

SHORT COMMUNICATION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroconversion in hematology–oncology patients

Paul W. Bird¹ | Vinay Badhwar² | Ben Kennedy³ | Sapna Ladani³ | Julian W.-T. Tang¹

¹Department of Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK

²Intensive Care Unit, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK

³Department of Hematology, University Hospitals of Leicester NHS Trust, Leicester, UK

Correspondence

Paul W. Bird, Department of Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Level 5 Sandringham Bldg, Infirmary Sq, Leicester LE1 5WW, UK.
Email: paul.bird@uhl-tr.nhs.uk

Abstract

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China at the end of 2019, the virus has spread rapidly across the globe leading to millions of infections and subsequent deaths. Although the virus infects those exposed indiscriminately, there are groups in society at an increased risk of severe infection, leading to increased morbidity. Patients suffering from hematological cancers, particularly leukemia, lymphoma, and myeloma, may be one such group and previous studies have suggested that they may be at a three to four times greater risk of severe COVID-19 after SARS-CoV-2 infection, leading to admissions to ICU, mechanical ventilation, and death compared to those without such malignancies. Serological testing for IgG seroconversion has been extensively studied in the immunocompetent, but fewer publications have characterized this process in large series of immunocompromised patients. This study described 20 patients with hematological cancers who tested positive for SARS-CoV-2 via PCR with 12 of the patients receiving further serological testing. We found that of the 12 patients screened for SARS-CoV-2 IgG antibodies, only 2 (16.6%) were able to generate an immune response to the infection. Yet despite this low seroconversion rate in this cohort, none of these patients died or became particularly unwell with COVID-19 or its related complications.

KEYWORDS

immune responses, immunoglobulin, SARS coronavirus, virus classification

1 | BACKGROUND

Patients with hematological cancers are at increased risk of coronavirus disease (COVID-19), in part due to their underlying malignancy, but also to their increased age (peak incident of cancer is 85–89 years) with any accompanying comorbidities. Of note is the increased production of angiotensin-converting enzyme-2 (a key enzyme for infectivity by coronaviruses) that occurs with advancing age.^{1,2}

Another aspect that can potentially increase the severity of COVID-19 disease in cancer patients is a reduced ability to mount an

adaptive immune response following the initial innate response. The situation becomes more complicated by patients on active cancer treatments, further impairing their immune response.³ Initial data from China revealed a 3.5-fold increase in COVID-19 infections in patients with cancer requiring admission to ICU, mechanical ventilation, and death compared to those without cancer.⁴ However, recent studies have revealed that patients with hematological cancers may be at a reduced risk of severe COVID-19 due to their inability to produce an excessive, aberrant immune response which leads to acute respiratory distress syndrome and death in severe cases.⁵ Rather, hematology patients with any of the other known high-risk

comorbidities for severe COVID-19 (hypertension, diabetes, and other chronic diseases) could be the main driver behind any increase in deaths associated with COVID-19, but larger studies are still required to confirm this.⁶

Seroconversion for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG occurs after 10–12 days and SARS-CoV-2 IgM seroconversion after 11–13 days following infection with SARS-CoV-2 in immunocompetent patients.⁷ However, there have been few publications detailing the serological responses and clinical outcomes to SARS-CoV-2 in hematology–oncology patients.

We present a case series of 20 hematology–oncology patients who tested positive for SARS-CoV-2, their symptoms, serological responses, and outcomes.

2 | REPORT OF 20 HEMATOLOGY–ONCOLOGY CASES WITH COVID-19

Twenty patients with hematological cancers who tested positive for COVID-19 between March 3, 2020 and June 30, 2020 are reported here. A positive COVID-19 result is defined as a nasopharyngeal swab that tested positive for SARS-CoV-2 RNA by reverse-transcriptase polymerase-chain-reaction (RT-PCR). The AusDiagnostics SARS-CoV-2 PCR assay (AusDiagnostics UK Ltd) was used for testing which targets the ORF1 and ORF8 genes, both targets were detected in all patient samples. Kit sensitivity and specificity have been reported as 97%–98% and 99%–100%, respectively, by the manufacturer and external sources.⁸ Patient sera were tested using the DiaSorin Liaison SARS-CoV-2 S1/S2 assay IgG Kit with manufacturer sensitivity and specificity reported as 97% (86.8%–99.5%) and 98.9% (97.5%–99.2%), respectively.

