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LETTER TO THE EDITOR

High mortality in fully vaccinated hematologic patients treated with anti-CD20 antibodies during the "Omicron wave" of COVID-19 pandemic

COVID-19 has severely hit hematological patients causing excess mortality. In Brescia (Italy), one of the first area interested by the pandemic, as well as in Italy, the COVID-19 attributable mortality was 37%–39% in March 2020.[1,2]

After this very heavy first wave, the severity of COVID-19 has weakened during subsequent periods starting as early as in April and May 2020.[3]

Nonetheless, during autumn and winter 2020–2021, before vaccination became available, COVID-19 mortality was still remarkable causing death of 25% of hematological patients.[4]

Mortality occurred in every type of hematological disorder; chronic myeloproliferative neoplasms were the only disorders relatively spared. Fatality rate was as high as 50% in acute leukemias (AL) and 56% in myelodysplastic-myeloproliferative syndromes (MDS-MPS). Age and active treatment were adverse prognostic factors.[1]

Vaccination against SARS-CoV2 virus became available on a large scale in Italy early in 2021. Hematological patients were included among at risk categories and were prioritized to receive two doses of mRNA vaccine starting in March 2021. A third dose was given as booster 6 months in autumn 2021.

During the pandemic evolution SARS-CoV-2 viral strains have changed and the recent Omicron variant was proclaimed a variant of concern by the WHO on 26 November 2021. It spread very rapidly in Italy and became the predominant strain causing a significant increase in the number of infected persons. By the end of January 2022, the variant was isolated in over 95% of newly infected subjects.

The clinical severity of the Omicron variant was markedly lower compared to earlier variants, probably because of protection conferred by a significant degree of preexisting immunity owing to vaccination or previous infection. As compared to the Delta variant it required hospitalization in 1.75% versus 3.95% of infected subjects. ICU admission occurred in 0.26% versus 0.78% and mechanical ventilation in 0.07% versus 0.43% of patients, respectively. Vaccination status was associated to reduced ICU stay and mortality.[5] The mortality rate of the Omicron "wave" of COVID-19 among hospitalized patients was 3.4%.[6]

We have been prospectively registering and following all hematological patients managed at our Institution since the early onset of the pandemic in March 2020. The study was approved by the local Ethical Committee. Between 1 December 2021 and 31 January 2022, a new SARS-CoV2 infection was documented in 94 patients, a number quite similar to the first pandemic wave. SARS-CoV-2 genotyping was performed in 19 patients and it confirmed that the Omicron variant was predominant (16, 84%). Ninety-two percent of patients had received a full vaccination course and 42% also the booster dose. While during the first COVID wave we observed a hospitalization rate of 98%, only 40 of 94 patients (43%) needed hospital admission during the Omicron wave, confirming a significantly lower severity ($p < 0.0001$).

The fatality rate was also lower, but it still reached a worrisome 12% of the entire cohort, as 11 of 94 patients died of COVID, and it was 28% among hospitalized patients (11/40). These figures are markedly higher than those recorded in the general population infected during the same period, with a five times higher probability of death, underscoring the high vulnerability of hematological patients who remain a very frail category, one of the more severely hit by COVID-19. Vaccination status did not impact on mortality, as none of the non-vaccinated patients died, whereas 8 (17%) out of 47 who received two vaccine doses and 3 (8%) out of 39 who also received the booster dose died of COVID-19 ($p = 0.33$). Data concerning COVID-19 specific treatment were only partially available. In detail, 2 out of 19 patients who received monoclonal antibodies and none of the 12 treated with remdesivir died.

Interestingly, comparing the most recent data with those reported during the first wave in March 2020,[1] we noted that the epidemiological scenario of COVID-19 in hematological patients has markedly changed. Although age, M/F ratio, frequency of hematologic disorders, disease status, and ongoing treatment did not change in the two cohorts (Table 1), the fatality rate was 0% among patients with multiple myeloma (MM), MDS-MPS or non-neoplastic hematological disorders, whereas it remained high in AL (3/12, 25%), in chronic lymphoproliferative disorders (CLD, 2/6, 33.3%) and, although less pronounced, in lymphoma (6/38, 15.7%) (Figure 1). All patients deceased during the Omicron wave were aged ≥70, whereas in the first wave 35% of patients were less than 70. Moreover, all lymphoma patients died had received anti-CD20 MoAb and 50% of them also bendamustine. Mortality was particularly high among lymphoma patients who had received rituximab (R) in the previous 6 months (5/13, 39%) and among patients who had received rituximab and bendamustine in combination (4/9, 44%).

