6 months	7/12 (58)	3/7 (43)	4/5 (80)	0.293
$>$ 6 months	0/12 (0)	0/7 (0)	0/5 (0)	
Never	5/12 (42)	4/7 (57)	1/5 (20)	
Number of treatment lines, median (IQR) (n = 12)	1 (0–3)	0 (0–2)	3 (1–3)	0.268

Table 1 continued

	All n = 13	Survivors n = 7	Non-survivors n = 6	*P* value
Recent or ongoing treatment (< 6 months)				
Chemotherapy	3 (23)	1 (14)	2 (33)	0.559
Allotransplant	1 (8)	1 (14)	0 (0)	1.000
Targeted drug	1 (8)	1 (14)	0 (0)	1.000
IMiDs	3 (23)	1 (14)	2 (33)	0.559
Proteasome inhibitor	2 (15)	1 (14)	1 (17)	1.000
Corticosteroids	5 (39)	2 (29)	3 (50)	0.592
None	6 (46)	4 (57)	2 (33)	0.592
Clinical, laboratory and radiological characteristics at day 1 (unless otherwise specified)				
Duration of symptoms, median (IQR), days	8 (3–10)	7 (3–10)	8 (1–20)	1.000
(n = 9)				
Symptoms				
Fever	12 (92)	7 (100)	5 (83)	0.462
Shortness of breath	8 (62)	5 (71)	3 (50)	0.592
Cough	5 (39)	3 (43)	2 (33)	1.000
Diarrhea	4 (31)	3 (43)	1 (17)	0.559
Nausea or vomiting	2 (15)	1 (14)	1 (17)	1.000
Sore throat	2 (15)	0 (0)	2 (33)	0.192
Nasal discharge	1 (8)	1 (14)	0 (0)	1.000
Headache	1 (8)	1 (14)	0 (0)	1.000
Muscle ache	1 (8)	0 (0)	1 (17)	0.462
Anosmia and/or agueusia	0 (0)	0 (0)	0 (0)	N/A
qSOFA score				
< 2	11 (85)	7 (100)	4 (67)	0.192
≥ 2	2 (15)	0 (0)	2 (33)	
CURB-65 score				
< 2	8 (62)	6 (86)	2 (33)	0.103
≥ 2	5 (39)	1 (14)	4 (67)	
Positive SARS-CoV-2 RT-PCR	11 (85)	5 (39)	6 (46)	0.462
Infiltrate on chest X-ray (n = 11)	8/11 (73)	3/11 (60)	5/11 (83)	0.545
Lung CT-scan (n = 10)				
Typical for COVID-19	5/10 (50)	4/6 (67)	1/4 (25)	0.333
Undetermined or atypical for COVID-19	4/10 (40)	2/6 (33)	2/4 (50)	
Negative	1/10 (10)	0/6 (0)	1/4 (25)	
Disease extent on CT-scan (n = 10)				
< 25%	7/10 (70)	4/6 (67)	3/4 (75)	1.000
25–50%	2/10 (20)	1/6 (17)	1/4 (25)	
> 50%	1/10 (10)	1/6 (17)	0/4 (0)	
Laboratory findings (normal range), median (IQR)				
C-reactive protein, mg/L (< 5)				
At day 1*	82 (50–170)	106 (50–177)	78 (48–170)	0.945
At day 7 (n = 12)	105 (48–120)	95 (22–107)	119 (107–120)	0.149
Hemoglobin level, mean ± SD, g/L	11.3 ± 2.2	12.5 ± 2.2	10.0 ± 1.4	**0.037**
(male 13.3–16.7; female 12.2–15)				
Neutrophils/μL (1600–7000)	4580 (2600–6960)	6240 (2460–7880)	4180 (2660–6410)	0.945
Neutropenia (≥ grade 3)	2 (15)	1 (14)	1 (17)	1.000
Lymphocytes/μL (800–5000)	1000 (280–3070)	990 (280–3490)	1595 (60–3070)	0.836