Patient demographics and clinical characteristics have been displayed in Tables 1 and 2. The median age of patients was 77.20 (s.d: 11.45, range: 56–93), of which 14 were male (60%) and 6 were female, 18 of which required admission with an average length of 13 days (s.d: 11.8, range: 3–43).

Out of the 20 patients, 7 had a lymphoma (35%), 7 had leukemia (35%), and 6 had myeloma (30%). Many patients had coexisting medical conditions: hypertension (50%), osteoporosis (25%), diabetes (20%), and a cognitive disorder (10%). The most common symptoms were fever (50%), shortness of breath (45%), cough (25%), and abdominal pain (2%).

Patient symptom severity was assessed using a COVID-19 symptom score (CSS) ranging from 1 to 15 (1–3 = low, 4–6 = medium, and >7 = severe) with individual symptoms each scoring 1, >65 years of age scoring 1, coexisting medical conditions scoring 1, chest X-rays consistent with COVID-19 scoring 2, ICU admission scoring 3, and death with COVID-19 scoring 4 (Table 2).

The CSS assessment revealed that 7/20 (35%) presented with low severity, 6/20 (30%) presented with medium severity, and 7/20 (35%) presented with severe symptoms. All patients with low or medium CSS survived their infections (13/20, 11 male, 2 female);

while all patients with severe CSS scores died with the infection (7/20, 3 male, 4 female). All surviving patients will continue with their follow-up appointments as part of their care pathway.

Seventeen of the cohort had chest X-rays performed (Table 2) with 15 reported to have features consistent with infection (88%). The median time from symptom onset to a PCR test was 3.8 days (s.d: 5.9, range: 0–24) while the median time from symptom onset to serum sample collection was 13 days (s.d: 9, range: 0–30; Table 2).

TABLE 1 Demographics of hematological patients with SARS-CoV-2

Characteristic	Value
Patients (n = 20)	
Patient age (years)	
Mean ± SD	77.20 ± 11.45
Range	56–93
Sex, n (%)	
Male	14 (70)
Female	6 (30)
Disease severity (%) ^a	
0	6 (30)
1	6 (30)
2	4 (20)
3	4 (20)
Cancer (%)	
Lymphoma	6 (30)
Leukemia	7 (35)
Myeloma	7 (35)
Symptoms (%)	
Fever	10 (50)
Cough	5 (25)
SOB	9 (45)
Abdominal pain	2 (10)
Comorbidities (%)	
Hypertension	10 (50)
Diabetes	4 (20)
Osteoporosis	5 (25)
Cognitive disorder	2 (10)
Alive/deceased (%)	
Alive	13 (65)
Deceased	7 (35)

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOB, shortness of breath.

^aDisease severity calculated by the number of symptoms.

TABLE 2 Characteristics of 20 hematology patients with COVID-19

Patient	Sex	Age on admission (years)	Length of admission (days)	Alive/deceased	COVID-19 symptom score	Hematological disease	Cancer treatment	Clinical features	SARS-CoV-2 Swab PCR	Finds on chest X-ray	Serology for anti-SARS-CoV-2 IgG	Time between Symptom onset and PCR sample (days)	Time between Symptom onset and serum sample (days)
1	F	89	12	Alive	6	Myeloma	Lenalidomide and dexamethasone	SOB, cough, and fever	Positive	Patchy opacification of lower zones bilaterally	Negative	11	11
2	F	86	6	Deceased	7	Myeloma	Lenalidomide and dexamethasone	Asymptomatic	Positive	Linear atelectasis in both lowers but no focal consolidation	Negative	0	18
3	M	70	3	Alive	6	Lymphoma	Tirabutininb	Fever, cough, and SOB	Positive	Extensive peripheral subpleural ground-glass opacities with consolidation	Negative	8	8
4	M	79	4	Alive	3	Lymphoma	Unknown	Asymptomatic	Positive	No lung parenchymal changes of COVID-19	Negative	0	25
5	M	87	14	Alive	3	Myeloma	Lenalidomide and dexamethasone	Asymptomatic	Positive	Bilateral peripheral ground-glass opacities	Negative	0	12
6	M	82	39	Alive	2	Myeloma	Lenalidomide and dexamethasone	Fever	Positive	No convincing features to suggest COVID-19	Negative	7	30
7	M	56	13	Alive	4	Leukemia	Unknown	Fever and SOB	Positive	Unilateral consolidation	Positive	6	19
8	M	74	27	Alive	4	Leukemia	Cytarabine venetoclax	Fever	Positive	Right side pleural effusion	Negative	6	8
9	M	93	19	Alive	1	Lymphoma	Unknown	Asymptomatic	Positive	No CXR results	Positive	6	13

