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RESEARCH ARTICLE

Severe acute respiratory syndrome coronavirus 2 infection in patients with hematological malignancies in the Omicron era: Respiratory failure, need for mechanical ventilation and mortality in seronegative and seropositive patients

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Abstract

Background: Patients with hematological malignancies (HM) have a high risk of severe coronavirus disease 2019 (COVID-19), also in the Omicron period.

Material and methods: Retrospective single-center study including HM patients with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV2) infection from January 2022 to March 2023. Study outcomes were respiratory failure (RF), mechanical ventilation (MV), and COVID-related mortality, comparing patients according to SARS-CoV2 serology.

Results: Note that, 112 patients were included: 39% had negative SARS-CoV2 serology. Seronegative were older (71.5 vs. 65.0 years, $p = 0.04$), had more often a lymphoid neoplasm (88.6% vs. 69.1%, $p = 0.02$), underwent anti-CD20 therapy (50.0% vs. 30.9% $p = 0.04$) and had more frequently a severe disease (23.0% vs. 3.0%, $p = 0.02$) than seropositive.

Kaplan-Meier showed a higher risk for seronegative patients for RF ($p = 0.014$), MV ($p = 0.044$), and COVID-related mortality ($p = 0.021$). Negative SARS-CoV2 serostatus resulted in a risk factor for RF (hazards ratio [HR] 2.19, 95% confidence interval [CI] 1.03–4.67, $p = 0.04$), MV (HR 3.37, 95% CI 1.06–10.68, $p = 0.04$), and COVID-related mortality (HR 4.26, 95% CI 1.09–16.71, $p = 0.04$).

Conclusions: : HM patients with negative SARS-CoV2 serology, despite vaccinations and previous infections, have worse clinical outcomes compared to seropositive

patients in the Omicron era. The use of serology for SARS-CoV2 diagnosis could be an easy tool to identify patients prone to developing complications.

KEYWORDS
COVID-19, hematological malignancies, serostatus

1 | BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was detected for the first time in 2019 [1]. Currently, there have been more than 760 million cases of coronavirus disease 2019 (COVID-19) including around 6.9 million deaths [2]. COVID-19 clinical presentation may be largely heterogeneous among different patients, ranging from flu-like symptoms to severe respiratory failure [3]. This heterogeneity became even more evident with the large spread of the Omicron variant starting from the first months of 2022, with the optimization of the distribution of vaccines and the slackening of isolation policies [4]. Some of the treatment and preventive measures available against SARS-CoV2 have lost effectiveness in the Omicron era, in particular monoclonal antibodies (mAbs) therapy [5].

People with hematological malignancies (HM) continue to represent a group of patients with a significantly higher risk of developing severe COVID-19 compared with immunocompetent patients in terms of morbidity, hospitalization, and mortality, regardless of their vaccination status [6]. Response to vaccination is lower than in the general population with a positive serology in about 80% of HM patients after three or four doses of the SARS-CoV2 vaccine [7, 8]. Specific therapies, such as anti-CD20 antibodies, BTK inhibitors, and stem cell transplantation, are known to be associated with lower rates of seroconversion [9–11].

In the Omicron era, overall mortality among hospitalized HM patients remains high at 16.5%, with 61% attributable to SARS-CoV2 infection [12]. Nevertheless, in this population rate of respiratory failure and COVID-related mortality is lower in the Omicron versus the pre-Omicron period (7.8% versus 36.8%) [13, 14]. Age, fewer vaccine doses, and diagnosis of acute myeloid leukemia or myelodysplastic syndrome are considered independent predictors of progression to severe COVID-19 or death in HM patients during the Omicron period [13].

Furthermore, the risk of prolonged shedding of the virus and of multiple clinical relapses is well-known in this subgroup of patients, especially in patients with B-cell depletion [15–18]. Prolonged carriage of SARS-CoV2 in these patients has negative implications not only socially and on a personal level, but often clinically as well, leading to delay in the initiation or continuation of specific chemotherapies.

To better understand and define the atypical SARS-CoV2 presentation in HM patients, recently, Belkin et al. proposed a disease entity termed "persistent inflammatory sero-negative COVID", probably caused by some combination between the persistence of the virus and an abnormal hyperactive inflammatory response. The authors suggested diagnostic criteria that combine the type of baseline immunodeficiency, clinical signs, virological persistence, and sero-negativity [19].

In this scenario, we performed this study to compare clinical COVID-19 outcomes in HM patients with SARS-CoV-2 positive serology and with SARS-CoV-2 negative serology. Indeed, although serology is certainly not the most comprehensive method to assess the immune response, it is a very simple, cheap, and easily achievable tool that can be used in clinical practice.

2 | METHODS

2.1 | Design of the study

We conducted a retrospective single-center study including all adult HM patients with confirmed SARS-CoV2 infection and evaluable serostatus referred to AOU Policlinico of Modena from January 2022 to March 2023.

