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# Survival in multiple myeloma and SARS-COV-2 infection through the COVID-19 pandemic: Results from the EPICOVIDEHA registry

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## Abstract

Patients affected by multiple myeloma (MM) have an increased risk of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection and subsequent coronavirus (20)19 disease (COVID-19)-related death. The changing epidemiological and therapeutic scenarios suggest that there has been an improvement in severity and survival of COVID-19 during the different waves of the pandemic in the general population, but this has not been investigated yet in MM patients. Here we analyzed a large cohort of 1221 patients with MM and confirmed SARS-CoV-2 infection observed between February 2020, and August 2022, in the EPICOVIDEHA registry from 132 centers around the world. Median follow-up was 52 days for the entire cohort and 83 days for survivors. Three-hundred and three patients died (24%) and COVID-19 was the primary reason for death of around 89% of them. Overall survival (OS) was significantly higher in vaccinated patients with both stable and active MM versus unvaccinated, while only a trend favoring vaccinated patients was observed in subjects with responsive MM. Vaccinated patients with at least 2 doses showed a better OS than those with one or no vaccine dose. Overall, according to pandemic waves, mortality rate decreased over time from 34% to 10%. In multivariable analysis, age, renal failure, active disease, hospital, and intensive care unit admission, were independently associated with a higher number of deaths, while a neutrophil count above $0.5 \times 10^9$/L was found to be protective. This data suggests that MM patients remain at risk of SARS-CoV-2 infection even in the vaccination era, but their clinical outcome, in terms of OS, has progressively improved throughout the different viral phases of the pandemic.

**KEYWORDS**
COVID-19, hematological malignancy, multiple myeloma, SARS-CoV-2

## 1 | INTRODUCTION

During the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) pandemic, infected patients with hematologic malignancies (HM) have clearly shown a significantly poorer outcome compared to the general population,[1–3] mainly due to inherent immunosuppression and effects of some treatments. In this regard, multiple myeloma (MM) represents a good example, since in this neoplastic disorder both humoral and cellular immunity are particularly compromised because of malignancy itself and plasma cells-directed therapies. Moreover, MM is characterized by high incidence in the elderly; this fact further contributes to increase the risk of infections[4] and, specifically, of poorer outcome of SARS-CoV-2 infection, particularly in those patients with high risk, active/progressive disease, and/or renal failure.[2,5–8]

Thus, vaccines against SARS-CoV-2 have become the most important preventive strategy to protect these patients from severe complications deriving from SARS-CoV-2 infections.[9] However, MM patients may develop lower antibody responses to anti SARS-CoV-2 vaccines, particularly after anti-CD38 and anti–B-cell maturation antigen (BCMA) drugs[10–18] or transplant/CAR-T procedures.[19–23] Therefore they remain at higher risk of breakthrough infections (13%–15%), compared to non-cancer patients (approximatively 4%), that are linked to still significant morbidity and mortality.[24–26] On the other hand, studies would suggest that severity of disease and mortality rates are ameliorated also in this category of patients, mainly thanks to appropriate vaccination policies.[2,27] Furthermore, some preliminary, encouraging data, has been reported about preexposure prophylaxis with monoclonal antibodies against SARS-CoV-2[28–30] and early start after SARS-CoV-2 infection with antiviral drugs[31,32] to prevent the progression to critical disease in severely immuno-compromised populations, such as MM patients.

Several investigations published about MM patients with SARS-CoV-2 infection during the first phases of pandemic have reported impressive mortality rates following infection up to 55%[2,5–8] and consensus guidelines have been produced to manage these parts of pandemic.[33] Here we describe the largest survey on MM patients with SARS-CoV-2 infection, also including individuals developing COVID-19 during the most recent waves of pandemic, with

**TABLE 1** Demographic and clinical features of 1221 patients with multiple myeloma at the time of SARS-CoV-2 infection diagnosis.

| | *N* | % |
|---|---|---|
| Sex | | |
| Female | 519 | 42.5 |
| Male | 702 | 57.5 |
| Age, years | | |
| Median (IQR) | 68 (60–76) | NA |
| Range | 30–95 | NA |
| Comorbidities | | |
| 0 | 410 | 33.5 |
| 1 | 415 | 34 |
| 2 | 234 | 19.2 |
| ≥3 | 162 | 13.3 |
| Comorbidities, type | | |
| Chronic cardiopathy | 467 | 38.2 |
| Chronic pulmonary disease | 177 | 14.5 |
| Diabetes mellitus | 192 | 15.7 |
| Liver disease | 44 | 3.6 |
| Obesity | 95 | 7.8 |
| Renal impairment | 188 | 15.4 |
| Smoking history | 148 | 12.1 |
| No risk factor identified | 404 | 33.1 |
| Vaccination status | | |
| One dose | 24 | 2 |
| Two doses | 143 | 11.7 |
| Three doses | 225 | 18.4 |
| Four doses | 24 | 2 |
| Not vaccinated | 805 | 65.9 |
| Neutrophils, $\times 10^9$/L | | |
| ≤0.5 | 30 | 2.5 |
| 0.501–0.999 | 53 | 4.3 |
| ≥1 | 1003 | 82.2 |
| Lymphocytes, $\times 10^9$/L | | |
| ≤0.2 | 121 | 9.9 |
| 0.201–0.499 | 203 | 16.6 |
| ≥0.5 | 897 | 73.5 |
| MM status | | |
| Controlled disease | 592 | 48.5 |
| Stable disease | 201 | 16.5 |
| Active disease | 390 | 31.9 |
| Unknown | 38 | 3.1 |
| Last/ongoing treatment | | |
| Allo-HSCT | 2 | 0.2 |

