REVIEW ARTICLE

MULTIPLE MYELOMA, GAMMOPATHIES

Management of patients with multiple myeloma and COVID-19 in the post pandemic era: a consensus paper from the European Myeloma Network (EMN)

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In the post-pandemic COVID-19 period, human activities have returned to normal and COVID-19 cases are usually mild. However, patients with multiple myeloma (MM) present an increased risk for breakthrough infections and severe COVID-19 outcomes, including hospitalization and death. The European Myeloma Network has provided an expert consensus to guide patient management in this era. Vaccination with variant-specific booster vaccines, such as the bivalent vaccine for the ancestral Wuhan strain and the Omicron BA.4/5 strains, is essential as novel strains emerge and become dominant in the community. Boosters should be administered every 6–12 months after the last vaccine shot or documented COVID-19 infection (hybrid immunity). Booster shots seem to overcome the negative effect of anti-CD38 monoclonal antibodies on humoral responses; however, anti-BCMA treatment remains an adverse predictive factor for humoral immune response. Evaluation of the immune response after vaccination may identify a particularly vulnerable subset of patients who may need additional boosters, prophylactic therapies and prevention measures. Pre-exposure prophylaxis with tixagevimab/cilgavimab is not effective against the new dominant variants and thus is no longer recommended. Oral antivirals (nirmatrelvir/ritonavir and molnupiravir) and remdesivir are effective against Omicron subvariants BA.2.12.1, BA.4, BA.5, BQ.1.1 and/or XBB.1.5 and should be administered in MM patients at the time of a positive COVID-19 test or within 5 days post symptoms onset. Convalescent plasma seems to have low value in the post-pandemic era. Prevention measures during SARS-CoV-2 outbreaks, including mask wearing and avoiding crowded places, seem prudent to continue for MM patients.

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INTRODUCTION

Multiple myeloma (MM) is a plasma cell neoplasm defined by the aberrant proliferation of clonal plasma cells. Infections are a significant cause of morbidity and death in patients with MM [1]. The overload of the monoclonal component comprised of defective immunoglobulin, together with decreased levels of normal immunoglobulin classes and defective cellular and innate immunity, leads to an inadequate host immune response to pathogens [2]. Patient-related factors including age, frailty and comorbidities may increase the susceptibility to infections [3, 4].

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Furthermore, the current standard of anti-myeloma care includes drug combinations with significant hematological toxicity, such as neutropenia and lymphopenia. Patients treated with immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) are at an increased risk of severe infections [5, 6]. Although CD38-directed monoclonal antibodies diminish immunosuppressive regulatory T cells, they also impair natural killer (NK) cells and increase susceptibility to viral and bacterial infections including atypical infections [7]. B-cell maturation antigen (BCMA)-directed therapies deplete the B-cell compartment, eliminate mature plasma cells, and impair humoral response to pathogens [8]. Long-term use of steroids, as well as autologous stem cell transplantation (ASCT), are also associated with substantial immunosuppression [9].

Coronavirus disease 2019 (COVID-19) pandemic had a substantial impact on the management of patients with MM [10, 11], as they are at increased risk for severe COVID-19 and adverse outcomes [12]. Although treatment administration is no longer modified and vaccination is widely used, patients with MM present a substantial risk for breakthrough infections [13].

Currently, the dominant SARS-CoV-2 variants are more transmissible than previous strains but produce usually mild or asymptomatic COVID-19 in otherwise healthy, vaccinated individuals. At the same time, restrictions, related to SARS-CoV-2 preventive measures, have been lifted in the western countries. As we enter the post pandemic era and SARS-CoV-2 becomes endemic, the European Myeloma Network (EMN) aimed to provide updated directions for the management of patients with MM and COVID-19 (Table 1).

METHODOLOGY

In October 2022, a panel of experts of the EMN convened to develop updated consensus on the management of COVID-19 in MM patients. After a comprehensive review of the literature (PubMed, MM meetings and EMN consortia) from January 2020 to March 2023, a preliminary draft of the manuscript was distributed to all members of the group, who were invited to comment on the proposed manuscript draft and make suggestions. After the first manuscript proposal, further rounds of reviews and amendments, a final paper version was produced and approved by all authors.