An evaluable serostatus was defined as a SARS-CoV2 serology test performed from 3 months before to 5 days after the first positive nasopharyngeal swab (NPS), in the absence of active or passive immunization from the date of the serology test until the time of infection.

At SARS-CoV2 infection diagnosis, patients were evaluated for antiviral or mAb treatment, according to national criteria [20]. Patients were evaluated both in outpatient and hospital settings. In particular, outpatients were referred to the infectious disease (ID) specialist by general practitioners, hematology specialists, or the emergency department. Outpatients were first assessed by telephone and, on the basis of their home drug treatment and co-pathologies, the most appropriate therapy was indicated. In-hospital patients were directly evaluated by the ID consultant. Hospitalized patients included both patients already evaluated in the hospital setting and outpatients who later needed hospitalization. Hospitalized patients included both COVID-related and unrelated hospitalization.

Individual characteristics and outcomes were compared between patients with a negative SARS-CoV2 serology ("seronegative" group) and patients with positive SARS-CoV2 serology ("seropositive" group).

The aim of the study was to compare respiratory failure, mechanical ventilation, and COVID-related mortality in seronegative and seropositive patients.

The Institutional Ethics Committee of Area Vasta Emilia Nord approved the study (396/2020/OSS/AOUMO–Cov-2 MO-Study). Due to the observational nature of the study, written informed consent was waived.

2.2 | Data collection

We collected data on baseline patient characteristics and comorbidities, hematological status and treatment, signs, and symptoms, tixagevimab/cilgavimab prophylaxis, SARS-CoV2 vaccination status and antiviral/mAb treatment, time from symptoms onset to access to treatment, hospitalization, general mortality at 30, 60, and 90 days from infection and overall COVID-related mortality.

2.3 | Hematological status definitions

Among all HM, we differentiate lymphoid and myeloid neoplasms, according to the WHO classification [21, 22]. Lymphoid leukemia (LL) includes both acute and chronic LL, while myeloid leukemia (ML) refers to acute and chronic ML. We defined active disease as a diagnosis of HM in the absence of laboratory features or radiological signs of remission at SARS-CoV2 infection.

Patients on active chemotherapy or on steroids included all patients who were on anticancer or corticosteroid therapy in the last 28 days before the COVID-19 diagnosis. High-dose steroid therapy was referred to as ≥ 20 mg prednisone per day for at least one month or equivalent.

Anti-CD20 therapy was defined as the administration of at least one dose of any anti-CD20 agent in the previous year before infection. A history of hematopoietic stem cell transplantation (HSCT), whether autologous or allogenic, was considered.

2.4 | SARS-CoV2 infection

SARS-CoV2 infection was defined as a positive result of real-time polymerase chain reaction or immunochromatographic and immunofluorescence (antigenic) techniques on NPS.

Each infection was categorized into the following classes at evaluation in accordance with National Institute of Health guidelines [23]:

- Asymptomatic: individuals who test positive in virological tests but have no symptoms;
- Mild disease: individuals presenting with any of the various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle aches, nausea, vomiting, diarrhea, taste and smell loss) but no tachypnoea, dyspnea, or changes in chest X-ray;
- Moderate disease: subjects who show evidence of lower respiratory tract disease during clinical/radiological assessment and who have an oxygen saturation measured by pulse oximetry (SpO_2) ≥94% in ambient air;
- Severe disease: subjects with SpO_2 < 94% in room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, a respiratory rate > 30 acts/min, or lung infiltrates > 50% on chest imaging;

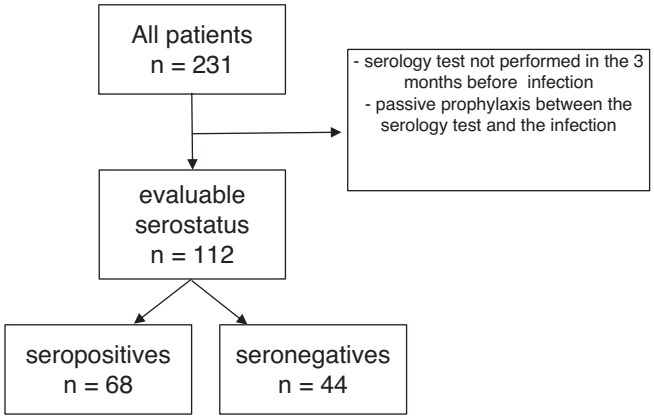

FIGURE 1 Study flowchart.

- Critical illness: severe respiratory failure, septic shock, and/or multiple organ dysfunction.

Relapse/re-infection was defined as the presence of two different positive NPS at least 90 days apart, regardless of the fact that there was a negative swab between the two, as suggested in the literature [24].

Regarding vaccination booster dose, it was considered as the third administration of mRNA BNT162b2 or mRNA-1273 vaccines or the second administration of Ad26.COV2.S vaccine.

