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The Burden of COVID-19 in Adult Patients With Hematological Malignancies: A Single-center Experience After the Implementation of Mass-vaccination Programs Against SARS-CoV-2

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Abstract. *Background/Aim: Despite the widespread mass-vaccination programs worldwide and the continuing evolution of COVID-19 therapeutics, the burden of SARS-CoV-2 infection in patients with hematological malignancies (HM) remains elusive. The aim of the present study was to assess the clinical characteristics, outcomes and therapeutic strategies applied in HM patients hospitalized during the post-vaccine period in Greece. Patients and Methods: From June 2021 to October 2022, 60 HM patients with COVID-19 were retrospectively analyzed. Exploratory end-points included the incidence of intubation, probability of recovery, mortality, and duration of remdesivir (RDV) administration. Results: Overall, mechanical ventilation (MV) was required for five patients and crude mortality was 8.3%. HM of lymphocytic origin (p=0.035) and obesity (p=0.03) were the main determinants of the risk of intubation and among several laboratory markers, only LDH>520 IU/l was proven to be an independent MV predictor (p=0.038). The number of co-existing comorbidities (p=0.05) and disease severity on admission (p<0.001) were found to rule the probability of recovery, and dexamethasone was associated with worse prognosis, particularly in patients with mild/moderate COVID-19. RDV was administered to the entire cohort, of whom 38 were managed with an extended course. In the multivariate analysis, patients with HM of lymphocytic origin were more likely to receive RDV for more than five days (p=0.002). Conclusion: Our study emphasizes the frailty of HM patients, even in the era of Omicron-variant predominance, and underlines the need to optimize therapy.*

The interplay between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and patients with hematological malignancies (HM) or solid tumors is evolving and the short- and long-term consequences of COVID-19 is a topic of great interest (1). Given that coronavirus disease 2019 (COVID-19) will remain a global health care issue for the foreseeable future and new virus variants with high infectivity rate may emerge, identifying the subset of frail patients at greater risk of adverse events and implementing a patient-tailored approach for the management and treatment of SARS-CoV-2 infection seem imperative.

Patients with HM represent a profoundly heterogeneous population that experiences disease- or therapy-induced immunosuppression (2); thus, the potential threat of severe and life-threatening infections is significant. In case of COVID-19,

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HM patients are disproportionally affected, and they are prone to longer and more severe disease course, as well as re-infections, due to humoral (delayed or reduced seroconversion, prolonged viral shedding) and cellular immunodeficiency (T-cell exhaustion, lack of long-term immunity) (3). As reported in several observational studies and meta-analyses, the incidence of hospital or Intensive Care Unit (ICU) admission and mechanical ventilation (MV) is increased and higher mortality rates, compared to general population and cancer patients have been observed (3-8). Notably, COVID-19-related mortality is approximately 30%, both in the pre- and in the post-vaccine era, with an immense impact on patients diagnosed with acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), and high-risk myelodysplastic syndromes (MDS), and those who had undergone hematopoietic stem cell transplantation or received chimeric antigen receptor (CAR)- T cell therapy (7, 9, 10). Moreover, type of malignancy, status of underlying disease, number of co-existing comorbidities, advanced age, and laboratory parameters (*e.g.,* lymphopenia, neutropenia, high C-reactive protein) were found to be determinants of COVID-19 severity in HM patients (1, 3, 6, 7, 9, 11-13). Lastly, prolonged viral shedding (14), frequently observed in these patients, represents a serious threat for both patients (*e.g.,* mandatory prolonged isolation, limited access to healthcare system, risk of clinical relapse, postponement or withdrawal of anti-cancer treatment, decreased quality of life) and the public health (*e.g.*, genomic evolution of the virus, emergence of new variants) (15-17). These considerations emphasize the major relevance of proper COVID-19 management in this frail patient population.

The aim of the present study was to assess the clinical characteristics, outcomes and therapeutic strategies applied in hematological patients with COVID-19 admitted to our clinic, after the implementation of mass-vaccination programs against SARS-CoV-2 in Greece.

Patients and Methods

Study design. This is a retrospective analysis of patients with HM and COVID-19, consecutively admitted to the Infectious Diseases Unit of Sotiria General Hospital, a reference hospital in Athens, Greece, between June 2021 and October 2022. This time-frame corresponds to the period during which i) displacement of the Delta variant and predominance of the Omicron variant and ii) implementation of mass-vaccination programs against COVID-19, accompanied by the gradual lifting of restrictive measures in Greece were recorded.

Patients. Adult patients, aged ≥18 years, with confirmed SARS-CoV-2 infection and a past medical history of HM, hospitalized during the third (Delta-variant predominance) and fourth pandemic waves (Omicron-variant predominance), were analyzed. Exclusion criteria were i) being younger than 17 years of age, ii) no laboratory-confirmed COVID-19, iii) hospitalization during the first or second pandemic wave and iv) lack of variables of interest.

The following data were retrospectively collected per COVID-19 case *via* routine care patient charts: age, sex, comorbidities, prior SARS-CoV-2 infection, history of COVID-19 vaccination (including number of doses administered and date of last dose prior to admission), administration of immunomodulatory agents as part of COVID-19 treatment and clinical outcomes. Regarding HM history, upon contact with the treating hematologist, the following variables were also collected: type and status of underlying disease, type of last or ongoing treatment, focusing on anti-CD20 monoclonal antibodies, Janus and Bruton tyrosine kinase (JAK/BTK) inhibitor therapy, history of stem cell transplantation and receipt of corticosteroids.

