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# COVID-19 in patients with lymphoproliferative diseases during the Omicron variant surge

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Despite extensive research on the outcome of hematologic patients during the COVID-19 pandemic, data on the Omicron outbreak are lacking. Here we report the clinical outcome of 131 hematologic patients with lymphoproliferative diseases, infected with SARS-CoV-2 during the Omicron surge in Israel, between January and March 2022. The patients were predominantly males (n = 95, 72.5%) with a median age of 68 (IQR 57–68) years. Fifty-nine (45.0%) patients had non-Hodgkin lymphoma (NHL), 36 (27.5%) multiple myeloma (MM), and 36 (27.5%) chronic lymphocytic leukemia (CLL); 68 (51.1%) were actively treated. Nineteen (14.5%) patients presented with severe/critical disease, and 35 (26.7%) required hospitalization after SARS-CoV-2 infection. In multivariate analysis, risk factors for hospitalization included active treatment (OR 2.9, 95% CI 1.2–6.9, p = 0.018) and CLL (OR 2.7, 95% CI 1.1–6.4, p = 0.025). Seven patients (5.3%) died from COVID-19 within 30 days of diagnosis, including 5 (71.4%) patients with CLL (13.9% of all patients with CLL [5/36], and 31.3% of all hospitalized CLL patients [5/16]). In conclusion, the outcomes in patients with lymphoproliferative diseases infected with the SARS-CoV-2 during the Omicron surge appear to be better than previously reported. However, patients who are actively treated and especially those with CLL are still at increased risk for severe disease, hospitalization need, and death.

Since the emergence of the SARS-CoV-2 Omicron variant of concern (VoC) in early November 2021, it has become the dominant variant in large parts of the world, whereas at the beginning of February 2022 it accounted for 99.9% of the total number of SARS-CoV-2 infections in the United States (COVID data tracker: Variant proportions). Recent studies suggested that infection with the Omicron VoC resulted in a milder COVID-19 (Christensen et al., 2022; Nyberg et al., 2022). However, data on the Omicron infection in patients with hemato-oncologic malignancies are lacking, and the potential efficacy of early administration of antiviral therapies in this setting is not fully elucidated. Herein, we report the clinical course and outcomes of patients with lymphoproliferative malignancies infected with SARS-CoV-2 during the Omicron VoC surge in Israel.

This retrospective single-center study included patients with lymphoproliferative malignancies (NHL, CLL, and MM) who were diagnosed with SARS-CoV-2 infection during the Omicron outbreak in Israel, between January and March 2022. The diagnosis of SARS-CoV-2 infection was confirmed by a positive reverse transcription-polymerase chain reaction assay on nasopharyngeal swabs. COVID-19 severity was graded according to the Israeli ministry of health guidelines (supplemental information). Clinical characteristics and laboratory data were obtained from the patients' medical records. The study was approved by the local institutional Helsinki ethics committee. For statistical analysis, see supplemental information.

A total of 131 patients with lymphoproliferative malignancies were included (patients' baseline demographic and disease characteristics are summarized in Table S1A). The patients were predominantly males (n = 95, 72.5%) with a median age of 68 (IQR 57.0–68.0) years, and most of the patients (n = 92, 70.2%) had at least one comorbidity that most commonly included hypertension (n = 51, 38.9%) and type 2 diabetes mellitus (n = 35, 26.7%) (Table S1B).

The majority of patients had B cell NHL (n = 59, 45.0%), followed by MM (n = 36, 27.5%) and CLL (n = 36, 27.5%). Sixty-eight patients (51.9%) were actively treated for lymphoproliferative malignancies at the time of COVID-19 or within the prior 3 months, 44 patients (33.6%) were previously treated, and 19 patients (14.5%) were treatment naive. Overall, 69 patients (52.7%) have been previously exposed to anti-CD20 therapy, of them 30 (43.5%) within 12 months prior to the diagnosis of SARS-CoV-2 infection.

One hundred and seventeen patients (89.3%) had symptoms, which most commonly included fatigue (n = 72, 55.0%), cough (n = 61, 46.6%), and fever (n = 44, 33.6%) (Table S1C). One hundred and twelve patients (85.5%) were presented with mild to moderate disease and 19 patients with severe/critical disease (14.5%) (Table S1D). All patients with severe/critical COVID-19 were males (n = 19, 100%), with a median age of 69.5 years (IQR 58.5–75.25); 10 (52.6%) had CLL, 15 (79%) were actively treated, and 12 (63.2%) had a substantial burden of two or more comorbidities.

Of the 124 patients with a known COVID-19 vaccination status, 108 (87.1%) were vaccinated with three or four doses (n = 58, 53.7%; or n = 50, 46.3%, respectively). Fifty-five patients

(42.0%) were tested for anti-spike IgG levels after receiving at least two vaccine doses, and 36 (65.5%) were seronegative. Among the 123 patients with available data on anti-COVID-19 treatment, 50 (40.7%) were treated with oral antiviral drugs (paxlovid and molnupiravir given to 38 and 11 patients, respectively; and one patient was treated with sotrovimab outside of Israel).