The antiviral therapy prescribed included remdesivir, molnupiravir, and nirmatrelvir/ritonavir; mAbs employed were casirivimab/imdevimab, sotrovimab, and tixagevimab/cilgavimab. Drugs were prescribed following the available evidence of efficacy during the period of the study. Some patients received more than one treatment.

2.5 | Serology

Serologies were performed in the microbiological laboratory of AOU Policlinico of Modena using LIAISON® SARS-CoV-2 TimericS IgG by Diasorin. A negative serology was defined if IgG < 33.8 BAU/ml, and a positive serology if IgG > 33.8 BAU/ml.

2.6 | Outcomes definitions

Respiratory failure was defined as P/F < 300 during the course of the SARS-COV2 infection with oxygen need.

Mechanical ventilation (MV) was defined as the use of non-invasive ventilation (CPAP, BiPAP, or HFNC) or orotracheal intubation (IOT) and invasive ventilation.

COVID-related mortality was defined as death due to SARS-CoV2 infection and complications.

TABLE 1 Baseline demographic clinical and SARS-CoV2 infection characteristics by serology status.

	Total	Seronegative	Seropositive	
	N = 112	*N* = 44	*N* = 68	*p*-Value
Age, years, median (± IQR)	68.5 (57.0–78.0)	71.5(62.3–79.0)	65.0 (54.3–77.8)	0.04
Female sex, *N* (%)	45 (40.2)	18 (40.9)	27 (39.7)	0.89
Hypertension, *N* (%)	62 (55.4)	21 (47.7)	41 (60.3)	0.19
DM, *N* (%)	17 (15.2)	6 (13.6)	11 (16.2)	0.71
Obesity, *N* (%)	16 (14.3)	4 (9.1)	12 (17.6)	0.27
Not vaccinated, *N* (%)	7 (6.3)	4 (9.1)	3 (4.4)	0.32
Booster dose, *N* (%)	92 (82.1)	34 (77.3)	58 (85.3)	0.28
Tixagevimab/cilgavimab prophylaxis, *N* (%)	19 (17.0)	11 (25.0)	8 (11.8)	0.07
Previous infection, *N* (%)	11 (9.8)	7 (15.9)	4 (5.9)	0.11
Lymphoid neoplasms, *N* (%)	86 (76.8)	39 (88.6)	47 (69.1)	0.02
Myeloid neoplasms, *N* (%)	26 (23.2)	5 (11.4)	21 (30.9)	0.02
HM, *N* (%)				
AML	8 (7.0)	1 (2.3)	7 (10.0)	0.04
ALL	4 (4.0)	2 (4.5)	2 (2.9)	
CML	6 (5.0)	0 (0.0)	6 (8.8)	
CLL	16 (14.0)	11 (25.0)	5 (7.4)	
NHL	45 (41.0)	23 (52.3)	22 (32.4)	
HL	8 (7.0)	0 (0.0)	8 (11.8)	
MM	13 (12.0)	3 (6.8)	10 (14.7)	
MDS	5 (5.0)	4 (5.9)	1 (2.3)	
Other	7 (5.0)	7 (5.0)	7 (5.0)	
Lymphoid leukemia (LL), *N* (%)	20 (17.9)	13 (29.5)	7 (10.3)	0.01
Myeloid lekemia (ML), *N* (%)	14 (12.5)	1 (2.3)	13 (19.1)	0.01
Active disease, *N* (%)	62 (55.4)	20 (47.6)	42 (62.7)	0.12
Active chemotherapy, *N* (%)	57 (50.9)	21 (47.7)	37 (54.4)	0.1
Steroid therapy, *N* (%)	28 (25.0)	10 (26.3)	18 (31.0)	0.62
Anti-CD20 therapy, *N* (%)	43 (38.4)	22 (50.0)	21 (30.9)	0.04
HSCT, *N* (%)	21 (18.8)	7 (15.9)	14 (20.6)	0.63
Autologous HSCT, *N* (%)	11 (9.8)	4 (9.1)	7 (10.3)	0.83
Allogeneic HSCT, *N* (%)	10 (8.9)	3 (6.8)	7 (10.3)	0.74
NIH Symptoms, *N* (%)				0.02
Asymptomatic	7 (6)	0 (0)	7 (10)	
Mild	80 (71)	29 (66)	51 (75)	
Moderate	13 (12)	5 (11)	8 (12)	
Severe	12 (11)	10 (23)	2 (3)	
Critical	0 (0)	0 (0)	0 (0)	
Time from symptoms onset to treatment, days, median (± IQR)	4 (2–5)	5.0 (3.3–8.0)	3 (1–4)	< 0.001
Start of SARS-CoV2 therapy in an outpatient setting, *N* (%)	76 (65)	32 (72.7)	44 (65.0)	0.09
Enrolled in early treatment, *N* (%)	101 (90.2)	39 (88.6)	62 (91.2)	0.26
Enrolled as an outpatient, *N* (%)	72 (71.3)	30 (76.9)	42 (67.7)	0.39
Enrolled as an inpatient, *N* (%)	29 (28.7)	9 (23.1)	20 (22.2)	0.29
Hospitalization after outpatient treatment, *N* (%)	16 (14.3)	11 (25.0)	5 (7.4)	0.01