Definitions. COVID-19 severity was assessed on admission based on clinical parameters and patients' oxygen requirements. Severe disease was designated when patients met one or more of the following criteria: i) oxygen saturation as measured by pulse oximetry (SpO2) ≤94% on room air, ii) PaO2/FiO2<300 mm Hg, iii) tachypnea (respiratory rate ≥30 breaths per minute) or iv) lung infiltrates>50%. Moderate disease was defined by evidence of lower respiratory disease during clinical assessment or imaging, with SpO2 ≥94% on room air (18).

Full vaccination was defined as a primary vaccination series of two doses of BNT162b2 (Comirnaty), mRNA-1273 (Spikevax) or ChAdOx1-S (Vaxzevria) until 09/2021, then followed by a booster at least six months later (from 10/2021 until now); boosted vaccinated were considered the patients that had received ≥3 vaccine doses.

Endpoints. We sought to assess the clinical characteristics, outcomes and therapeutic strategies applied in hematological patients with COVID-19 admitted to our clinic, after the implementation of mass-vaccination programs against SARS-CoV-2. Therefore, endpoints were the incidence of intubation, cumulative probability of recovery, mortality, and duration of remdesivir (RDV) treatment course.

Statistical analysis. Baseline characteristics were summarized using descriptive statistics, including mean and standard deviation (SD) for normally distributed variables, medians and interquartile ranges (IQRs) for non-normally distributed variables and absolute (N) and relative (%) frequencies for categorical ones. Chi square and Fisher's exact tests were used for the comparison of proportions and *t*-tests were performed to compare the continuous variables between two groups.

Multiple logistic regression models were conducted for the detection of factors possibly associated with the exploratory points of interest. Survival analysis using Cox proportional hazards model and Kaplan-Meier estimator was performed to evaluate the association of HM to survival with censoring at 15 and 30 days. Log-rank analyses compared the risk of categorical variables. Cox proportional hazards models were used to investigate other factors related to the risk of endpoint occurrence and odds ratios (OR) [95% confidence intervals (CI)] were reported for the variables retained in the final model. Cumulative probability of recovery is presented as median (95%CI) time. Time to recovery was analyzed using log-rank tests and Cox model stratified by COVID-19 disease severity. All reported *p* values are two-tailed.

Patients were also divided into two groups according to the type of underlying HM in order to evaluate plausible differences between patients with: i) Hodgkin lymphoma (HL), Non-Hodgkin lymphoma (NHL) and chronic lymphoblastic leukemia (CLL), and ii) other hematological malignancies.

Statistical significance was set at 0.05 level and the analyses were performed using STATA/MP13 (Stata Corp., College Station, TX, USA).

Ethical issues. The study protocol was approved by the Institutional Review Board of SOTIRIA General Hospital (approval number: 4835/22-02-2023) and was conducted in accordance with the Helsinki Declaration of Human Rights. In compliance with the local regulations, informed consent form was waived because of the retrospective design of the study and anonymous clinical data were used in the analysis.

Results

Data from 60 hematological patients (female: n=32, 53.3%) were analyzed and study population baseline characteristics are depicted in Table I. Median age was 71 years (IQR=58-77) and 66.7% aged 65 years or more. The median number of coexisting comorbidities was 1 (IQR=0-2.5). Patients with NHL represented the largest subgroup (n=26, 43.3%), followed by patients with CLL (n=11, 18.3%) and those with myeloproliferative disorders (MPDs) (*e.g.*, chronic myelogenous leukemia, essential thrombocythemia, myelofibrosis and polycythemia vera) (n=10, 16.7%). The vast majority had active disease (n=46), of whom 45% were currently undergoing treatment and 31.7% were on maintenance therapy. The most frequent treatments received for the underlying HM were targeted therapies either alone (anti-CD20 monotherapy: n=10; JAK inhibitors: n=3; BTK inhibitors: n=4) or in combination (anti-CD20 monotherapy & other: n=9; JAK inhibitors & other: n=1; BTK inhibitors & other: n=2). Only 4 patients had undergone stem cell transplantation (autologous: n=3, allogenic: n=1) and 14 were in long-term corticosteroid therapy as part of their oncological treatment. Previous documented SARS-CoV-2 infection was reported by 7 patients. Lastly, 38 patients were vaccinated, of whom 68.4% (n=26) were fully, 18.4% (n=7) were boosted (>3 doses) and 13.2% (n=5) partially vaccinated. The median interval between last vaccination and hospital admission was five months (IQR=3-7).

COVID-19 clinical presentation and radiological findings on admission, as well as the therapies administered, are shown in Table I. Thirty-seven patients (61.7%) presented with severe disease on admission. During hospitalization, 21.7% (n=13) were at some time point in need of greater oxygen requirements and the main determinants identified were obesity [OR=33.6 (95%CI=0.99-1136.44; p=0.05)] and lymphocytic type of HM [OR=0.13 (95%CI=0.02-0.78; p=0.025)].