(Continues)

TABLE 1 (Continued)

| | N | % |
|---|---|---|
| Auto-HSCT | 61 | 5 |
| CAR-T | 4 | 0.3 |
| IMids (thalidomide, lenalidomide, pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib, ixazomib) | 698 | 57.2 |
| Conventional chemotherapy (cyclophosphamide, melphalan) | 50 | 4.1 |
| Monoclonal antibodies (daratumumab, isatuximab, elotuzumab) | 247 | 20.2 |
| Antibody-drug coniugate (belantamab mafodotin) and bispecific antibodies (teclistamab, talquetamab, cevostamab) | 20 | 1.6 |
| Supportive/Palliative | 34 | 2.8 |
| Unknown | 19 | 1.6 |
| No treatment | 86 | 7 |
| Symptoms | | |
| Pulmonary | 451 | 36.9 |
| Pulmonary + extrapulmonary | 277 | 22.7 |
| Extrapulmonary | 224 | 18.4 |
| Screening | 269 | 22 |
| SARS-CoV-2 infection severity | | |
| Critical infection | 169 | 13.8 |
| Severe infection | 471 | 38.6 |
| Mild infection | 350 | 28.7 |
| Asymptomatic | 231 | 18.9 |
| Stay during SARS-CoV-2 infection | | |
| Admitted to hospital | 775 | 63.5 |
| Duration of stay in hospital, days median (IQR) | 12 (7–120) | NA |
| Range | 1–120 | NA |
| Admitted to ICU | 169 | 13.8 |
| Duration of ICU stay, days median (IQR) | 10 (6–14) | NA |
| Range | 1–56 | NA |
| Invasive MV | 107 | 8.8 |
| Non-invasive MV | 61 | 5 |
| At home | 446 | 36.5 |
| SARS-CoV-2 infection treatment | | |
| No specific treatment reported | 270 | 22.1 |
| Antivirals +/− corticosteroids +/− plasma | 135 | 11.1 |
| Antivirals + monoclonal antibodies +/− corticosteroids +/− plasma | 23 | 1.9 |
| Monoclonal antibodies +/− corticosteroids +/− plasma | 84 | 6.9 |
| Plasma +/− corticosteroids | 10 | 0.8 |
| Corticosteroids | 94 | 7.7 |
| Unknown | 605 | 49.5 |
| Outcome | | |
| Alive | 918 | 75.2 |
| Observation time, days median (IQR) | 83.5 (28–162) | NA |

TABLE 1 (Continued)

| | N | % |
|---|---|---|
| Range | 0–741 | NA |
| Dead | 303 | 24.8 |
| Observation time, days median (IQR) | 13 (7–30) | NA |
| Range | 0–763 | NA |
| Reason for death | | |
| COVID-19 | 196 | 64.7 |
| COVID-19 + multiple myeloma | 72 | 23.8 |
| Multiple myeloma +/− other reasons | 35 | 11.5 |

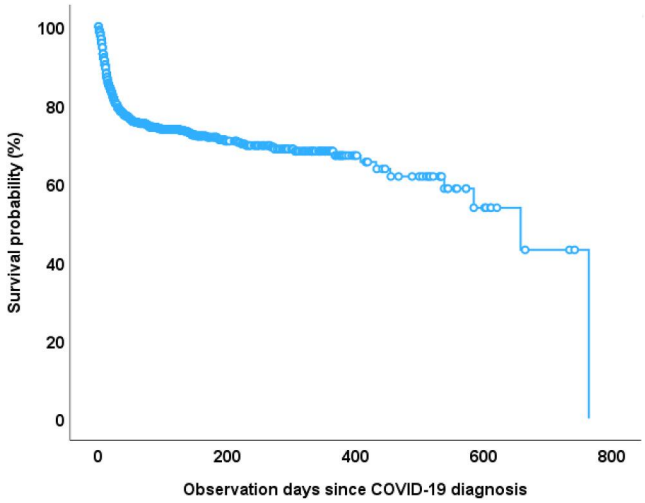



FIGURE 1 Overall survival (OS) of patients with SARS-CoV-2 infection and multiple myeloma.

particular attention to overall survival (OS) after the introduction of vaccines and the progressive appearance of new viral variants of concern (VOC).