(Continues)

TABLE 1 (Continued)

	Total	Seronegative	Seropositive	
	N = 112	*N* = 44	*N* = 68	*p*-Value
Antivirals, *N* (%)	60 (53.6)	19 (43.2)	41 (60.3)	0.07
Remdesivir, *N* (%)	35 (34.7)	11 (28.2)	24 (38.7)	0.28
Nirmaltervir/ritonavir, *N* (%)	21 (20.8)	7 (17.9)	14 (22.6)	0.57
Molnupiravir, *N* (%)	8 (7.9)	2 (5.1)	6 (9.7)	0.48
mAbs, *N* (%)	55 (49.1)	25 (56.8)	30 (44.1)	0.25
Casirivimab/Indevimab, *N* (%)	3 (2.7)	2 (4.5)	1 (1.5)	0.56
Sotrovimab, *N* (%)	46 (41.1)	22 (50.0)	24 (35.3)	0.12
Tixagevimab/cilgavimab, *N* (%)	8 (7.1)	1 (2.3)	8 (10.3)	0.25
More than one treatment for a single infection, *N* (%)	25 (22.3)	10 (22.7)	15 (22.1)	0.93
Two treatments, *N* (%)	22 (19.6)	8 (18.2)	14 (20.6)	0.32
Three treatments, *N* (%)	3 (2.7)	2 (4.5)	1 (1.5)	0.32
Hospitalization, *N* (%)	53 (47.3)	22 (50.0)	29 (42.6)	0.44
Respiratory failure, *N* (%)	29 (25.9)	17 (38.6)	12 (17.6)	0.01
Mechanical ventilation, *N* (%)	14 (12.5)	9 (20.5)	5 (7.4)	0.08
30-day mortality, *N* (%)	5 (4.5)	2 (4.5)	3 (4.4)	1
60-day mortality, *N* (%)	14 (12.5)	7 (15.9)	7 (10.3)	0.38
90-day mortality, *N* (%)	17(15.2)	9 (20.5)	8 (11.8)	0.21
COVID-related mortality, *N* (%)	13 (11.6)	9 (20.5)	4 (5.9)	0.02

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, Chronic Lymphocytic Leukemia; CML, chronic myeloid leukemia; DM, Diabetes Mellitus; HL, Hodgkin lymphoma; HM, hematological malignancies; HSCT, hematopoietic stem cell transplantation; mAbs, monoclonal antibodies; MDS, myelodysplastic syndrome; MM, multiple myeloma; N, number; NHL, non-Hodgkin lymphoma; NIH, National Institute of Health; STD, standard deviation.

2.7 | Statistical analysis

For descriptive analysis, patient baseline characteristics at first positive SARS-CoV2 NPS were compared by serostatus group. Categorical variables were described as numbers and percentages (%), while continuous variables were summarized as the median and interquartile range (IQR). Differences in baseline characteristics of the patients were tested via Chi-square and Fisher exact for the categorical variables, and Mann-Whitney U for the continuous variables, as appropriate.

Multivariate Cox regression models were built to explore the contribution of demographic, clinical, laboratoristic, and therapeutical variables to respiratory failure, MV, and COVID-related mortality, respectively. Multivariate models were performed with the backward stepwise method, including covariates with a *p*-value less than 0.10 from univariate analysis or clinically important, based on literature data. Key confounders for respiratory failure were identified as age, diabetes mellitus, hypertension, previous or present solid tumor, active disease, relapse/reinfection, serostatus, and anti-CD20 use. For mechanical ventilation, we adjusted for age, diabetes mellitus, hypertension, active disease, relapse/reinfection, serostatus, and anti-CD20 therapy. Regarding mortality outcome, covariates considered were age, early treatment enrollment, active disease, relapse/reinfection, negative serostatus, anti-CD20 therapy, mechanical ventilation, and hospitalization.

Pearson correlation was used to identify colinear variables, which were excluded from multivariate analysis. The survival analysis was plotted by the Kaplan–Meier Method and the log-Rank test was performed to compare the curves according to the serostatus. A *p*-value less than 0.05 was considered statistically significant. All statistical analysis was performed using 'Statistical Package for The Social Sciences' v28 for Windows (SPSS).

3 | RESULTS

A total of 231 patients with HM and SARS-CoV-2 infection were evaluated for antiviral therapy or mAbs administration, according to national criteria [20]. Among them, 112 of them had an evaluable serostatus. Forty-four patients (39%) had a seronegative status while the remaining 68 patients (61%) had a seropositive status (Figure 1).