Regarding the applied treatments (Table I), RDV was administered to the entire cohort, dexamethasone to 35% and prolonged corticosteroid therapy, mostly attributed to difficulties in weaning from supplemental oxygen therapy, to 26.7%. Anticoagulants were given to 53 patients and the dosage was determined based on disease severity and risk stratification for adverse events (prophylactic: n=39, 73.5%; intermediate: n=4, 6.7%; therapeutic: n=10, 16.7%). Lastly, 9 patients (15%) were managed with immunomodulatory agents (tocilizumab: n=5, 8.33%; anakinra: n=1, 1.66%; baricitinib: n=3, 5%) and 5 (8.33%) received intravenous immune globulin due to hypogammaglobulinemia.

Clinical outcomes. In the entire cohort, the median length of hospital stay was 10 (IQR=8-13) days. Six patients were admitted to ICU and MV was required for five. Notably, all of them presented with severe disease on admission. The median time from admission to intubation was 3.5 (IQR=2-11) days and the median duration of hospitalization was 16 (IQR=9-24) days.

In the multivariate analysis (Table II), obesity conferred an increased risk of MV [OR=26.09 (95%CI=1.37-497.78; p=0.03)], whereas patients with NHL, HL or CLL were less prone to intubation [OR=0.05 (95%CI=0.01-0.81; p=0.035)]. Furthermore, cut-off values for several factors associated with MV included: i) PaO2/FiO2 <300 mg Hg [OR=13.14 (95%CI=2.02-85.65; p=0.007)], ii) CRP >8 mg/dl, [OR=7 (95%CI=1.14-42.97; p=0.036)], iii) Creatinine >1.2 mg/dl, [OR=8.8 (95%CI=1.41-54.91; p=0.020)], iv) SGOT >37IU/l, [OR=19.55 (95%CI=2.07-184.86; p=0.010)] and v) LDH >520 IU/l [OR=50 (95%CI=4.46-560.28; p=0.002). Among them, only LDH >520 IU/l [OR=24.39 (95%CI=1.19-499.82; p=0.038)] remained an independent predictor for intubation in the multivariate analysis (Table III).

Mortality was 8.3% and of the five deaths recorded, four occurred while the patients were intubated and one in the post-intubation period. Four out of 55 patients discharged needed supplemental oxygen therapy at home.

Five patients were re-admitted to hospital at a median of 6.5 (4.5, 8.5) days after their discharge. All of them had HM of lymphocytic origin (*e.g.*, NHL, HL or CLL) and re-hospitalization was not related to any of the studied factors.

Cumulative probability of recovery. Cumulative probability of recovery by time since hospital admission is shown in Figure 1, Figure 2, Figure 3, and Figure 4 illustrate the probability of recovery by disease severity on admission, type of underlying HM and both disease severity and HM type, respectively. As expected, the median (IQR) time to recovery was shorter in patients with mild/moderate disease (9, IQR=6-10 *vs*. 12, IQR=10-18 days). Similarly, patients with HM of lymphocytic origin (*e.g.*, NHL, HL or CLL) recovered at a median time of 10 (IQR=9-12) days compared to patients with another HM type (13, IQR=7-20 days). Interestingly, dexamethasone administration on admission conferred a diminished probability of recovery, particularly in the subset of patients with mild/moderate COVID-19 (Figure 5). Lastly, only the number of co-existing comorbidities and disease severity were significantly associated with recovery (Table IV).

Cumulative probability of recovery was also assessed by vaccination status. As presented in Figure 6, median time to recovery (95%CI) was 10 days (9-13) for boosted and fully,

20 days (9-20) for partially and 11 (7-13) days for unvaccinated patients. Cumulative probability of recovery was higher at 10 days for boosted patients (p=0.04), but not statistically significant for all time points (p=0.658).

Duration of RDV treatment course. As mentioned above, the entire cohort was administered RDV, of whom 38.3% received the standard 5-day course. The others were managed with an extended, up to 10 days, RDV course, mostly determined by the type and status of underlying HM, as well as COVID-19 severity. Of note, in the subset of patients with previously documented SARS-CoV-2 infection or re-admitted to our clinic upon recent discharge, a surrogate of viral load on day 5 since antiviral treatment initiation, as expressed by the cycle threshold of the PCR in the nasopharyngeal swab, was the main determinant of RDV course duration.

In the multivariate regression analysis (Table V), upon adjustment for several confounders (*e.g.*, sex, age, comorbidities, type of underlying HM, COVID-19 severity on admission, vaccination status), an increased likelihood of receiving an extended RDV course was observed in patients with HM of lymphocytic origin (*e.g.*, NHL, HL and CLL) [OR=13.83 (95%CI=2.64-72.53; p=0.002)].

Discussion

The present study aimed to evaluate the incidence of intubation, the probability of recovery and mortality, as well as the duration of RDV administration, in HM patients with COVID-19 after the implementation of mass-vaccination programs against SARS-CoV-2 in Greece. According to our analysis, which exclusively included HM patients hospitalized during the third (Delta-variant predominance) and fourth (Omicron-variant predominance) pandemic waves, an increased likelihood of intubation was recorded in obese patients, diagnosed with HM other than NHL, HL or CLL and having LDH>520 IU/l on admission. Additionally, patients with HM of lymphocytic origin were more likely to be administered RDV beyond the standard 5-day course. However, since the prolongation of RDV treatment was at the discretion of the treating physician, this association probably reflects the severity of COVID-19 and the persisting viral load on day five of treatment. However, the above essentially delineate the profile of frail HM patients at greater risk for COVID-19-related adverse events and suggest a therapeutic alternative. It is noteworthy that most of the studies exploring the impact of COVID-19 in HM patients were conducted on the first or second pandemic wave, during which there was a lack of effective therapeutic options and other variants with lower infectivity rate and higher morbidity prevailed. Therefore, they may not reflect the current situation.