(Continues)

TABLE 2 (Continued)

Patient	Sex	Age on admission (years)	Length of admission (days)	Alive/deceased	COVID-19 symptom score	Hematological disease	Cancer treatment	Clinical features	SARS-CoV-2 Swab PCR	Finds on chest X-ray	Serology for anti-SARS-CoV-2 IgG	Time between symptom onset and PCR sample (days)	Time between symptom onset and serum sample (days)
10	M	63	6	Alive	2	Lymphoma	Pomalidomide, dexamethasone, and apixaban	Asymptomatic	Positive	Bilateral lower lobe pulmonary embolism	Not tested	0	-
11	M	69	14	Alive	4	Leukemia	Lenalidomide, dexamethasone, and daratumumab	Fever	Positive	Right-side pleural effusion	Negative	6	7
12	M	79	8	Deceased	7	Myeloma	Pomalidomide and dexamethasone	Fever and SOB	Positive	No CXR results	Not tested	0	-
13	M	77	5	Alive	3	Lymphoma	Dexamethasone	Cough and SOB	Positive	No CXR results	Negative	0	0
14	M	60	8	Deceased	9	Leukemia	Not on treatment	Fever, cough, and SOB	Positive	Coarsened airspace shadowing in both lungs	Not tested	0	-
15	F	86	8	Deceased	8	Leukemia	Not on treatment	Abdominal pain	Positive	Left basal apical linear atelectasis	Not tested	1	-
16	F	92	18	Alive	3	Leukemia	Mycophenolate and prednisolone	Asymptomatic	Positive	Patchy bibasal consolidation	Not tested	0	-
17	M	88	0	Deceased	8	Leukemia	Radiotherapy	SOB	Positive	Patchy bilateral perihilar inflammatory changes	Not tested	1	-
18	F	68	43	Deceased	8	Lymphoma	Not on treatment	SOB	Positive	Bilateral patchy air-space opacification	Not tested	0	-

TABLE 2 (Continued)

Patient	Sex	Age on admission (years)	Length of admission (days)	Alive/deceased	COVID-19 symptom score	Hematological disease	Cancer treatment	Clinical features	SARS-CoV-2 Swab PCR	Finds on chest X-ray	Serology for anti-SARS-CoV-2 IgG	Time between Symptom onset and PCR sample (days)	Time between symptom onset and serum sample (days)
19	F	85	0	Deceased	9	Lymphoma	Not on treatment	Fever and abdominal pain	Positive	Bibasilar consolidation with bilateral pleural effusions	Not tested	24	-
20	M	61	5	Alive	5	Lymphoma	Atorvastatin	Fever, cough, and SOB	Positive	Bilateral air space shadowing	Negative	0	2

Abbreviations: CXR, chest X-ray; F, female; M, male; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOB, shortness of breath.

Thirteen of the patients presented here (65%) survived while the remaining seven patients (35%) died with the SARS-CoV-2 infection. Of the seven deceased patients, four were female (median age: 81.15, s.d: 8.84, range: 68–86) and three were male (median age: 75.66, s.d: 14.3, range: 60–88). In terms of hematological cancer and mortality, two had myelomas, three had leukemias, and two had lymphomas. Note that for the patients who died with SARS-CoV-2 infection, we cannot be certain that this was the definitive cause of their death without additional post-mortem investigations.

Out of the 20 patients included in this case series, 12 were tested for SARS-CoV-2 IgG seroconversion from stored serum samples with two patients successfully seroconverting (16.6%; Table 2). The two patients (Cases 7 and 9) positive for SARS-CoV-2 IgG had a mean time for onset of symptoms to serum testing of 16 days (s.d.: 4.2, range: 13–19), while for negative anti-SARS-CoV-2 patients the meantime between symptoms and serum testing was 12.1 days (s.d: 10.1, range: 0–30).