TABLE 1 Patients' characteristics in the two cohorts

Patients	March 2020[1] (*N* = 102)	Dec 2021–Jan 2022 (*N* = 94)
Male sex	66 (64.7%)	56 (59.6%)
Age≥70 years	51 (50%)	49 (52.1%)
Hematological disease		
• AL	• 8 (7.8%)	• 12 (12.8%)
• MDS-MPS	• 16 (15.7%)	• 17 (18.1%)
• Lymphoma	• 42 (42.2%)	• 38 (40.4%)
• Multiple Myeloma	• 18 (117.6)	• 14 (14.9%)
• Chronic lymphoproliferative disorders	• 11 (10.8%)	• 6 (6.4%)
• Non-malignant hematological disease	• 7 (6.9%)	• 7 (7.4%)
Hematological disease status		
• Diagnosis	• 16 (15.7%)	• 12 (12.8%)
• Remission	• 40 (39.2%)	• 39 (41.5%)
• Stable disease	• 24 (23.5%)	• 22 (23.4%)
• Relapse/refractory	• 22 (21.6%)	• 21 (22.3%)
Active chemo/immunosuppressive therapy	60 (58.8%)	62 (66%)

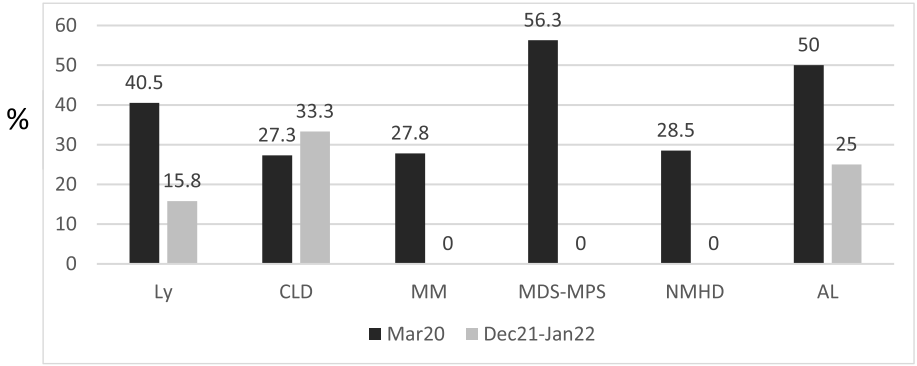

FIGURE 1 COVID-related mortality according to hematologic disease. The black bars refer to mortality rate observed in March 2020; the gray bars to that observed in December 2021 and January 2021 ("Omicron wave")

Considering patients with lymphoma and CLD, the fatality rate decreased from 38% during the first wave to 18% during the "Omicron wave" (Fisher's: $P = 0.1$), whereas in other hematologic disorders it decreased significantly from 43% to 6% ($P < 0.0001$). Treatment given was crucial. All lymphoma patients dead had received anti-CD20 MoAb and 50% of them also bendamustine. Mortality was highest in nine patients treated with both anti-CD20 MoAb and bendamustine (44%).

Limitations of these observations are their single center origin, the limited number of cases and lack of data on response to vaccination. However, the demonstrated lack of humoral response to COVID-19 in patients treated with anti-CD20 MoAb[7] and the recent metaanalysis[8] of 44 studies in over 7000 hematological patients showing overall neutralizing antibody response of 57%–60% and cellular response rates of 40%–75% to vaccination indirectly support our results. Moreover, bendamustine, an agent inducing marked lymphopenia, could also contribute to an impairment in cellular immune defense mechanisms. Preliminary data on hematological COVID-19 vaccinated patients confirm a higher risk of death compared to vaccinated controls,[9] although the percentage of deceased patients apparently decreased.[10]

In conclusion, these data show that selected hematological patients remain highly vulnerable to COVID-19 and frequently die from the purportedly less severe "Omicron" variant of SARS-CoV2, even if fully vaccinated. These observations need to be confirmed on larger number of cases and may significantly impact on vaccination policies as well as on hematological treatment programs.

KEYWORDS
COVID-19, hematological malignancies, Omicron wave, outcome

CONFLICT OF INTEREST

The authors declare no competing financial interests.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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