## 2 | METHODS

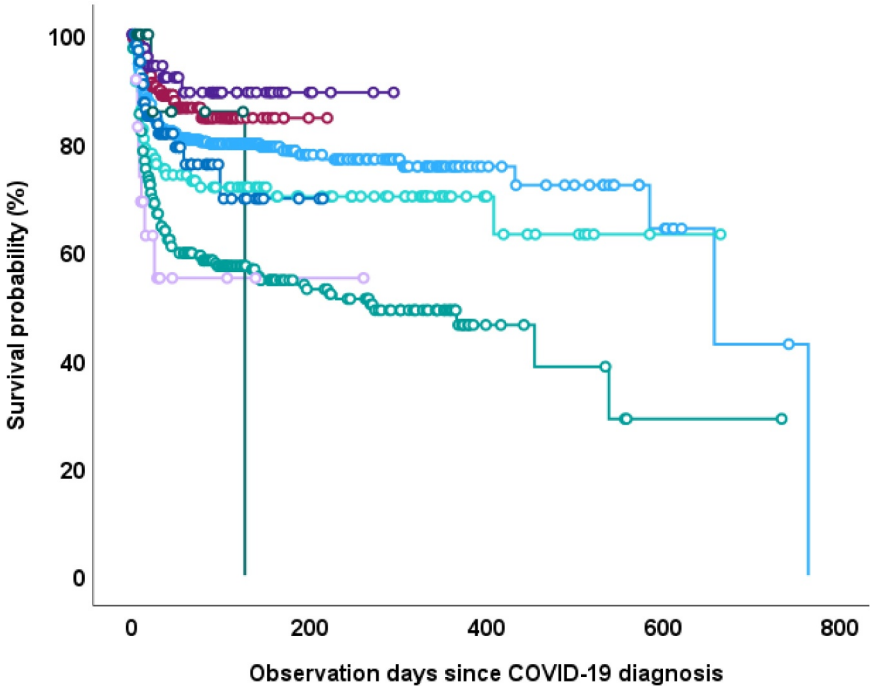
EPICOVIDEHA (www.clinicaltrials.gov; ID NCT04733729), is an international open web-based registry for patients with HM and SARS-CoV-2 infection, initiated in February 2020, by members of the Scientific Working Group Infection in Hematology of the European Hematology Association.[34] It was approved by the local ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (ID 3226). All consecutive MM patients diagnosed with SARS-CoV-2 infection were potentially captured and registered in this web-based registry. The respective local ethics committee of each participating institution approved as appropriate. The electronic case report form is accessible online via www.clinicalsurveys.net (EFS Summer 2021, TIVIAN GmbH, Cologne, Germany).[35] Each entry was reviewed and validated by infectious diseases and hematology experts. Patient conditions at SARS-CoV-2 infection diagnosis (i.e., age, sex, comorbidities, MM status and clinical management, vaccination status, SARS-CoV-2 infection management and outcome) were recorded. Disease status of MM at SARS-CoV-2 infection onset and last follow up was defined as active (progressive disease, newly diagnosed MM), controlled (at least partial response or stable disease), according to IMWG criteria and based on reports from the respective participating institution. COVID-19 severity was graded according to international standards, as previously described.[36]

The primary objective of this study was to evaluate OS and its possible changes of MM patients with SARS-CoV-2 infection during the different epidemic waves. The secondary objective was to evaluate the factors possibly affecting OS, mainly according to disease phase, laboratory analyses, most recent MM treatment received, comorbidities, vaccine status, severity, and treatments of COVID-19.

Continuous data are presented as median, interquartile range (IQR) and absolute range, and categorical variables are as counts and percentages. Cox regression model was used for mortality analysis. Variables with a *p*-value of 0.1 in the univariable analyses were included in the multivariable analysis. A backward Wald method was used in the multivariable Cox regression model. The Kaplan-Meier survival curve was also used to assess mortality. A log-rank test was performed to compare the survival probabilities of patients included in the different models. Statistical significance was defined as a *p*-value of 0.05. SPSSv25.0 (IBM Corp.) was used for statistical analysis.

## 3 | RESULTS

Between February 2020, and August 2022, 1221 adult patients with MM and confirmed SARS-CoV-2 infection were reported in the EPICOVIDEHA registry by 132 centers from 32 countries around the world, mainly in Europe (Supplemental Table S1). Demographic and clinical characteristics of patients are reported in Table 1. The median age at the time of SARS-CoV-2 infection was 68 years (interquartile range [IQR]: 60–76), with a male predominance (702, 57.5%). Eight hundred eleven patients (66.4%) had at least one underlying comorbidity, mostly (407, 38.2%) a cardiovascular disease. With




Overall log-rank test p value <0.001

| | Controlled + Not vaccinated | Controlled + Vaccinated | Stable + Not vaccinated | Stable + Vaccinated | Active + Not vaccinated | Active + Vaccinated | Unknown + Not vaccinated |
|---|---|---|---|---|---|---|---|
| Controlled + Vaccinated | 0.078 | | | | | | |
| Stable + Not vaccinated | 0.077 | **0.001** | | | | | |
| Stable + Vaccinated | **0.047** | 0.409 | **0.002** | | | | |
| Active + Not vaccinated | **<0.001** | **<0.001** | **0.005** | **<0.001** | | | |
| Active + Vaccinated | 0.495 | **0.041** | 0.359 | **0.020** | **0.003** | | |
| Unknown + Not vaccinated | **<0.001** | **<0.001** | 0.085 | **<0.001** | 0.376 | **0.008** | |
| Unknown + Vaccinated | 0.864 | 0.431 | 0.603 | 0.207 | 0.255 | 0.916 | 0.175 |