3 | DISCUSSION

The median age for our cohort was 77.20 with a range of 56–93 years, which correlates well with the increased incidence of cancer and cases of COVID-19 with advancing age.^{1,2} Our cohort was predominately male (60%) but of those who died with COVID-19 (SARS-CoV-2 infection), the majority were female (57.1%). Studies on otherwise immunocompetent patients with COVID-19 have found that male patients tend to have more severe disease and higher mortality.⁵

The hematological cancers among our cohort were evenly distributed with similar numbers of patients with lymphoma, leukemia, and myeloma. This even distribution was also seen in the patients who died (two lymphoma, three leukemia, and two myeloma cases).

In terms of CSS and symptoms, our cohort again reflected those of other studies with the most common symptom being fever, followed by breathlessness, then cough, and finally abdominal pain (Table 1).^{9,10} However, within our cohort females presented with higher CSS scores than males and a higher death rate, which differs from the findings of other studies involving non-hematology patients.^{5,11}

Immunological responses to SARS-CoV-2 in immunocompetent patients have been investigated by several research groups, all giving a range of seroconversion rates for IgG and IgM of 11–20 days.^{7,12,13} The average time between symptom onset and serum sample was 13 days (range: 0–30) which is adequate time for an immunological response in most immunocompetent patients.⁷ The SARS-CoV-2 IgG seroconversion rates vary widely with some studies stating seroconversion rates of 44% to as high as 89%.^{13,14} In our cohort, we report a seroconversion rate of 2/12 (16.6%), far below the average for immunocompetent patients, which may not be unexpected for immunocompromised hosts, particularly in this hematology patients cohort where some were on anti-CD-20 therapies that will reduce antibody responses to such viral infections.^{3,4} This lack of immune

response could, paradoxically, give increased protection to hematology patients from SARS-CoV-2 due to a decrease in the interleukin 6 production, a key interleukin in the hyperinflammatory phase of the COVID-19 disease.¹⁵

Of our cohort that was tested for SARS-CoV-2 IgG, 6/12 (50%) were less than 14 days post-symptom onset (Table 2). This included nine patients who were tested positive 13 days post-symptom onset. Therefore, it is feasible that the remaining patients, given more time, could have developed an immunological response. There are relatively few studies investigating the antibody response in cancer patients, and in those published, they generally exclude patients who are less than 21 days post-symptom onset due to their delayed immune responses, while some studies have waited up to 50 days before serological testing.^{10,16,17}

Earlier data from China demonstrated a 3.5-fold increase in COVID-19 infections amongst patients with cancer who eventually required ICU admission.⁴ However, of the seven patients within our cohort who died with COVID-19 infection, four (Cases 14, 15, 18, 19) were not on any form of immunosuppressive treatment (57%). Therefore, it is feasible that due to the cessation of anticancer therapy their partially reconstituted host immune response may have contributed to their more severe COVID-19 presentation, increasing their risk of severe disease and death.¹⁸

In contrast, two independent studies on large hematology case series from the United Kingdom have advocated the continuation of anticancer therapy in such patients, as the impact of COVID-19 on these cancer cases was deemed to be less of a risk than their underlying malignancy progressing.^{19,20}

4 | CONCLUSION

This retrospective study demonstrates the possibility of more severe clinical outcomes in hematological patients with COVID-19. However, other studies with contrasting findings and recommendations^{4,19,20} demonstrate the need for further studies into how the severity of COVID-19 and clinical outcomes correlates to the varied immunological response of this group—which may vary substantially between individual cases.

Hematological patients who have been off chemotherapy or have been on minimum immunosuppression for some time, allowing partial host immune reconstitution may manifest stronger and potentially more aberrant immune responses that may impact on their clinical severity and outcomes of COVID-19. In contrast, patients already on chemotherapy to suppress the progression of their underlying malignancy may need to continue these even in the presence of COVID-19, the clinical impact of which may be blunted due to the continuing immunosuppression from such therapies.

CONFLICT OF INTERESTS

The authors have no conflict of interests to declare. All coauthors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the

submission is original work and is not under review at any other publication.

AUTHOR CONTRIBUTIONS

Julian W.-T. Tang conceived the presented idea. Ben Kennedy, Sapna Ladani, and Julian W.-T. Tang identified relevant patients. Paul W. Bird performed all testing of samples. Paul W. Bird and Vinay Badhwar collated the patient data and performed the data analysis. Paul W. Bird, Vinay Badhwar, and Julian W.-T. Tang drafted the manuscript. All authors reviewed the manuscript and made amendments before submission.

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