

Letter

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SARS-CoV-2 Infection in Patients With Waldenström's Macroglobulinemia: A Multicenter International Cohort Study

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The coronavirus disease 2019 (COVID-19) pandemic has represented a huge challenge for vulnerable patients affected with hematological malignancies.^{1,2} So far, heterogeneous series on patients with lymphoma and COVID-19 have been published with mortality rates ranging from 25% to 40%,³⁻⁸ with only limited information about specific neoplasms.

Waldenström's macroglobulinemia (WM) is a rare indolent lymphoma characterized by bone marrow infiltration with lymphoplasmacytic cells associated with a serum monoclonal IgM.⁹ WM patients are at higher risk of severe complications from COVID-19 due to their age and immunologic impairment.¹⁰ However, data regarding severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) infection characteristics and outcome in WM patients have not been published so far.

The main purpose of this study was to determine the characteristics and outcomes of SARS-CoV-2 infection in a real-life population of WM patients during the COVID-19 pandemic. We also identified factors associated with COVID-19 severity and inferior survival.

We carried out an international, multicenter, retrospective study including WM patients who contracted SARS-CoV-2 infection. One-hundred ninety patients from 12 countries were registered between March 2020 and May 2022 (Supplemental Digital Content).

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Patients already diagnosed with WM who had a proven SARS-CoV-2 infection ($n = 174$) or clinical characteristics strongly suspicious for SARS-CoV-2 infection ($n = 10$) for whom polymerase chain reaction test was not available were included in the analyses. Six patients who received WM diagnosis after a prior SARS-CoV-2 infection were excluded from the analyses. Patients who were receiving WM treatment or who had received WM treatment within 3 months before COVID-19 diagnosis were considered on active treatment. Conversely, patients who had received WM treatment >3 months before SARS-CoV-2 infection were considered off-therapy.

The study was approved by the local Ethics Committee and was conducted according to the Declaration of Helsinki.

The primary end point of the study was overall survival (OS), defined as the time between the date of SARS-CoV-2 infection and the date of death from any cause or last follow-up. Data cut-off was September 2022. Secondary end point was COVID-19 fatality rate (CFR), defined as the proportion of deaths due to SARS-CoV-2 infection out of the total number of patients. Statistical methods are reported on Supplemental Digital Content.

From March 2020 to May 2022, a total of 184 WM patients with SARS-CoV-2 infection were reported. The median duration of follow-up after COVID-19 diagnosis was 3.4 months (interquartile range [IQR], 1.4–10.2 mo). Patients' and COVID-19 characteristics and management are depicted in Table 1.

The median age was 70 years (IQR, 60–77), 114 (63%) were males and 98 (53%) were Italian. Median Charlson Comorbidity Index was 4 (IQR, 3–5) and a quarter of patients were current or former smokers. Median time between WM diagnosis and SARS-CoV-2 infection diagnosis was 4.3 years (IQR, 1.7–9.0).

Regarding WM history, 107 of 182 patients (59%) had received at least 1 treatment. The median number of WM treatment lines was 1 (IQR, 0–1; range, 0–5) with 44 patients (24%) having received at least 2 lines of therapy. At the time of SARS-CoV-2 infection, 75 patients (41%) had never been treated for WM, 56 (31%) were on active WM treatment, and 41 (23%) were off-therapy. In 10 of 107 patients, information about type and timing of WM treatment was not available. The most common treatments before SARS-CoV-2 infection were rituximab-based regimens and Bruton tyrosine kinase inhibitors (Table 1). Median time from last therapy to SARS-CoV-2 detection was 23.2 months (IQR, 4.6–37.1), with 11 of 41 off-therapy patients being treated within 12 months before infection.

The course of SARS-CoV-2 infection was classified as mild in 55% of patients, severe in 30%, and critical in 10%. The proportion of severe or critical cases in 2020 was not significantly different compared with the 2021–2022 period (44% versus 37.5%, respectively; $P = 0.425$). Hospitalization was required in 91 of 179 patients (51%), including 23% having mild COVID-19. The length of hospital stay was available for 42 patients; median was 16 days (IQR, 7–23 d) and 5 patients were still hospitalized after 30 days. Noninvasive ventilation was registered in 31% of cases. Admission to intensive care unit (ICU) was reported in 12% and 6 patients were intubated; ICU admission rate did not show any differences according to the year of COVID-19 diagnosis (2020 versus 2021–2022: 11% versus 15%, $P = 0.482$), and neither did hospitalization (2020 versus 2021–2022: 53% versus 49%; $P = 0.757$).