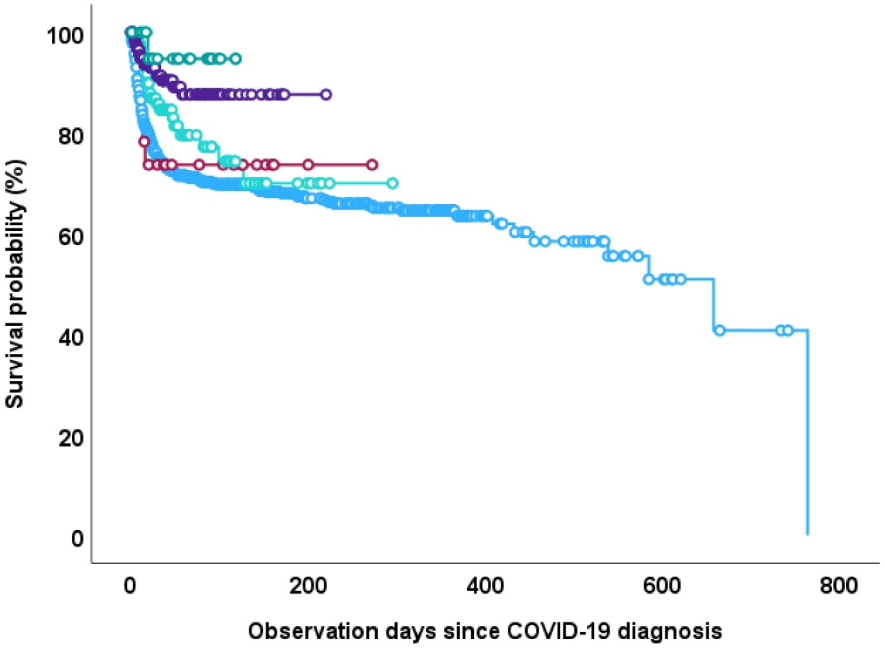
**FIGURE 2** Survival probability by malignancy- and vaccine-status.

regard to vaccination status against SARS-CoV-2, 805 patients (65.9%) were not vaccinated when they were infected, while 416 (34.1%) had received at least one dose, and 225 (18.4%) had received three doses. At infection onset, 30 (2.5%) and 121 (9.9%) patients had neutrophil and lymphocyte counts below $0.5 \times 10^9$/L and $0.2 \times 10^9$/L, respectively.

Concerning malignancy status, 793 patients (64.9%) had controlled or stable disease, while in 390 (31.9%) MM was active, including 56 newly diagnosed patients, 66.1% of whom were not vaccinated. Regarding last MM treatment before SARS-CoV-2 infection, most patients (57.2%) had received IMids (thalidomide, lenalidomide, pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib, ixazomib), followed (20.2%) by monoclonal antibodies (daratumumab, isatuximab, elotuzumab); 61 patients (5%) had received autologous stem cell transplantation, 2 patients (0.2%) allogenic stem cell transplantation (Allo-SCT), and 4 patients (0.3%) CAR-T cell therapy.

At SARS-CoV-2 infection onset, 728 patients (59.7%) had pulmonary symptoms, 224 (18.4%) exhibited only extra-pulmonary symptoms and 269 (22%) were incidentally diagnosed after screening for SARS-CoV-2 infection. COVID-19 was critical in 169 patients (13.8%), severe in 471 (38.6%), mild in 350 (28.7%), and asymptomatic in the remaining cases (18.9%). Four hundred and forty-six patients (36.5%) could stay at home and were managed as outpatients during SARS-CoV-2 infection, while 775 patients (63.5%) were hospitalized for a median of 12 days (IQR: 7–120). One hundred and sixty-nine patients (13.8%) were admitted to an intensive care unit (ICU) for a median stay of 10 days (IQR: 6–14); 107 of them required invasive mechanical ventilation (63.3%; 8.8% of all patients).

No specific targeted drug for SARS-CoV-2 infection was used in 270 patients (22.1%), while in 346 (28.3%) individuals antivirals, monoclonal antibodies, corticosteroids, and convalescent plasma as single or combined therapies were given. However, in 605 (49.5%) patients, it was not reported whether therapies against SARS-CoV-2




Overall log-rank test p value <0.001

| | Not vaccinated | One dose | Two doses | Three doses |
|---|---|---|---|---|
| One dose | 0.800 | | | |
| Two doses | **0.034** | 0.488 | | |
| Three doses | **<0.001** | **0.029** | 0.059 | |
| Four doses | **0.027** | **0.043** | 0.127 | 0.401 |

**FIGURE 3** Survival probability by vaccine doses.

infection were employed. Thirty-seven cases of reinfections were reported, but data about these patients were fragmentary and, therefore, not analyzed in detail. After a median follow-up of 52 days (IQR: 16–143; range: 0–763) for the entire cohort and 83.5 days for survivors, 303 patients died (24.8%); mortality at 30 days and at 100 days post SARS-CoV-2 infection diagnosis in the whole cohort was 18.8% and 24.5% respectively (Figure 1). The reported primary reason for death was COVID-19 in 196 (64.7%) patients, a combination of MM and COVID-19 in 72 (23.8%) and a combination of MM and other reasons in 35 (11.5%).