Table 1 continued

	All n = 13	Survivors n = 7	Non-survivors n = 6	*P* value
Lymphopenia (any grade)	5 (39)	3 (43)	2 (33)	1.000
NLR				
At day 1 (n = 12)	2.7 (1.9–10.6)	4.4 (2.3–14.8)	2.1 (1.7–2.8)	0.432
At day 3 (n = 11)	3.6 (2.0–9.6)	4.2 (2.4–5.8)	2.3 (2.0–37.3)	0.931
At day 5 (n = 10)	2.2 (1.2–5.1)	3.5 (1.9–5.1)	1.5 (0.6–16.2)	0.476
Eosinophils/μL (30–600)	0 (0–10)	0 (0–10)	10 (0–20)	0.295
Basophils/μL (< 200)	10 (0–10)	10 (0–10)	10 (0–20)	0.628
Platelets, mean ± SD, × 10^3/μL (150–450)	141 ± 73	151 ± 78	129 ± 72	0.606
Lactate dehydrogenase, U/L (< 250)	317 (178–449)	315 (172–601)	326 (178–367)	0.731
Aspartate aminotransferase, U/L (13–35)	41 (25–62)	28 (20–73)	50 (27–62)	0.445
Alanine aminotransferase, U/L (7–35)	33 (15–57)	16 (11–67)	35 (28–39)	1.000
Creatine kinase, U/L (n = 10) (20–180)	110 (59–284)	116 (59–284)	84 (16–1014)	0.833
Ferritin, μg/L (n = 5) (13–150)	644 (161–776)	644 (161–2105)	401 (25–776)	0.800
D-dimer, mg/L (n = 5) (< 250)	729 (359–986)	544 (180–1228)	986 (986–986)	1.000
Fibrinogen, mg/dL (n = 8) (150–450)	585 (462–699)	655 (569–743)	491 (400–601)	0.250
Treatments				
Hydroxychloroquine	10 (77)	7 (100)	3 (50)	0.070
Azithromycin	1 (8)	0 (0)	1 (17)	0.462
Methylprednisolone	2 (15)	1 (14)	1 (17)	1.000
Lopinavir/ritonavir	1 (8)	0 (0)	1 (17)	0.462
Antibiotics (for antibacterial purpose)	9 (69)	5 (71)	4 (67)	1.000
Life support, complications and outcome				
Most invasive respiratory support required				
Ambient air	2 (15)	2 (29)	0 (0)	0.462
Nasal cannula or mask	9 (69)	4 (57)	5 (83)	
High flow nasal cannula	1 (8)	1 (14)	0 (0)	
Mechanical ventilation	1 (8)	0 (0)	1 (17)	
Documented bacterial co-infection	4 (31)	1 (8)	3 (23)	0.266
ICU admission				
Not required	6 (46)	6 (86)	0 (0)	0.002
Declined (therapeutic limitation)	5 (39)	0 (0)	5 (83)	
Yes	2 (15)	1 (14)	1 (17)	
Length of stay (until death or discharge), days	12 (7–16)	13 (7–16)	11 (7–16)	0.628

Data are N (%) unless otherwise specified

BMI body mass index, *COVID-19* coronavirus disease 2019, *ECOG* Eastern Cooperative Oncology Group, *ICU* intensive care unit, *IQR* interquartile range, *IMiDs* Immuomodulatory Imide Drugs, *N/A* not applicable, *NLR* neutrophil to lymphocyte ratio, *RT-PCR* reverse transcriptase polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2, *SD* standard derivation, *WBC* white blood cells

*Day 1 is the day of patient presentation if COVID-19 was the admitting diagnosis or the day when the secondary diagnosis of COVID-19 was made otherwise

Significance of *P* value < 0.05 are shown in bold

caused by *Escherichia coli* probably secondary to mucositis in a patient with febrile neutropenia). Overall, 6 patients (46%) died during their stay in our COVID-19 units (n = 5) or ICU (n = 1). Comparing survivors and non-survivors, we observed that non-survivors were significantly older than survivors with a median age of 80 [interquartile range (IQR) 70–83] versus 60 (IQR 45–79; $P = 0.043$) respectively. Of interest, the hemoglobin level at day 1 was lower in non-survivors [mean ± standard derivation (SD) 10.0 ± 1.4] than in survivors (mean ± SD 12.5 ± 2.2; $P = 0.037$) besides not being correlated to age ($r = -0.09$; $P = 0.765$). No specific type, status or treatment of hematological disease was shown to be associated with a higher mortality in our series.

We identified two covariates that were significantly associated with worse outcomes in our patients: older age and lower hemoglobin level at day 1.

A higher mortality in older patients was already shown elsewhere [3, 5]. The association between lower hemoglobin level at presentation and a higher mortality rate was also found by Mehta et al. [4]. Of interest, they demonstrate that myeloid malignancies show a trend for higher mortality compared to lymphoid malignancies. Like highlighted by Martin-Moro et al. [3], it can be discussed whether this effect is intrinsic to the myeloid character of the disease or rather due to other covariates [e.g. older age and presence of a symptom-reduction-intention treatment often present in patients with myeloproliferative neoplasm (MPN) or myelodysplastic syndromes (MDS)] [3]. In our small cohort of patients, we found no association between the myeloid/lymphoid character of the underlying disease and COVID-19 fatality (data not shown) but, to mention, our series did not include any MPN or MDS except under the form of a progression to secondary acute myeloid leukemia.

In conclusion, patients with hematologic malignancies are very vulnerable to COVID-19. Age and low hemoglobin level (on day 1) seems to be factors associated with poor outcome. Larger prospective and cohort study are needed to identify other factors associated with mortality in this population.

Acknowledgements All authors contributed to the management of patients.

Author Contributions RL, HY, and JCY designed the research study, analyzed data and wrote the paper. DG and SB help for the writing of the paper.

Compliance with Ethical Standards

Conflict of interest All authors confirm that there is no conflict of interest.

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