A decoupling of intubation and mortality rates (8.3% for both) compared to previously published reports was also documented in our study (3-10). Out of the 60 patients analyzed, only five who presented with severe disease on admission progressed to MV and all of them eventually died. The observed rates are among the lowest recorded in the literature and may be attributable to early admission, the available treatment options, and the effect of mass-vaccination programs implemented in Greece including this vulnerable population. Of note, the therapeutic algorithm followed in our clinic included an extended RDV course in patients with a perceived greater risk for adverse events according to the literature, such as patients with NHL, HL or CLL and those with persisting high viral loads in the nasopharyngeal swab on day five of treatment. In EPICOVIDEHA, an international open web-based registry supported by the European Hematology Association, 593 HM patients infected with Omicron-variant were analyzed. The overall and attributable mortality were 31.2% and 22.2%, respectively, and proven to be age-dependent with higher rates observed among patients aged over 70 years (6). Similarly, of 115 HM patients infected early in 2022, who were either managed in an ambulatory clinic or hospitalized, 11 died (9.7%) (COVID-19-related: n=9, underlying disease: n=2) and in-hospital mortality was 16.9% (19). Following a COVID-19 outbreak in a hematological ward in February 2022, Taenaka and colleagues reported a mortality rate of 22% (20). Moreover, 3,473 haemato-oncological patients from 34 centers across three countries (UK, Spain, and Italy) were recruited in the OnCOVID European Study. Of them, 58.5% were diagnosed during the pre-vaccination phase, 31% during the Alpha-Delta phase and 10.5% during the Omicron phase. The 28-day fatality rate was 13% during Omicron-variant predominance, lower than in the pre-vaccination (29%) and Alpha-Delta phase (23.9%), yet higher than the mortality rate reported in our study (21). Mikulska and colleagues examined the outcomes of the early treatment of SARS-CoV-2 infection in HM patients and found a COVID-19-related mortality of 3.4%, which was as high as 21% in the pre-Omicron period and decreased to 2.3% in the Omicron era. Interestingly, in their cohort, the overall mortality doubled from day 30 to day 90 (22). A similar observation was made by Heldman and colleagues who examined mortality beyond day 28 in a group of 936 solid-organ transplant recipients; >20% of deaths occurred between 28 and 90 days following SARS-CoV-2 diagnosis (23). The indirect impact of COVID-19 on patients' survival, such as delayed or postponed oncological therapy, and later complications related to SARS-CoV-2 infection may have contributed to the delayed mortality observed in both studies.

To the best of our knowledge, this is the first study to report experience with the administration of an extended RDV treatment course in hospitalized HM patients with COVID-19. Despite the discordant trial outcomes, RDV is the first antiviral drug authorized by regulatory bodies (*e.g.*, U.S Food

and Drug Administration, European Medicines Agency) for the treatment of hospitalized COVID-19 patients who are either in need of conventional oxygen therapy, high-flow nasal cannula oxygen therapy or non-invasive mechanical ventilation or are considered at high risk of progressing to severe COVID-19 even if they do not require oxygen supplementation yet (24, 25). Data on the routine use of RDV in oncological and HM patients are scarce and derived from small observational studies and case series, since this subset of patients is usually excluded from clinical trials or underrepresented. For instance, in the Adaptive COVID-19 Treatment Trial-1 (ACTT-1), the main study that focused on time to recovery and paved the pathway for RDV authorization, approximately 8% of the population consisted of cancer patients (26). A total of 313 HM patients were analyzed in a multicenter retrospective study designed by Levy and colleagues, and RDV was independently associated with lower mortality risk (p=0.021) (27). Furthermore, the potential role of COVID-19 treatments in patients with invasive cancer and laboratory-confirmed SARS-CoV-2 infection was evaluated in a large observational study that comprised 2,186 adults, of whom 470 were diagnosed with HM. RDV alone led to a lower 30-day all-cause mortality rate than other treatments, such as high-dose corticosteroids and tocilizumab, but the reported trend was not statistically significant (28). In an international multicenter study of 3,966 COVID-19 patients, primarily designed to evaluate 30-day mortality in patients with (n=1,115) or without cancer (n=2,851), RDV was the only therapeutic agent that independently decreased 30-day all-cause mortality in the entire population (p=0.036), including the oncological patients [OR=0.44 (95%CI=0.20-0.96; p=0.04)]. Of note, in line with ACTT-1 findings, RDV benefit was more pronounced in patients with pneumonia and mild hypoxia who were receiving low-flow oxygen (≤6 l/min) (26, 29). Lastly, the contributing factors to increased mortality in cancer patients were sought in the real-world CSOVID-19 study and 222 haemato-oncological patients (HM: n=60, other type of malignancy: n=162) with active disease were analyzed. RDV prompt and timely initiation resulted in an 80% reduction in early mortality (30). The aforementioned studies focused on the benefits or optimal timing of RDV administration, but none of them explored the potential effect of duration of RDV on immunocompromised patients that are prone to longer and more severe disease course and may experience prolonged viral shedding. Given that continuing viral evolution represents a major threat, partially or unsuccessfully treated HM patients may be an emerging source of new variants. Garcia and colleagues stated that 1 in 4 HM patients of their cohort presented prolonged viral replication, which was more common among patients with lymphoma, hypogammaglobinemia or prior chemotherapy intake (14). Likewise, a retrospective study of 328 HM patients with mild or moderate COVID-19, mostly infected during the Omicron-variant period, documented that even in case of early treatment, 12% were still SARS-CoV-2-positive beyond day 30 and male sex, comorbidities and HM of lymphocytic origin (*e.g.*, NHL or CLL) were the key determinants of prolonged viral shedding (22). Consequently, a personalized diagnostic approach and specific therapeutic strategies, including extended antiviral therapy with RDV, seem necessary to address this critical issue.