Estimated OS was significantly higher in vaccinated patients with both stable and active MM versus the unvaccinated (Figure 2, $p = 0.002$ and $p = 0.003$, respectively), while only a trend favoring vaccinated patients was observed in subjects with controlled disease ($p = 0.078$). A sub-analysis focused on the number of vaccine doses received, and revealed that vaccinated patients with ≥2 doses (Figure 3) showed a better outcome (particularly with 3 or 4 doses) than those with ≤1 dose.

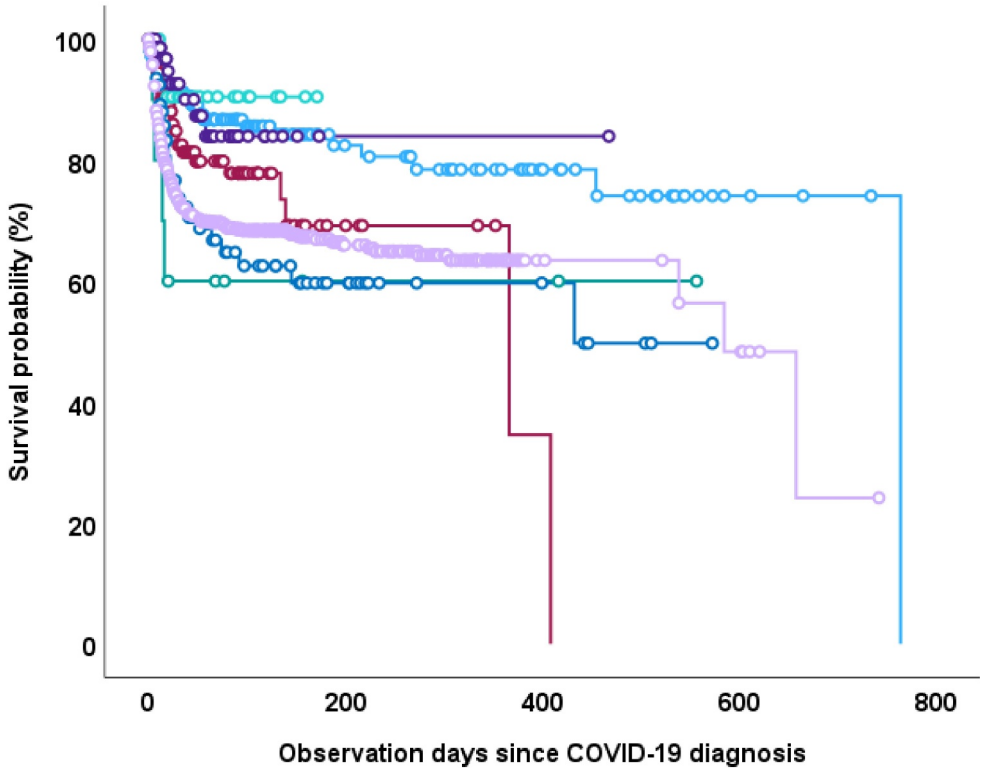
Finally, when treatment for SARS-CoV-2 infection was evaluated, we found that OS was significantly longer in patients receiving a combination of antivirals and monoclonal antibodies, with or without adjunct corticosteroids and/or plasma (Figure 4).

Overall, according to pandemic waves due to SARS-CoV-2 variants, mortality rates decreased over time (Wildtype (WT): 34%; Alpha/Beta/Gamma: 25.3%; Delta: 20.4%; Omicron: 10.2%) (Supplemental Table S2). In particular, differences observed were statistically significant between WT and Omicron waves ($p$=<0.001) and between Delta and Omicron waves ($p = 0.042$), respectively (Figure 5).

At univariable analysis (Table 2) age, chronic cardiopathy, chronic pulmonary disease, renal failure, active MM at SARS-CoV-2 infection onset, use of steroids, hospital admission and ICU admission were significantly associated with a worse OS. On the contrary, neutrophil or lymphocyte count above $0.5 \times 10^9$/L, extrapulmonary symptoms or absence of symptoms, use of antivirals +/− monoclonal antibodies and ≥2 vaccine doses were associated with reduced mortality. However, at multivariable Cox regression analysis, only age, renal failure, active disease, hospital and ICU admission were independently associated with poor survival. At the opposite, neutrophil count above $0.5 \times 10^9$/L was found to be protective.

## 4 | DISCUSSION

Here we present, to the best of our knowledge, the largest survey of MM patients infected by SARS-CoV-2, followed during the different phases of the COVID-19 pandemic, with the longest follow-up encompassing subsequent infection periods with different viral VOC (WT, Alpha/Beta/Gamma, Delta, and Omicron). Overall, our data suggest that MM patients remain vulnerable to SARS-CoV-2 infection even in the vaccination era, but also that these patients have progressively improved their OS throughout the different viral phases of pandemic.