Baseline demographic, clinical, and SARS-CoV2 infection characteristics of patients by serology status are shown in Table 1.

Seropositives were younger than seronegative patients (65.0 vs. 71.5 years, $p = 0.04$). Seronegative had more often a lymphoid neoplasm (88.6% vs. 69.1%, $p = 0.02$) and a lower percentage of myeloid neoplasms (11.4% vs. 30.9%, $p = 0.02$). Seronegative patients underwent anti-CD20 therapies in the previous year more often than seropositive (50.0% vs. 30.9% $p = 0.04$); moreover, seronegative were

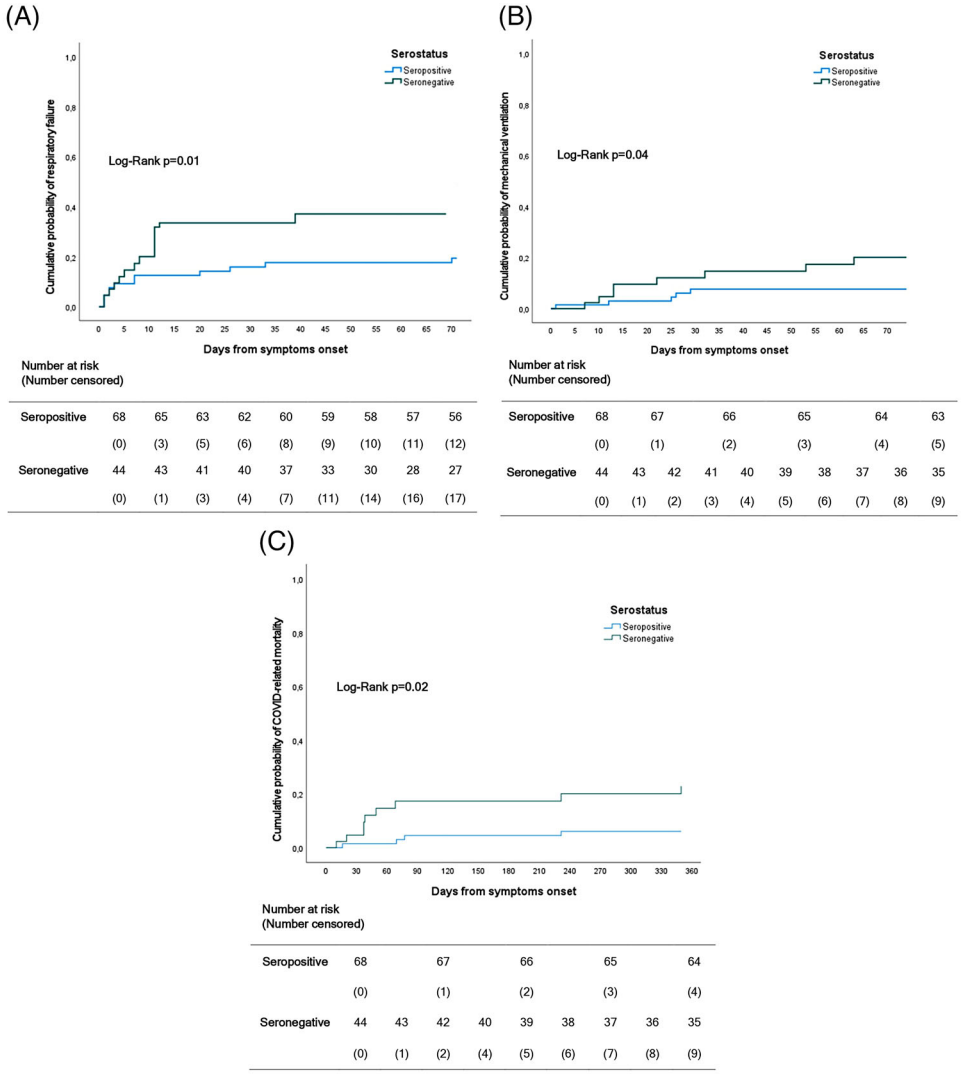

FIGURE 2 Kaplan-Meier for respiratory failure (A), mechanical ventilation (B), and coronavirus disease (COVID)-related mortality (C) by serostatus group.

more prone to have a severe SARS-CoV2 disease (23.0% vs. 3.0%, $p = 0.02$). The time from symptoms onset until access to treatment was shorter for seropositive patients (3 days vs. 5, $p < 0.001$).

The majority of patients were enrolled in early treatment (90.2%), most of them as outpatients rather than in the hospital setting (71.3% vs. 28.7%). Among the 53 patients that were hospitalized, 16 of them were admitted after already being treated as outpatients, with a prevalence of seronegative (25% vs. 7.4%, $p = 0.01$).

Remdesivir was the most frequently prescribed antiviral (34.7%), followed by nirmaltervir/ritonavir (20.8%) and molnupiravir (7.9%). As for mAbs, patients were administered mainly sotrovimab (41.1%), then tixagevimab/cilgavimab (7.1%) and casirivimab/indevimab (2.7%).