Thirty-five patients (26.7%) were admitted to the hospital due to COVID-19, with a median hospitalization duration of 6 days (IQR 4.0–9.75). Most hospitalized patients were males (n = 30, 85.7%), with a median age of 72 years (IQR 64.0–80.8) (Table S1E). Sixteen patients (45.7%) had CLL, 10 (28.6%) NHL, and 9 (25.7%) MM, and 25 patients (71.4%) were actively treated. Of 17 hospitalized patients previously tested for anti-spike IgG levels, 12 (70.6%) were seronegative. Twenty-two patients (62.9%) required oxygen support, including 5 (22.7%) who needed mechanical ventilation.

Only 11 (31.4%) of the hospitalized patients were treated with oral anti-COVID-19 treatment prior to their hospitalization. During hospitalization, 23 patients (65.7%) were treated with dexamethasone, 17 (48.6%) with remdesivir, 4 (11.4%) with remdesivir plus tocilizumab or baricitinib, and 4 (11.4%) with tocilizumab or baricitinib.

In univariate analyses (Table S1E), the statistically significant risk factors for COVID-19 hospitalization were male sex (OR = 2.86, 95% CI 1.01–8.09, p = 0.041), hypertension (OR = 2.4, 95% CI 1.1–5.2, p = 0.030), diagnosis of CLL (OR = 3.2, 95% CI 1.4–7.3, p = 0.005), and active hematologic treatment (OR = 3.1, 95% CI 1.3–7.1, p = 0.007). In multivariate analysis, the independent variables that retained statistically significance included active hematologic treatment (OR 2.9, 95% CI 1.2–6.9, p = 0.018) and CLL (OR 2.7, 95% CI 1.1–6.4, p = 0.025) (Table S1G). In univariate analysis confined to patients with CLL, anti-CD20 therapy (OR 4.5, 95% CI 1.1–19.0, p = 0.036) and lack of pre-hospitalization antiviral treatment (paxlovid or molnupiravir) (OR 5.3, 95% CI 1.2–23.3, p = 0.024) were the significant risk factors for hospitalization (Table S1H).

During the follow-up period (median 73 days, IQR 54.0–81.5), a total of seven patients (5.3%) died from COVID-19 within 30 days of diagnosis. Of the deceased patients (n = 7), 5 patients (71.4%) had CLL [13.9% of all patients with CLL (5/36), and 31.3% of all hospitalized CLL patients (5/16)], 1 had NHL, and 1 had MM. Their median age on COVID-19 detection was 68 years (IQR 58.5–76.0), all were males, and 6 (85.7%) had hypertension. The majority (n = 6, 85.7%) were actively treated (2 treated with BTKis and 2 with venetoclax plus rituximab for CLL, 1 with bendamustine plus rituximab for NHL and 1 with daratumumab plus dexamethasone for MM). None of the patients received an anti-COVID-19 treatment prior to hospitalization, and 1 patient was not vaccinated. Three patients with known anti-spike IgG levels were all seronegative.

In summary, in our entire cohort of patients with lymphoproliferative diseases, the overall mortality (~5%) from COVID-19 during the Omicron outbreak appears to be lower than previously reported in the pandemic of other VOCs. During the early phase of the pandemic, the reported risk of death in patients with hematologic malignancies was 34% (Vijenthira et al., 2020), while the 30-day mortality rate in vaccinated patients with hematologic malignancies has been reported to be 12.5% (Pagano et al., 2022). The apparent decrease in mortality during the Omicron outbreak may be attributed to improved clinical management overtime, including administration of one to two vaccine boosters and new antiviral therapies. Nevertheless, the mortality rates in patients with CLL seem to remain high (~14 versus ~2% and ~3% in patients with NHL and MM, respectively), especially among hospitalized patients (31.3%) and are similar to that reported in the earlier period of the pandemic in this patient population (Chatzikonstantinou et al., 2021; Mato et al., 2020; Roeker et al., 2021; Scarfo et al., 2020). Accordingly, more patients with CLL (45.7%) were hospitalized due to COVID-19 compared to NHL (28.5%) and MM (25.7%) patients. The worse outcome in patients with CLL is consistent with their poor response to COVID-19 vaccination (Herishanu et al., 2021, 2022) and especially in those who are actively treated with B cell-directed therapies.

We were unable to demonstrate that early treatment with paxlovid or molnupiravir improved outcomes in our entire cohort, and it may have been due to a relatively small number of patients receiving these drugs. However, we found that these antiviral drugs reduced the risk of hospitalization in patients with CLL, possibly because they are particularly vulnerable to COVID-19.