Serum LDH is a well-established prognostic biomarker for several hematological diseases and solid tumors (31, 32). In HL and NHL patients, elevated LDH has been recognized as a survival predictor and is eventually listed as a risk factor in both the age-adjusted International Prognostic Index (IPI) and IPI for NHL (31, 33, 34). In the case of COVID-19, among diverse biomarkers that potentially herald disease severity, elevated serum LDH was strongly correlated with unfavorable outcomes (35, 36). Additionally, Kojima and colleagues recently identified LDH [HR=1.003, (95%CI=1.001-1.005)] as a factor independently associated with the development of severe COVID-19 pneumonia (37). In our cohort, LDH>520 IU/L on admission was shown to drive the risk of intubation, thus it may be useful in clinical practice for the screening and risk stratification for developing subsequent severe disease in HM patients.

A surprising result of our study was the impact of dexamethasone on the probability of recovery. Specifically, dexamethasone was associated with a diminished probability of recovery, particularly in the subset of patients with mild/moderate COVID-19, even if it was administered according to the National and International recommendations reflecting studies that highlight its beneficial role (24, 38-40). In a cohort of 222 haemato-oncological patients, dexamethasone resulted in worse prognosis and higher early in-hospital mortality (p=0.0243), but its significance was lost in multivariate analysis (p=0.2824). It is noteworthy that in this study, dexamethasone was introduced relatively early, during the first 5 days from diagnosis (median 2 days) (30). On the contrary, in our clinic and according to the International and National algorithms for the therapeutic management of hospitalized COVID-19 patients with severe disease, dexamethasone was administered after the 7th day of symptoms onset (24, 41, 42). Based on this, the association of dexamethasone with a worse prognosis casts doubt on whether HM patients are good candidates for the same therapeutic algorithm as non-HM-patients. These findings point out the difficulty in the management of HM patients and the uncertainty about which component, viral or inflammatory, is primarily responsible for their clinical deterioration and thereby which therapeutic approach is most appropriate.

The results of the present study should be interpreted and generalized with caution as they are subject to certain limitations. First, we conducted a retrospective analysis of a small number of HM patients that were consecutively

Table I. *Study population baseline characteristics*.