Regarding outcomes, seronegative patients had a higher rate of respiratory failure (38.6% vs. 17.6%, p 0.01) and COVID-related mortality (20.5% vs. 5.9%, $p = 0.02$).

Unweighted Kaplan-Meier estimates showed the cumulative risk for respiratory failure (A), mechanical ventilation (B), and COVID-related mortality (C) by the serostatus group.

The cumulative probabilities estimated with Kaplan-Meier analyses for all groups were 25.9% (95% confidence interval [CI] 18.1–33.7) for the endpoint of respiratory failure, 12.5% (95% CI 9.6–15.4) for mechanical ventilation and 11.6% (95% CI 4.7–17.5) for COVID-related mortality.

The proportion of patients with respiratory failure was 38.6% (95% CI 24.3–52.9) for the seronegative group versus 17.6% (95% CI 8.6–26.6) for the seropositive group (log-rank $p = 0.014$, Figure 2A).

The proportion of patients that underwent mechanical ventilation was 20.5% (95% CI 9.2–31.8) for the seronegative group versus 7.4% (95% CI 1.5–14.3) for the seropositive group (log-rank $p = 0.044$, Figure 2B).

TABLE 2 Univariate and multivariate analyses for respiratory failure.

Univariate			Multivariate	
Variable	**HR (95% CI)**	***p*-Value**	**aHR (95% CI)**	***p*-Value**
Gender, female	1.48 (0.71–3.06)	0.30		
Age	1.04 (1.01–1.06)	0.02		
Enrolled in early treatment	0.58 (0.22–1.53)	0.27		
Obesity	1.27 (0.48–3.32)	0.63		
Hypertension	1.92 (0.88–4.22)	0.10		
Diabetes mellitus	2.65 (1.17–5.99)	0.02	3.37 (1.38–8.25)	0.01
Previous or present solid tumor	2.15 (0.95–4.87)	0.07	6.33 (2.13–18.86)	< 0.001
Active HM disease	1.75 (0.79–3.86)	0.17		
Steroid	1.60 (0.73–3.49)	0.24		
High dose steroid	1.88 (0.64–5.50)	0.25		
Anti-CD20 last year	2.39 (1.14–5.01)	0.02	2.36 (1.07–5.19)	0.03
Active chemotherapy	1.22 (0.56–2.62)	0.62		
Relapse/Re-infection	3.50 (1.49–8.22)	0.004		
Antivirals	1.25 (0.59–2.62)	0.55		
Not vaccinated	0.53 (0.07–3.92)	0.54		
NHL	1.90 (0.92–3.96)	0.09		
Negative serostatus	2.43 (1.16–5.09)	0.02	2.48 (1.15–5.39)	0.02
Lymphoid leukemia	2.01 (0.89–4.55)	0.09		
MM	0.55 (0.13–2.33)	0.42		

Abbreviations: aHR, adjusted hazards ratio; HL, Hodgkin lymphoma; HM, hematological malignancies; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

The COVID-related mortality was 20.5% (95% CI 14.7–26.3) for the seronegative group versus 5.9% (95% CI 0.1–11.7) for the seropositive group (log-rank $p = 0.021$, Figure 2C).

Univariate and multivariate analyses of conditions associated with respiratory failure are shown in Table 2.

Risk factors associated with respiratory failure at the univariate analysis were age (hazards ratio [HR] 1.04, 95% CI 1.01–1.06, $p = 0.02$), diabetes (HR 2.65, 95% CI 1.17–5.99, $p = 0.02$), administration of anti-CD20 agents in the year before the infection (HR 2.39, 95% CI 1.14–5.01, $p = 0.02$), relapse/re-infection (HR 3.50, 95% CI 1.49–8.22, $p = 0.004$) and negative serostatus (HR 2.43, 95% CI 1.16–5.09, $p = 0.02$).

After adjustments for covariates, the independent risk factors for respiratory failure were diabetes (HR 3.37 95% CI 1.38–8.25, $p = 0.01$), previous or present solid tumor (HR 6.33 95% CI 2.13–18.86, $p < 0.001$), anti-CD20 last year (HR 2.36, 95% CI 1.07–5.19, $p = 0.03$) and negative serostatus (HR 2.48, 95% CI 1.15–5.39, $p = 0.02$).

Table 3 shows the univariate and multivariate analyses for mechanical ventilation.

Regarding the risk of mechanical ventilation, at the univariate analysis diabetes mellitus (HR 3.52, 95% CI 1.18–10.51, $p = 0.02$), relapse/re-infection (HR 6.01, 95% CI 2.01–17.97, $p = 0.01$) and negative serostatus (HR 2.93, 95% CI 1.01–8.72, $p = 0.05$) resulted as risk factors. Among them, negative serostatus was confirmed to be an independent positive predictor for mechanical ventilation also at the multivariate analysis (HR 3.37, 95% CI 1.06–10.68, $p = 0.04$), as shown in Table 3.