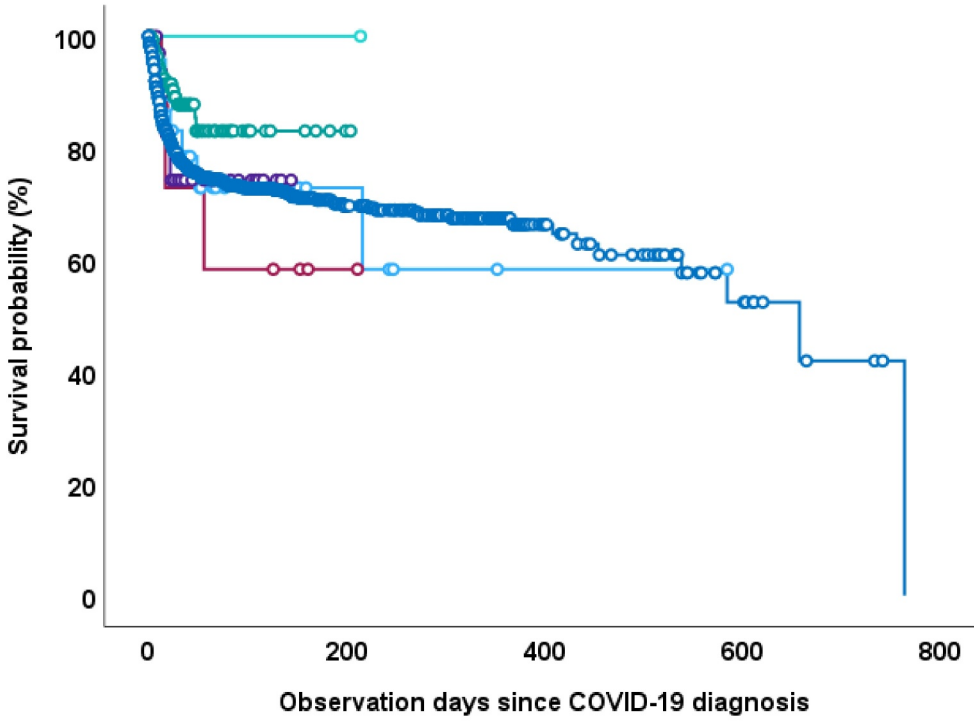

Overall log-rank test p value <0.001

| | No specific treatment | Antivirals +/- corticosteroids +/- plasma | Antivirals + monoclonal antibodies +/- corticosteroids +/- plasma | Monoclonal antibodies +/- corticosteroids +/- plasma | Plasma +/- corticosteroids | Corticosteroids |
|---|---|---|---|---|---|---|
| **Antivirals +/- corticosteroids +/- plasma** | **0.015** | | | | | |
| **Antivirals + monoclonal antibodies +/- corticosteroids +/- plasma** | 0.668 | 0.235 | | | | |
| **Monoclonal antibodies +/- corticosteroids +/- plasma** | 0.770 | 0.109 | 0.712 | | | |
| **Plasma +/- corticosteroids** | **0.025** | 0.589 | **0.027** | **0.014** | | |
| **Corticosteroids** | **<0.001** | 0.210 | **0.047** | **0.007** | 0.617 | |
| **Unknown** | **<0.001** | 0.085 | 0.053 | **0.003** | 0.531 | 0.743 |

**FIGURE 4** Survival probability by SARS-CoV-2 infection treatment.

Indeed, in our study, the majority of MM patients (52.4%) showed a critical/severe infection requiring hospitalization (63.5%), while the global mortality rate following infection (24.8%), due to COVID-19 in the large majority of cases, was coherent with that reported in previous studies (ranging from 22% to 54.8%) and significantly higher than in the general population and in patients with other malignancies.[5–8] In particular, hospital and/or ICU admission had the most significant negative impact on COVID-19 outcome, showing a strong correlation with an increased mortality at multivariable analysis, along with older age, renal failure and active MM disease. By contrast, neutrophil count above 0.5 $\times$ $10^9$/L was found to be significantly protective. Notably, most recent line of treatment received, other comorbidities (including pulmonary disorders) and absolute lymphocyte count did not impact on OS at multivariable analysis.