	Severe disease (n=37)	Mild/Moderate disease (n=23)	Total (n=60)	*p*-Value
Age (median, IQR)	71 (64.77)	72 (47.77)	71 (58.77)	0.280
Age ≥65 yo (%)	27 (72.97)	13 (56.52)	40 (66.67)	0.189
Sex		0.887		
Female (%)	20 (54.05)	12 (52.17)	32 (53.33)	
Type of HM		0.826		
NHL	15 (40.54)	9 (39.13)	24 (40)	
HL	1 (2.7)	2 (8.7)	3 (5)	
CML	2 (5.41)	0	2 (3.33)	
CLL	8 (21.62)	4 (17.39)	12 (20)	
Myelofibrosis	3 (8.11)	1 (4.35)	4 (6.67)	
Essential thrombocythemia	2 (5.41)	1 (4.35)	3 (5)	
MDS	2 (5.41)	3 (13.04)	5 (8.33)	
Multiple myeloma	2 (5.41)	1 (4.35)	3 (5)	
Polycythemia vera	1 (2.7)	0	1 (1.67)	
Waldenström macroglobulinemia	1 (2.7)	1 (4.35)	2 (33.33)	
AML	0	1 (4.35)	1 (1.67)	
Years since diagnosis (median, IQR)	3 (1-7)	3 (1-5)	3 (1-6)	0.855
Status of underlying disease				0.507
Under initiation treatment	17 (45.95)	10 (43.48)	27 (45)	
Under maintenance therapy	13 (35.14)	6 (26.09)	19 (31.67)	
Under surveillance- not receiving treatment	7 (18.92)	6 (26.09)	13 (21.67)	
Last/ongoing treatment		0.719		
Anti-CD20 monotherapy	5 (13.51)	5 (21.74)	10 (16.67)	
JAK inhibitors	2 (5.41)	1 (4.35)	3 (5)	
BTK inhibitors	4 (10.81)	0 (0)	4 (6.67)	
Anti-CD20 antibodies & other	6 (16.22)	3 (13.04)	9 (15)	
JAK inhibitors & other	1 (2.7)	0 (0)	1 (1.67)	
BTK inhibitors & other	1 (2.7)	1 (4.35)	2 (3.33)	
Allogeneic stem cell transplantation	0 (0)	1 (4.35)	1 (1.67)	0.201
Autologous stem cell transplantation	3 (8.33)	0 (0)	3 (5.08)	0.155
Chemoprophylaxis intake at home	14 (37.83)	10 (43.47)	24 (40)	0.388
Long-term corticosteroid therapy as part of the oncological treatment	9 (24.32)	5 (21.74)	14 (23.33)	0.818
Comorbidities				
Hypertension	15 (40.54)	8 (34.78)	23 (38.33)	0.656
Diabetes	7 (18.92)	6 (26.09)	13 (21.67)	0.512
Obesity	5 (13.51)	0 (0)	5 (8.33)	0.066
COPD	4 (10.81)	1 (4.35)	5 (8.33)	0.379
CAD	3 (8.11)	3 (13.04)	6 (10)	0.536
Established CVD	5 (13.51)	1 (4.35)	6 (10)	0.250
Dyslipidemia	11 (29.73)	6 (26.09)	17 (28.33)	0.761
Number of co-existing comorbidities	1 (0-3)	1 (0-2)	1 (0-2.5)	0.533
COVID-19 vaccination				0.430
Unvaccinated	14 (37.84)	8 (34.78)	22 (36.67)	
Partially vaccinated (≤2 doses)	5 (13.51)	0	5 (8.33)	
Fully vaccinated (3 doses)	15 (40.54)	11 (47.83)	26 (43.33)	
Boosted vaccinated (>3 doses)	3 (8.11)	4 (17.39)	7 (11.67)	
Previous documented SARS-CoV-2 infection	5 (13.51)	2 (8.70)	7 (11.67)	0.572
Time (months) since prior to SARS-CoV-2 infection (median, IQR)	1.1 (0.7-4.7)	9.4 (8-10.9)	4.6 (0.8-8)	0.064
Pre-admission COVID-19 treatment				
Antibiotics	9 (24.32)	1 (4.34)	10 (16.66)	0.315
Dexamethasone	2 (5.41)	0 (0)	2 (3.51)	0.290
Number of co-existing symptoms (median, IQR)	1 (0.5-2)	0 (0-1)	1 (0-2)	0.050
Time interval (days) from symptoms onset to hospital admission (median, IQR)	5 (1-8)	5 (2-8)	5 (1-8)	0.987

Table I. *Continued*

Table I. *Continued*

	Severe disease (n=37)	Mild/Moderate disease (n=23)	Total (n=60)	*p*-Value
Baseline severity				<0.0001
Not requiring supplemental oxygen	2 (5.41)	23 (100)	25 (41.67)	
Requiring supplemental oxygen *via* nasal cannula or Venturi mask	31 (83.78)	0	31 (51.66)	
On non-rebreather mask or HFNC	4 (10.81)	0	4 (6.66)	
CT scan findings				
No infiltrates	0	7 (30.43)	7 (11.66)	
Barely marked infiltrates	1 (2.7)	3 (13.04)	4 (6.66)	
GGOs bilaterally	12 (32.43)	16 (69.56)	28 (46.66)	
GGOs & consolidations bilaterally	9 (24.32)	7 (30.43)	16 (26.66)	
COVID-19 treatment				
Remdesivir	37 (100)	23 (100)	60 (100)	
Dexamethasone	19 (51.35)	2 (8.69)	21 (35)	0.001
Tocilizumab	5 (13.51)	0 (0)	5 (8.33)	0.066
Anakinra	1 (2.70)	0 (0)	1 (1.66)	0.437
Baricitinib	3 (8.1)	0 (0)	3 (5)	0.155
IVIG	4 (10.81)	1 (4.35)	5(8.33)	0.379
Antimicrobial therapy	26 (70.27)	9 (39.13)	35 (58.33)	0.017
Anticoagulation therapy	31 (83.78)	22 (95.65)	53 (83.33)	0.198

AML: Acute myeloid leukemia; BTK: Bruton tyrosine kinase; CAD: coronary artery disease; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; GGO: ground-glass opacity; HL: Hodgkin's lymphoma; HM: hematological malignancy; IVIG: intravenous immune globulin; IQR: interquartile ranges; JAK: Janus kinase; MDS: myelodysplastic syndromes; NHL: Non-Hodgkin's lymphoma.

hospitalized in our clinic during the Delta- and Omicron-pandemic waves. Although we evaluated the effect of the extended RDV course in the clinical outcomes of HM patients, we did not collect nasopharyngeal swabs at the time of RDV treatment initiation or completion, thus it is uncertain whether SARS-CoV-2 PCR negativization was achieved in the respiratory samples and patients were successfully treated. Last, we performed survival analyses with censoring at 15 and 30 days and we did not consider delayed mortality, which is frequent in HM patients.

Conclusion

In the era of Omicron-variant predominance, our study in a population with HM revealed a crude mortality of 8.3% which is lower than the rates reported from large databases. An increased likelihood of intubation was recorded in obese patients, diagnosed with HM than NHL, HL or CLL and having LDH >520 IU/l on admission.