Table 4 shows univariate and multivariate analyses for COVID-related mortality.

Univariate analysis demonstrated that age (HR 1.16, 95% CI 1.08–1.25, $p < 0.001$), negative serostatus (HR 3.79, 95% CI 1.17–12.31, $p = 0.03$), mechanical ventilation (HR 3.53, 95% CI 1.09–11.49, $p = 0.04$) and hospitalization (HR 4.38, 95% CI 1.21–15.93, $p = 0.03$) were associated with an increased risk of COVID-related mortality, while the early enrollment to anti-SARS-CoV2 treatment was a protective factor (HR 0.16, 95% CI 0.05–0.49, $p < 0.001$). At the multivariate analysis, age (HR 1.22, 95% CI 1.09–1.34, $p < 0.001$), active HM disease (HR 5.86, 95% CI 1.16–29.62, $p = 0.03$), negative serostatus (HR 4.26, 95% CI 1.09–16.71, $p = 0.04$) and mechanical ventilation (HR 10.25, 95% CI 2.21–47.55, $p = 0.003$) were confirmed as independent predictors of COVID-related mortality as shown in Table 4.

4 | DISCUSSION

In our study, HM patients with SARS-CoV-2 negative serology showed worse clinical outcomes compared to seropositive patients in the Omicron era. In particular, they showed a two-fold higher probability of respiratory failure (HR 2.19, CI 10.03-4.67, *p* 0.04), a three-fold higher probability of MV (HR 3.37, 95% CI 1.06–10.68, *p* 0.04), and a

TABLE 3 Univariate and multivariate analyses for mechanical ventilation.

Univariate			Multivariate	
Variable	**HR (95% CI)**	***p*-Value**	**aHR (95% CI)**	***p*-Value**
Gender, female	0.83 (0.28–2.47)	0.63		
Age	1.04 (0.99–1.08)	0.08		
Enrolled in early treatment	0.78 (0.17–3.39)	0.71		
Obesity	0.98 (0.22–4.38)	0.98		
Hypertension	2.10 (0.66–6.69)	0.21		
Diabetes mellitus	3.52 (1.18–10.51)	0.02		
Previous or present solid tumor	1.37 (0.38–4.90)	0.63		
Active HM disease	1.19 (0.39–3.67)	0.75		
Steroid	1.05 (0.32–3.40)	0.94		
High dose steroid	1.65 (0.30–9.02)	0.56		
Anti-CD20 last year	2.15 (0.75–6.19)	0.16		
Active chemotherapy	0.77 (0.25–2.39)	0.65		
Relapse/Re-infection	6.01 (2.01–17.97)	0.01		
Antivirals	0.86 (0.30–2.45)	0.78		
Not vaccinated	0.05 (0.00–492.24)	0.51		
NHL	1.08 (0.38–3.11)	0.89		
Negative serostatus	2.93 (1.01–8.72)	0.05	3.37 (1.06–10.68)	0.04
Lymphoid leukemia	2.75 (0.92–8.21)	0.07		
MM	0.59 (0.08–4.55)	0.62		

Abbreviations: aHR, adjusted hazards ratio; HL, Hodgkin lymphoma; HM, hematological malignancies; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

four-fold higher probability of COVID-19 related mortality (HR 4.26, CI 1.09–16.71, *p* 0.04).

The fact that individuals with SARS-CoV-2 negative serology have worse outcomes than seropositive patients can be quite intuitive. In fact, SARS-CoV-2 serology can be considered an appropriate surrogate marker of patient immune response, being demonstrated that the higher the titer of the anti-S antibody, the higher the likelihood of neutralization in neutralization assays [25].

Nevertheless, this is the first study that shows that HM seronegative patient outcomes remain worse also in a period characterized by the Omicron variant in which effective antivirals and mAbs are easily available and routinely used.

In the seronegative group, 38.6% of patients developed respiratory failure and the COVID-related mortality was 20.5%, despite the fact that 43.2% of patients received antivirals, 56.8% received mAbs plus the standard of care, and 22.7% received more than one treatment.

It is not easy to compare our results to the literature since recently published studies take into consideration different baseline populations and different outcomes and no study differentiates between seronegative and seropositive patients. For example, the study from Minoia et al. [26] showed a respiratory failure rate of 23%, similar to our rate in the general HM population, while COVID-19-related death was lower (6.1%) but was calculated at 28 days from infection.

Mikulska et al. considered only patients who underwent an early treatment with antivirals or mAbs. In this population treatment failure developed in 9.5% of patients and COVID-19-associated mortality in 3.4% [13].

