# HemaSphere

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

Irene Defrancesco[1,2], Virginia Valeria Ferretti[3], Pierre Morel[4], Charalampia Kyriakou[5], Efstathios Kastritis[6], Ibrahim Tohidi-Esfahani[7], Alessandra Tedeschi[8], Christian Buske[9], Ramón García-Sanz[10], Josephine M.I. Vos[11], Veronica Peri[12], Gloria Margiotta Casaluci[13], Angela Ferrari[14], Francesco Piazza[15,16], Rimke Oostvogels[17], Ester Lovato[18], Lydia Montes[4], Luc Matthieu Fornecker[19], Alexander Grunenberg[20], Meletios Athanasios Dimopoulos[6], Constantine S. Tam[21,22,23], Shirley D'Sa[5], Veronique Leblond[24], Judith Trotman[7,25], Francesco Passamonti[26], Luca Arcaini[1,27], Marzia Varettoni[1], on behalf of the European Consortium for Waldenström's Macroglobulinemia

**Correspondence:** Marzia Varettoni (m.varettoni@smatteo.pv.it).

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).

[1]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[2]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Italy
[3]UOS Clinical Epidemiology and Biostatistic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[4]Service d'Hematologie Clinique et Therapie Cellulaire, Centre Hospitalier Universitaire d'Amiens-Picardie, France
[5]Centre for Waldenström's Macroglobulinaemia and Related Conditions, University College London Hospitals National Health Service Foundation Trust, London, United Kingdom
[6]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Greece
[7]Haematology Department, Concord Repatriation General Hospital, Sydney, NSW, Australia
[8]ASST Grande Ospedale Metropolitano Niguarda Hospital, Milan, Italy
[9]Institute of Experimental Cancer Research, Comprehensive Cancer Center Ulm, University Hospital of Ulm, Germany
[10]Hematology Department, University Hospital of Salamanca, Research Biomedical Institute of Salamanca (IBSAL), CIBERONC and Center for Cancer Research-IBMCC (University of Salamanca-CSIC), Spain
[11]Department of Hematology, Amsterdam UMC, Location University of Amsterdam, Cancer Center Amsterdam and LYMMCARE (Lymphoma and Myeloma Center Amsterdam), the Netherlands
[12]Hematology Division, "AOU Città della Salute e della Scienza di Torino," Italy
[13]Division of Hematology, Department of Translational Medicine, Hospital Maggiore della Carità, Novara, Italy
[14]Hematology Unit, Azienda USL-IRCCS Reggio Emilia, Italy
[15]Laboratory of Myeloma and Lymphoma Pathobiology, Veneto Institute of Molecular Medicine (VIMM) and Foundation for Advanced Biomedical Research (FABR), Padua, Italy
[16]Hematology Division, Azienda Ospedaliera Universitaria and Department of Medicine, University of Padua, Italy
[17]Hematology, UMC Utrecht Cancer Center, Utrecht, the Netherlands
[18]Department of Medicine, Hematology Unit, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[19]Service d'Hematologie, Institut de Cancerologie Strasbourg Europe, Strasbourg, France
[20]Department of Internal Medicine III, University Hospital Ulm, Germany
[21]Peter MacCallum Cancer Centre and University of Melbourne, VIC, Australia
[22]Alfred Health and Monash University, Melbourne, VIC, Australia
[23]Central Clinical School, Monash University, Melbourne, VIC, Australia
[24]Département d'Hématologie Hôpital Pitié-Salpêtrière APHP, UPMC Université Paris, France
[25]University of Sydney, Camperdown, NSW, Australia
[26]Department of Hematology, University Hospital "Ospedale di Circolo e Fondazione Macchi - ASST SetteLaghi," University of Insubria, Varese, Italy
[27]Department of Molecular Medicine, University of Pavia, Italy
ID and VVF have contributed equally to this work.
Supplemental digital content is available for this article.

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

**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] |

[a]The 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).
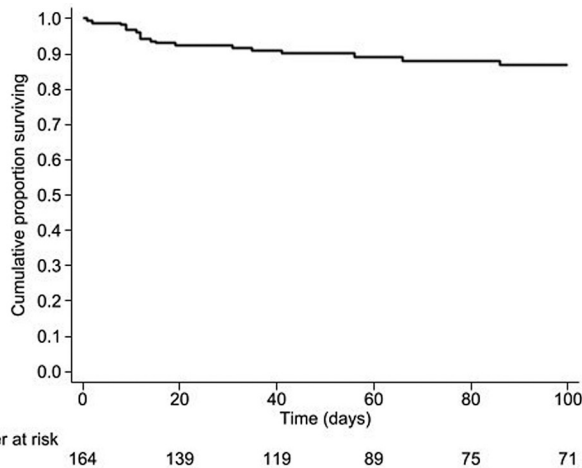
**Figure 1. OS at 100 d from SARS-CoV-2 infection in WM patients.** d = days; OS = overall survival; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WM = Waldenström's macroglobulinemia.

We did not find any significant difference in terms of OS according to the WM treatment status at the time of SARS-CoV-2 infection. Also, the type of last WM treatment at the time of SARS-CoV-2 infection was not significantly associated with OS.