Despite the widespread of mass-vaccination programs worldwide and the continuing evolution of COVID-19 therapeutics, patients with HM represent a frail population probably requiring more targeted therapies according to their viral replication profile and their specific inflammatory response to COVID-19.

Table II. *Multivariate logistic regression analysis of factors associated with intubation.*

	OR	95%CI	*p*-Value
Female *vs*. males	0.45	0.04-4.61	0.499
Age ≥65 years old	0.12	0.01-2.57	0.177
Obesity	26.09	1.37-497.78	0.030
NHL or HL or CLL	0.05	0.01-0.81	0.035
LOS	1.09	0.92-1.29	0.311

CI: Confidence interval; CLL: chronic lymphocytic leukemia; HL: Hodgkin's lymphoma; LOS: length of hospital stay; NHL: Non-Hodgkin's lymphoma; OR: odds ratio.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, V.R.; A.P. and G.P.; methodology, V.R.; A.P. and G.P.; software, V.R.; validation, V.R.; formal analysis, G.K. and E.P.; investigation, V.R; A.P.; G.K.; M.E.L; P.A; and E.P; data curation, V.R.; writing—original draft preparation, V.R.; writing—review and editing, A.P.; G.K.; M.E.L.; P.A.; E.P.; N.K.S.; N.S.; A.C. and G.P.; visualization, V.R.; supervision, G.P.; All Authors have read and agreed to the published version of the manuscript.

Table III. *Logistic regression analysis of clinical and laboratory parameters associated with intubation and their cut-off values.*

	Univariate			Multivariate		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
PaO_2/FiO_2<300	13.14	2.02-85.65	0.007	7.72	0.35-170.92	0.196
CRP >8 mg/dl	7	1.14-42.97	0.036	9.27	0.24-356.57	0.232
Creatinine >1.2 mg/dl	8.8	1.41-54.91	0.020	4.28	0.09-206.67	0.463
SGOT >37 IU/l	19.55	2.07-184.86	0.010	6.37	0.25-162.84	0.263
LDH >520 IU/l	50	4.46-560.28	0.002	24.39	1.19-499.82	0.038

CI: Confidence interval; CRP: c-reactive protein; FiO2: fraction of inspired oxygen; LDH: lactate dehydrogenase; OR: odds ratio; PaO2: arterial oxygen pressure; SGOT: serum glutamic-oxaloacetic transaminase.

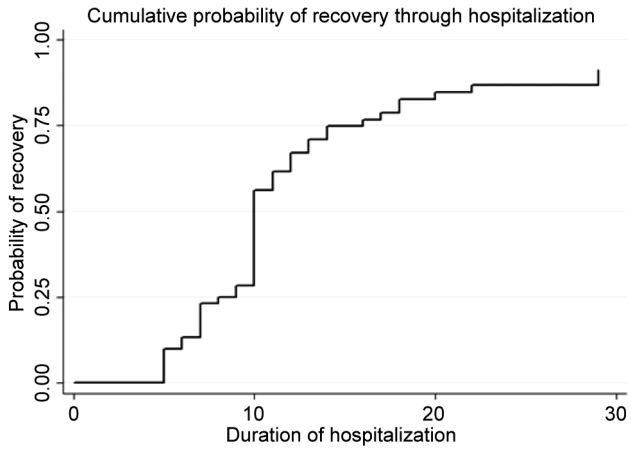

Figure 1. *Cumulative probability of recovery through hospitalization.*

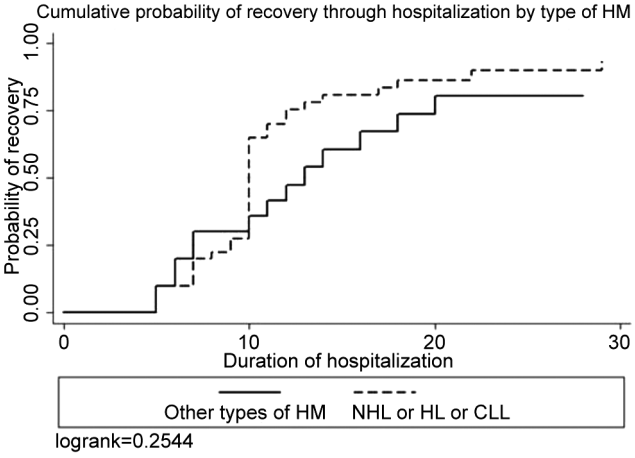

Figure 3. *Cumulative probability of recovery by type of HM [Non-Hodgkin's lymphoma (NHL)/Hodgkin's lymphoma (HL), chronic lymphocytic leukemia (CLL) vs. other].*

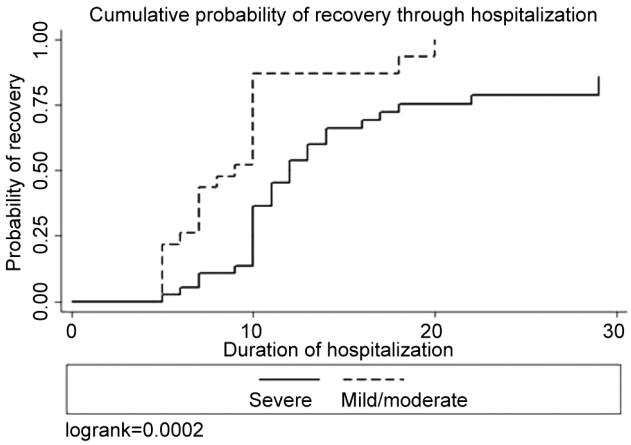

Figure 2. *Cumulative probability of recovery by COVID-19 severity on admission (mild/moderate vs. severe disease).*