In conclusion, our study demonstrates improved outcomes in patients with lymphoproliferative diseases infected with the SARS-CoV-2 during the Omicron VoC surge compared to that reported during the prior outbreaks of the pandemic. However, patients who are actively treated and especially those with CLL are still at increased risk for severe disease, need for hospitalization and death.

## SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2022.04.015.

## DECLARATION OF INTERESTS

Y.H. reports honoraria from Janssen, AbbVie, Roche, Astra-Zeneca, and Medision, not related to this study. I.A. reports speaker's bureau for Gilead, Novartis, AbbVie, and Janssen and served as a consultant for Janssen, MSD, AbbVie, Novartis, and Roche, not related to this study. The other authors declare no competing interests.

## REFERENCES

Chatzikonstantinou, T., Kapetanakis, A., Scarfo, L., Karakatsoulis, G., Allsup, D., Cabrero, A.A., Andres, M., Antic, D., Baile, M., Baliakas, P., et al. (2021). COVID-19 severity and mortality in patients with CLL: an update of the international ERIC and Campus CLL study. Leukemia *35*, 3444–3454. https://doi.org/10.1038/s41375-021s4101450-8.

Christensen, P.A., Olsen, R.J., Long, S.W., Snehal, R., Davis, J.J., Ojeda Saavedra, M., Reppond, K., Shyer, M.N., Cambric, J., Gadd, R., et al. (2022). Signals of significantly increased vaccine Breakthrough, decreased hospitalization rates, and less severe disease in patients with Coronavirus disease 2019 Caused by the omicron variant of severe Acute Respiratory Syndrome Coronavirus 2 in Houston, Texas. Am. J. Pathol. *192*, 642–652. https://doi.org/10.1016/j.ajpath.2022.01.007.

Herishanu, Y., Avivi, I., Aharon, A., Shefer, G., Levi, S., Bronstein, Y., Morales, M., Ziv, T., Shorer Arbel, Y., Scarfo, L., et al. (2021). Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood *137*, 3165–3173. https://doi.org/10.1182/blood.2021011568.

Herishanu, Y., Rahav, G., Levi, S., Braester, A., Itchaki, G., Bairey, O., Dally, N., Shvidel, L., Ziv-Baran, T., Polliack, A., et al.; on behalf of the Israeli CLL Study Group (2022). Efficacy of a third BNT162b2 mRNA COVID-19 vaccine dose in patients with CLL who failed standard 2-dose vaccination. Blood *139*, 678–685. https://doi.org/10.1182/blood.2021014085.

Mato, A.R., Roeker, L.E., Lamanna, N., Allan, J.N., Leslie, L., Pagel, J.M., Patel, K., Osterborg, A., Wojenski, D., Kamdar, M., et al. (2020). Outcomes of COVID-19 in patients with CLL: a multicenter

international experience. Blood *136*, 1134–1143. https://doi.org/10.1182/blood.2020006965.

Nyberg, T., Ferguson, N.M., Nash, S.G., Webster, H.H., Flaxman, S., Andrews, N., Hinsley, W., Bernal, J.L., Kall, M., Bhatt, S., et al. (2022). Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet *399*, 1303–1312. https://doi.org/10.1016/s0140-6736(22)00462-7.

Pagano, L., Salmanton-Garcia, J., Marchesi, F., Lopez-Garcia, A., Lamure, S., Itri, F., Gomes-Silva, M., Dragonetti, G., Falces-Romero, I., van Doesum, J., et al. (2022). COVID-19 in vaccinated adult patients with hematological malignancies: preliminary results from EPICOVIDEHA. Blood *139*, 1588–1592. https://doi.org/10.1182/blood.2021014124.

Roeker, L.E., Eyre, T.A., Thompson, M.C., Lamanna, N., Coltoff, A.R., Davids, M.S., Baker, P.O., Leslie, L., Rogers, K.A., Allan, J.N., et al. (2021). COVID-19 in patients with CLL: improved survival outcomes and update on management strategies. Blood *138*, 1768–1773. https://doi.org/10.1182/blood.2021011841.

Scarfo, L., Chatzikonstantinou, T., Rigolin, G.M., Quaresmini, G., Motta, M., Vitale, C., Garcia-Marco, J.A., Hernandez-Rivas, J.A., Miras, F., Baile, M., et al. (2020). COVID-19 severity and mortality in patients with chronic lymphocytic leukemia: a joint study by ERIC, the European Research Initiative on CLL, and CLL Campus. Leukemia *34*, 2354–2363. https://doi.org/10.1038/s41375-020s4130959-x.

Vijenthira, A., Gong, I.Y., Fox, T.A., Booth, S., Cook, G., Fattizzo, B., Martin-Moro, F., Razanamahery, J., Riches, J.C., Zwicker, J., et al. (2020). Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood *136*, 2881–2892. https://doi.org/10.1182/blood.2020008824.