At the time of SARS-CoV-2 diagnosis, 46 patients (25%) had received at least 1 dose of vaccination against SARS-CoV-2. Among the vaccinated patients, 11 (24%) presented severe COVID-19, 20 (43%) were hospitalized, and 6 (13%) were admitted to ICU; 33 patients (72%) were receiving or had received WM treatment at the time of SARS-CoV-2 infection.

As shown in Figure 1, OS at 100 days from SARS-CoV-2 infection was 87% (95% confidence interval [CI], 79.8%–91.7%) among 164 evaluable patients. At data cut-off, a total

Table 1

Patients' Characteristics and SARS-CoV-2 Infection Data in WM Population

Characteristics	All Patients (n = 184)
Age, y; median (IQR)	70 (60–77)
Gender, n (%) [missing]	[2]
Male	114 (63)
Female	68 (37)
CCI, median (IQR) [missing]	4 (3–5) [7]
Smoking history, n (%) [missing]	[43]
Never	105 (75)
Former	23 (16)
Current	13 (9)
No. lines of therapy, median (IQR)	1 (0–1)
Vaccination against SARS-CoV-2, n (%) [missing]	46 (25) [3]
WM treatment status at COVID-19 diagnosis, n (%) [missing]	107 (59) [2]
Untreated	75 (41)
Ongoing therapy	56 (31)
Off-therapy	41 (23)
Unknown	10 (5)
Last WM treatment at COVID-19, n (%) [missing]	[7]
Rituximab-containing	54 (50) ^a
BTK inhibitors	32 (30)
BTK inhibitors + rituximab	5 (5)
Other	11 (10)
Year of COVID-19 diagnosis, n (%) [missing]	[2]
2020	111 (61)
2021	50 (27)
2022	21 (12)
COVID-19 severity, n (%) [missing]	[10]
Mild	102 (59)
Severe	54 (31)
Critical	18 (10)
Hospital admission, n (%) [missing]	91 (51) [5]
ICU admission, n (%) [missing]	22 (12) [6]
Type of ventilation, n (%) [missing]	
Noninvasive ventilation	25 (31) [102]
Invasive ventilation	6 (7) [100]

^aThe most frequent regimens were rituximab + bendamustine ($n = 22$) and dexamethasone + rituximab + cyclophosphamide ($n = 11$).

BTK = Bruton tyrosine kinase; CCI = Charlson Comorbidity Index; COVID 19 = coronavirus disease 2019; ICU = intensive care unit; IQR = interquartile range; WM = Waldenström's macroglobulinemia; y = years.

of 26 patients had died: 22 patients died due to complications related to COVID-19 (corresponding to a CFR of 13%), 1 patient died from lymphoma, and 3 cases for unknown reasons. CFR was significantly higher during 2020 compared with the 2021–2022 period (19% versus 4%, $P = 0.005$) and in severe/critical cases than in the mild ones (30% versus 3%; $P < 0.001$). No deaths were observed among patients vaccinated against SARS-CoV-2.

Univariable and multivariable analyses of factors influencing COVID-19 severity and OS are reported in Suppl. Tables S1 and S2, respectively. At multivariable analysis for COVID-19 severity, age >70 years retained its prognostic significance (OR, 2.23 [95% CI, 1.18–4.22]; $P = 0.014$). Regarding OS, age >70 years (hazard ratio [HR], 3.76 [95% CI, 1.21–11.68]; $P = 0.022$), male gender (HR, 5.07 [95% CI, 1.15–22.35]; $P = 0.032$), and COVID-19 severity (HR, 11.03 [95% CI, 2.51–48.41]; $P = 0.001$; Suppl. Figure S1) were independently associated with worse OS.

The OS was significantly better in vaccinated WM patients compared with the unvaccinated ones (100 d-OS 100% versus 82%, respectively; $P = 0.008$) (Suppl. Figure S2) and in the 2021–2022 period compared with 2020 (100 d-OS 97% versus 81%, respectively; $P = 0.014$) (Suppl. Figure S3).

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