Regarding anti-SARS-CoV-2 treatments, combination of antivirals and monoclonal antibodies (+/− steroids and/or plasma) apparently resulted in a better survival, but available data were too heterogeneous and imprecise to draw definitive conclusions. Curiously, and differently from recent data reported in the general population,[37] the use of steroids was associated with a worse outcome at univariate analysis, a fact that was not confirmed, however, at multivariable analysis. Steroid-related further immune-suppression, in addition to that intrinsic to MM, and concomitant treatments, could explain this quite unexpected finding that requires, however, further confirmation. Notably, while the effects of steroids in the




Overall log-rank test p value p=0.195

| | Wild type | Alpha variant | Beta variant | Delta variant | Omicron variant |
|---|---|---|---|---|---|
| Alpha variant | 0.475 | | | | |
| Beta variant | 0.579 | 0.483 | | | |
| Delta variant | 0.862 | 0.480 | 0.588 | | |
| Omicron variant | 0.294 | 0.136 | 0.668 | 0.208 | |
| Not tested | 0.985 | 0.567 | 0.547 | 0.784 | **0.010** |

**FIGURE 5** Survival probability by COVID-19 waves (variants of concern).

inflammatory phase of SARS-CoV-2 infection needing oxygen administration would be positive, their use in the earlier viral infection phase not requiring oxygen therapy was reported to be associated to detrimental results.[37,38]

Overall, OS was significantly longer in vaccinated versus unvaccinated patients, including those with scarcely controlled disease, thus suggesting the possible efficacy of vaccines even in this population of patients, despite their generally described inadequate capacity of humoral immune response.[39–41] In particular, vaccinated patients with ≥2 doses showed a better OS than those unvaccinated or having receives only one dose, highlighting the need of a complete cycle of vaccination, also in individuals with MM, particularly in those with scarce immune-reaction after the first two doses.[42–45] Notwithstanding, even full vaccinations, though statistically significant at univariable analysis, did not enter into the multivariable model, where other clinical variables, in particular age, active disease, and COVID-19 severity requiring hospital/ICU admission, had a major impact. In this setting, more recent VOC,[46] reduced production of neutralizing antibodies[47,48] and impaired T-cell response,[49] as well increasing hybrid[50] and herd immunity in MM patients could have also played a role.

Above all, we observed that OS rates progressively improved throughout the different pandemic waves. In particular, mortality rates declined from first (34%) to last (10.2%) wave. The overall improvement likely reflects a combination of factors, mainly healthcare worker experience dealing with this type of patients, targeted treatments for symptomatic COVID-19, extensive vaccine policies, as well as detection of a larger number of asymptomatic/mild cases by screening programs. In this context, regarding the role of more recently prevalent VOC, in November 2021, the World Health Organization (WHO) declared the Omicron variant (B.1.1.529) of SARS-CoV-2, as a new VOC, while, since January 2022, BA.2.12.1, BA.4,

**TABLE 2** Overall mortality predictors in patients with multiple myeloma and SARS-CoV-2 infection.

| | Univariable | | | | Multivariable | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| | *p* Value | HR | Lower limit | Upper limit | *p* Value | HR | Lower limit | Upper limit |
| Sex | | | | | | | | |
| Female | - | - | - | - | | | | |
| Male | 0.804 | 1.030 | 0.817 | 1.297 | | | | |
| Age | <0.001 | 1.031 | 1.019 | 1.042 | **<0.001** | 1.032 | 1.018 | 1.045 |
| Comorbidities | | | | | | | | |
| Chronic cardiopathy | <0.001 | 1.671 | 1.330 | 2.100 | 0.435 | 1.122 | 0.841 | 1.497 |
| CPD | 0.006 | 1.498 | 1.123 | 1.996 | 0.768 | 0.954 | 0.696 | 1.306 |
| Diabetes mellitus | 0.209 | 1.207 | 0.900 | 1.620 | | | | |
| Liver disease | 0.728 | 1.108 | 0.622 | 1.975 | | | | |
| Obesity | 0.747 | 0.932 | 0.609 | 1.427 | | | | |
| Renal failure | <0.001 | 2.226 | 1.720 | 2.881 | **0.004** | 1.526 | 1.143 | 2.038 |
| Smoking history | 0.120 | 1.286 | 0.936 | 1.767 | | | | |
| No risk factor | <0.001 | 0.551 | 0.419 | 0.724 | 0.956 | 1.010 | 0.706 | 1.445 |
| Neutrophils | | | | | | | | |
| <501 | - | - | - | - | - | - | - | - |
| 501–999 | 0.022 | 0.391 | 0.175 | 0.873 | **0.036** | 0.411 | 0.179 | 0.943 |
| >999 | 0.014 | 0.496 | 0.284 | 0.866 | 0.053 | 0.557 | 0.308 | 1.007 |
| Lymphocytes | | | | | | | | |
| <201 | - | - | - | - | - | - | - | - |
| 201–499 | 0.334 | 0.835 | 0.580 | 1.203 | 0.723 | 0.933 | 0.636 | 1.368 |
| >499 | <0.001 | 0.481 | 0.349 | 0.663 | 0.111 | 0.757 | 0.538 | 1.066 |
| Multile myeloma status | | | | | | | | |
| Controlled disease | - | - | - | - | - | - | - | - |
| Stable disease | 0.355 | 1.191 | 0.822 | 1.724 | 0.574 | 1.117 | 0.759 | 1.643 |
| Active disease | <0.001 | 2.447 | 1.897 | 3.158 | **<0.001** | 1.655 | 1.256 | 2.182 |
| Unknown | 0.001 | 2.791 | 1.494 | 5.213 | **0.043** | 1.988 | 1.022 | 3.868 |
| Symptoms due to SARS-CoV-2 infection (at onset) | | | | | | | | |
| Pulmonary | - | - | - | - | - | - | - | - |
| Pulmonary + extrapulmonary | 0.148 | 0.810 | 0.610 | 1.078 | 0.727 | 0.947 | 0.698 | 1.285 |
| Extrapulmonary | <0.001 | 0.459 | 0.315 | 0.668 | 0.273 | 0.795 | 0.528 | 1.198 |
| Screening | <0.001 | 0.554 | 0.401 | 0.765 | 0.455 | 1.143 | 0.805 | 1.622 |
| SARS-CoV-2 vaccination status | | | | | | | | |
| Not vaccinated | - | - | - | - | - | - | - | - |
| One dose | 0.814 | 0.907 | 0.404 | 2.041 | 0.977 | 0.987 | 0.408 | 2.385 |
| Two or more doses | <0.001 | 0.438 | 0.315 | 0.609 | 0.215 | 0.752 | 0.479 | 1.180 |
| Stay during SARS-CoV-2 infection episode | | | | | | | | |
| Home | - | - | - | - | - | - | - | - |
| Hospital | <0.001 | 9.299 | 5.483 | 15.772 | **<0.001** | 5.967 | 3.381 | 10.532 |
| Intensive care unit | <0.001 | 26.887 | 15.666 | 46.144 | **<0.001** | 17.007 | 9.353 | 30.925 |