Even though seronegative patient outcomes remain terrible, in our study 30-day mortality in the whole HM population was 4.5%. This percentage is much lower than the mortality rates described in HM patients during the first waves in 2020 (33%) [27], characterized by different variants of interest and no therapies at all. These data confirm a lower COVID-19 mortality in the Omicron period. Mortality in the general Italian population in the same period was reported to be 0.2%—0.4% [28], showing how, even if outcomes are improving during time in the HM population, they remain much worse than in the general population.

Indeed, HM patients remain one of the few populations for which SARS-CoV-2 infection continues to be a clinical problem that needs to be faced in clinical practice despite multiple vaccinations and/or previous infections.

Lee et al. showed an RR of 0.63 in HM patients compared to the general population to seroconversion after two doses of vaccine [29]. In our study, 90.9% of seronegative patients were vaccinated and 77.3% received a booster dose, confirming how the response to the SARS-CoV-2 vaccine can be ineffective in HM patients. For this reason, it is necessary to focus on these patients to find a personalized approach for seronegative HM. On one hand, it should be a priority to continue vaccinating HM patients, in order to improve their immunological response; on the other hand, different research groups have started to

TABLE 4 Univariate and multivariate analyses for coronavirus disease (COVID)-related mortality.

Univariate			Multivariate	
Variable	**HR (95% CI)**	***p*-Value**	**aHR (95% CI)**	***p*-Value**
Gender, female	0.95 (0.31–2.91)	0.93		
Age	1.16 (1.08–1.25)	< 0.001	1.22 (1.09–1.34)	<0.001
Enrolled in early treatment	0.16 (0.05–0.49)	< 0.001		
Obesity	0.48 (0.06–3.67)	0.48		
Hypertension	1.92 (0.59–6.24)	0.28		
Diabetes mellitus	1.84 (0.51–6.68)	0.36		
Previous or present solid tumor	2.39 (0.74–7.76)	0.15		
Active disease	3.99 (0.88–18.23)	0.07	5.86 (1.16–29.62)	0.03
Steroid	1.09 (0.34–3.55)	0.88		
High dose steroid	0.47 (0.11–1.96)	0.30		
Anti-CD20 last year	1.37 (0.46–4.08)	0.57		
Anti-CD20 last 6 months	2.07 (0.22–19.92)	0.53		
Active chemotherapy	1.11 (0.35–3.49)	0.86		
Relapse/Re-infection	0.72 (0.09–5.54)	0.75		
Antivirals	1.39 (0.45–4.25)	0.57		
Not vaccinated	–	–		
NHL	1.79 (0.60–5.34)	0.29		
Negative serostatus	3.79 (1.17–12.31)	0.03	4.26 (1.09–16.71)	0.04
Lymphoid leukemia	1.44 (0.39–5.21)	0.59		
MM	0.04 (0.00–57.05)	0.39		
Mechanical ventilation	3.53 (1.09–11.49)	0.04	10.25 (2.21–47.55)	0.003
Hospitalization	4.38 (1.21–15.93)	0.03		

Abbreviations: aHR, adjusted hazards ratio; HL, Hodgkin lymphoma; HM, hematological malignancies; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

perform off-label treatments either combining more than one antiviral such as remdesivir plus nirmatrelvir/ritonavir [30, 31] or prolonging the approved duration of label treatment [32].

Serology performed at the beginning of the hospitalization could be an easy tool to perform in the real-practice in order to rapidly select patients with expected unfavorable outcomes that could benefit from the beginning of an off-label treatment.

Patients with active hematological disease showed a 5-fold higher probability of COVID-related mortality. These data suggest the fact that in HM the interplay between SARS-CoV-2 infection and the underlying hematological disease is crucial. We do not know if, due to SARS-CoV-2 infection, chemotherapy was avoided or postponed and this would be an important subject to analyze in further studies.

This study has some limitations, mainly due to its retrospective nature and the small sample size. First of all, not all evaluated patients had an available serology so we had to exclude almost half of the patients. It is probable that serology was performed especially in patients considered at higher risk by the ID specialist. Second, since our study was conducted between 2022 and 2023, different subvariants with different expected responses to different mAbs were present and we did not perform the analysis of the subvariants. However, our study has some strengths. In particular, it is the first study that addresses the role of serostatus on HM patient outcomes with a real-life approach.

In conclusion, this study shows that performing a serologic evaluation at baseline in HM patients with SARS-CoV-2 infection is a suitable and easy tool to identify patients more prone to developing complications related to SARS-CoV-2 infection. Further studies are needed to understand if these patients can benefit from a personalized off-label approach.

AUTHOR CONTRIBUTIONS

Designed the research study: E. Franceschini, C. Mussini, and A. Santoro

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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No external funding was received.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy restrictions.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and the Institutional Ethics Committee of Area Vasta Emilia Nord approved the study (396/2020/OSS/AOUMO–Cov-2 MO-Study).

PATIENT CONSENT STATEMENT

Due to the observational nature of the study, written informed consent was waived.

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