So far, limited, not directly retrievable, information on the characteristics and outcomes of WM patients who contracted SARS-CoV-2 infection has been reported. Herein, we presented the results of the first multicenter international study describing SARS-CoV-2 infection characteristics and outcome in a large series of WM patients.

Regarding COVID-19 severity predictors, we verified some risk factors previously reported,[1,2,7,11,12] such as advanced age (>70 y) and the presence of comorbidities. However, at multivariable analysis, only age >70 years was independently associated with severe or critical COVID-19 in this study.

The OS at 100 days from SARS-CoV-2 infection was 87%, better than previously described in patients with lymphoma or chronic lymphocytic leukemia (CLL) and COVID-19, where the mortality rate ranged from 20% to 35%.[3,5–8,12,13]

The inclusion of COVID-19 cases from the most recent period and vaccinated patients may account for the better survival observed in our study. This is supported by the significantly higher OS in 2021–2022 as compared with the first pandemic period (2020), although hospital admission and severe COVID-19 rates did not differ according to the year of SARS-CoV-2 infection. Improvements in therapeutic management of COVID-19 patients, widespread vaccination use, and ultimately the emergence of new, less virulent variants may explain these findings.

In our series, WM vaccinated individuals had significantly survival advantage compared with unvaccinated patients, suggesting that WM patients may exhibit an effective response to vaccination, translating into reduced mortality.

Besides COVID-19 severity, patient-related features (age >70 y and male gender) were associated with higher risk of death to patients with WM at multivariable analysis, in line with data from the general population.[14] Similar results have been reported in patients with lymphoid neoplasms and CLL.[3,4,8]

We did not observe any differences in survival according to the WM treatment status at the time of SARS-CoV-2 infection and type of last regimen administered. Regarding the impact of active treatment on COVID-19 course and mortality, conflicting results have been reported in patients with lymphoma and CLL[2,4–6,8] with some studies showing higher risk of death in patients on active hematologic treatment. Therefore, caution should be used in interpreting this data, as the relatively small number of WM patients receiving active treatment in our series may have not allowed to find statistically significant differences. More data are needed to address this issue in the WM population.

In addition, as this is primarily an observational retrospective study including WM patients with reported SARS-CoV-2 infection, an unintentional patients' selection bias should be considered because of the low rate of testing at the beginning of the pandemic and the growing number of asymptomatic cases, together with the inclusion of patients from different countries and COVID-19 waves.

Nevertheless, our study includes the largest number of patients with WM and COVID-19 and to the best of our knowledge, it is the first report on SARS-CoV-2 infection outcomes and risk factors in this rare hematologic disease. Our findings suggest that patient-related features, COVID-19 severity, and anti-SARS-CoV-2 vaccination, rather than WM treatment characteristics, influence the outcome of WM patients with SARS-CoV-2 infection.

## REFERENCES

1. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol.* 2020;7:e737–e745.
2. Pagano L, Salmanton-García J, Marchesi F, et al. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA). *J Hematol Oncol.* 2021;14:168.
3. Merli M, Ferrarini I, Merli F, et al. SARS-CoV-2 infection in patients with chronic lymphocytic leukemia: the Italian Hematology Alliance on COVID-19 cohort. *Hematol Oncol.* 2022;41:128–138.
4. Visco C, Marcheselli L, Mina R, et al. A prognostic model for patients with lymphoma and COVID-19: a multicentre cohort study. *Blood Adv.* 2022;6:327–338.
5. Lamure S, Duléry R, Di Blasi R, et al. Determinants of outcome in Covid-19 hospitalized patients with lymphoma: a retrospective multicentric cohort study. *EClinicalMedicine.* 2020;27:100549.
6. Duléry R, Lamure S, Delord M, et al. Prolonged in-hospital stay and higher mortality after Covid-19 among patients with non-Hodgkin lymphoma treated with B-cell depleting immunotherapy. *Am J Hematol.* 2021;96:934–944.
7. Regalado-Artamendi I, Jiménez-Ubieto A, Hernández-Rivas JA, et al. Risk factors and mortality of COVID-19 in patients with lymphoma: a multicenter study. *HemaSphere.* 2021;5:e5381–e5388.
8. Mato AR, Roeker LE, Lamanna N, et al. Outcomes of COVID-19 in patients with CLL: a multicenter international experience. *Blood.* 2020;136:1134–1143.

9.  Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375–2390.

10. Talaulikar D, Advani RH, Branagan AR, et al. Consensus statement on the management of Waldenström Macroglobulinemia patients during the COVID-19 pandemic. *HemaSphere*. 2020;4:e433.

11. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood*. 2020;136:2881–2892.

12. Chatzikonstantinou T, Kapetanakis A, Scarfò L, et al. COVID-19 severity and mortality in patients with CLL: an update of the international ERIC and Campus CLL study. *Leukemia*. 2021;35:3444–3454.

13. Pagano L, Salmanton-García J, Marchesi F, et al. Breakthrough COVID-19 in vaccinated patients with hematologic malignancies: results from EPICOVIDEHA survey. *Blood*. 2022;140:2773–2787.

14. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584:430–436.