TABLE 2 (Continued)

| | Univariable | | | | Multivariable | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| | *p* Value | HR | Lower limit | Upper limit | *p* Value | HR | Lower limit | Upper limit |
| SARS-CoV-2 infection treatment | | | | | | | | |
| No specific treatment | - | - | - | - | - | - | - | - |
| AVs +/− corticosteroids +/− plasma | 0.035 | 1.745 | 1.041 | 2.924 | 0.156 | 0.666 | 0.381 | 1.167 |
| AVs + MoABs +/− corticosteroids +/− plasma | 0.629 | 0.703 | 0.169 | 2.932 | 0.127 | 0.324 | 0.076 | 1.377 |
| MoABs +/− corticosteroids +/− plasma | 0.722 | 0.862 | 0.381 | 1.952 | 0.220 | 0.581 | 0.244 | 1.383 |
| Corticosteroids +/− plasma | 0.027 | 3.226 | 1.141 | 9.119 | 0.640 | 1.291 | 0.442 | 3.773 |
| Corticosteroids | <0.001 | 2.627 | 1.600 | 4.311 | 0.710 | 0.904 | 0.530 | 1.542 |
| Unknown | <0.001 | 2.458 | 1.696 | 3.561 | 0.794 | 1.059 | 0.688 | 1.630 |

*Note*: Bold values are statistically significant.

Abbreviations: AVs, antivirals; CI, confidence interval; CPD, chronic pulmonary disease; HR, Hazard ratio; MoABs, monoclonal antibodies; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2.

BA.5, BQ.1.1, and XBB.1 omicron VOC new sub-variants have become largely prevalent (BQ.1.1 and XBB.1, particularly Europe and the United States). All these variants exhibit higher transmissibility than previous ones and manifest multiple novel spike protein mutations that have raised concerns about clinical outcome of SARS-CoV-2 infection infected by these strains, antiviral treatments and vaccine efficiency in MM patients.[51,52] However, these more recent dominant Omicron SARS-CoV-2 variants usually also often induce mild or asymptomatic disease with respect to the first waves of pandemic, sustained by SARS-CoV-2 ancestral WT, alpha and delta strains (all currently considered "de-escalated" variants), thus mimicking, though clearly to a lesser extent, what has been observed in the general population and also in other types of hematological and non-hematological cancers.[3]

These findings suffer from the unavoidable limitations of the observational nature of the study and the heterogeneity of the examined population, that is, incomplete dataset regarding some laboratory features; lack of evidence about humoral and cellular response to vaccines and VOC; variability of MM and SARS-CoV-2 infection management, and diverse vaccine policies followed in different countries.

Notwithstanding, our data indicates that a combination of complete vaccination programs and an appropriate general management, possibly along with the emergence of more transmissible, but less aggressive VOC, have significantly improved OS of MM patients infected by SARS-CoV-2 during the pandemic waves that have occurred over time. However, despite these improvements and the recent declaration of the end of pandemic by WHO (5 May 2023), it should be remembered that MM patients remain at risk of breakthrough infections and severe related complications. It is, therefore, still mandatory to maintain attention on these individuals.[53] In this setting, the European Myeloma Network has recently provided an updated expert consensus to guide MM patient management also in this "post-pandemic" era.[54]

## AUTHOR CONTRIBUTIONS

Pellegrino Musto, Jon Salmanton-García, Nicola Sgherza, Francesco Marchesi, Oliver A. Cornely and Livio Pagano contributed to study design, study supervision, statistical plan, data interpretation and wrote the paper. Jon Salmanton-García performed the analysis. All authors recruited participants and collected and interpreted data, contributed to manuscript writing and review of the manuscript, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and have read and agreed to the published version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

This manuscript was written as part of our routine work. Authors declare no conflict of interest regarding the submitted work.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## PEER REVIEW

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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