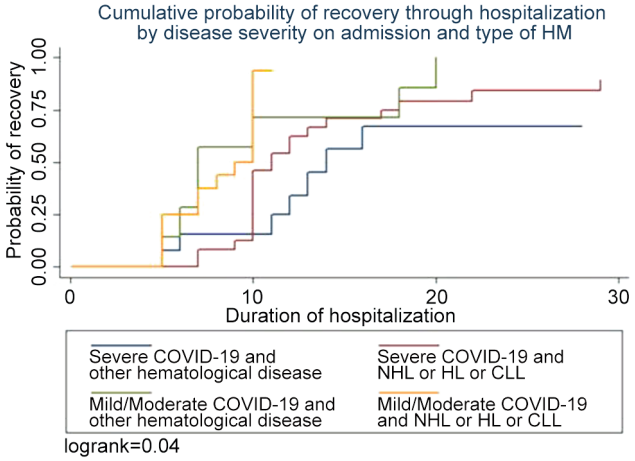

Figure 4. *Cumulative probability of recovery by type of HM and COVID-19 severity on admission.*

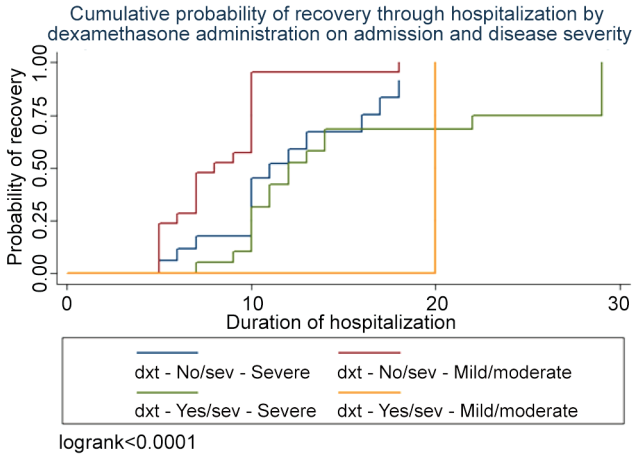

Figure 5. *Cumulative probability of recovery by dexamethasone administration and disease severity on admission.*

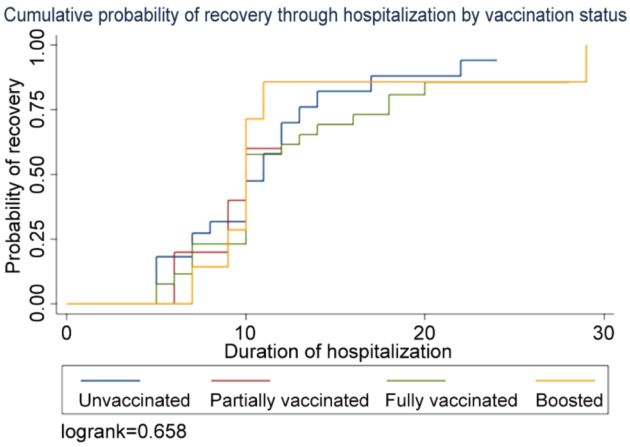

Figure 6. *Cumulative probability of recovery by time since hospital admission and 4-scale vaccination status.*

Table IV. *Cox regression analysis of factors associated with the probability of recovery.*

	HR	95%CI	*p*-Value
			0.0018
Female *vs*. Males	0.61	0.34-1.09	0.095
Number of co-existing comorbidities	0.83	0.69-1.00	**0.050**
NHL or HL or CLL *vs*. other types of HM	1.29	0.66-2.50	0.451
Mild/Moderate *vs*. Severe disease on admission	3.12	1.68-5.80	**<0.001**
Being vaccinated	0.88	0.48-1.59	0.664

CI: Confidence interval; CLL: chronic lymphocytic leukemia; HL: Hodgkin's lymphoma; HM: hematological malignancy; HR: hazard ratio; NHL: Non-Hodgkin's lymphoma. Statistically significant *p*-values are shown in bold.

Table V. *Multivariate logistic regression of factors associated with extended RDV treatment course.*

	OR	95%CI	*p*-Value
			0.001
Female *vs*. males	2.99	0.65-13.59	0.159
Age	1.02	0.97-1.37	0.506
Number of comorbidities	0.83	0.51-1.37	0.472
Mild/Moderate disease *vs*. Severe	0.23	0.04-1.20	0.081
NHL or HL or CLL *vs*. other HM type	13.83	2.64-72.53	**0.002**
Partially vaccinated	0.27	0.02-4.74	0.370
Fully vaccinated	2.71	0.56-13.16	0.217
Vaccinated with a boosting dose	13.92	0.49-394.64	0.123
Dexamethasone receipt	2.50	0.47-13.23	0.282

CI: Confidence interval; CLL: chronic lymphocytic leukemia; HL: Hodgkin's lymphoma; HM: hematological malignancy; OR: odds ratio; NHL: Non-Hodgkin's lymphoma. Statistically significant *p*-values are shown in bold.

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