COVID-19 in MM patients; prognostic factors and role of SARS-CoV-2 variants

Since 2019, SARS-CoV-2 infection appeared as a clinically heterogeneous disorder, ranging from a completely asymptomatic phase to mild or moderate respiratory symptoms, up to severe pneumonia, respiratory distress syndrome, multiorgan failure and death [14, 15]. Extra-pulmonary manifestations and various types of long-term complications were also subsequently recognized [16–19]. Patients with MM or other hematology malignancies (HM) are at high risk for severe COVID-19, compared to the general (healthy and non-cancer) population [20, 21] and possibly also to other cancer patients [22–24]. They may develop acute respiratory distress syndrome (ARDS) and thrombotic complications that can induce high in-hospital mortality [25]. This is due to MM patients' advanced age, co-existing medical conditions, as well as to humoral and cellular immunity compromised by the disease itself and by concomitant, often prolonged-applied targeted and immunosuppressive therapies, including steroids, monoclonal antibodies [26, 27], ASCT [28], and novel cellular therapies [29, 30]. Furthermore, MM patients often show low/suboptimal rates (in terms of percentage of responders and magnitude of response) of both humoral and functional T-cell immune responses to anti-SARS-CoV-2 vaccines [31–34]; this further contributes to an increased risk of severe COVID-19, need of hospitalization and higher mortality rates [35]. Notably, an appropriate use of one [36–40] or two [41, 42] "booster" doses may significantly improve vaccine performance, particularly among patients who failed to respond to the initial two doses with mRNA vaccines. However, several of these patients may still have vaccine failure due to severe immune impairment, particularly those who receive anti-BCMA treatments [39, 41].

It has been recently reported that the expression of angiogenic factors and glutamine deficiency could link COVID-19 severity and MM in the pathogenesis of thrombotic and other cardiovascular complications [43]. Furthermore, a longer time to respiratory deterioration after SARS-CoV-2 infection, compared to non-hematological subjects, also predicts mortality in MM patients, which suggests that prolonged clinical monitoring may be needed [44]. Finally, whilst SARS-CoV-2 infection may exacerbate the development of acute kidney injury and neurological complications in MM patients, the occurrence of secondary infections has also been associated with poor COVID-19 outcome [45].

Several papers have addressed the outcome of COVID-19 in MM patients, during the first waves of pandemic, sustained by SARS-CoV-2 ancestral Wuhan strain (WA1), alpha (B.1.1.7) and delta (B.1.617.2) variants (all currently considered "de-escalated" variants) in the pre-vaccination era, before December 2020 (Table 2) [11, 12, 21, 46–52].

Looking specifically at the data collected after the start of vaccination (grossly from December 2020), Ho et al. [4] reviewed the medical records of 174 MM patients with COVID-19 infection seen at Mayo Clinic between December 2019, and August 2021. The infection rate in this cohort was relatively low (2% among 9225 patients with MM or AL-amyloidosis), but one-fourth of the COVID-19 infections were severe. Nineteen (10%) patients required ICU admission and 5 (3%) patients needed mechanical ventilation. The mortality rate among hospitalized patients with COVID-19 was 22% (16/72 patients). On multivariate analysis, treatment with CD38 antibody within 6 months of COVID-19 infection, and cardiac or pulmonary comorbidities were independent predictors for ICU admission. Cardiac comorbidity [RR 2.6 (95% CI: 1.1, 6.5), $p = 0.038$] was an independent predictor of mortality, whereas unsurprisingly, achieving MM-remission was associated with lower mortality [RR 0.4 (95% CI: 0.2–0.8); $p = 0.008$].

On 26 November 2021, the WHO declared the Omicron variant (B.1.1.529) of SARS-CoV-2, as a new variant of concern (VOC), while since January 2022, BA.2.12.1, BA.4, BA.5, BQ.1.1, and XBB.1 Omicron VOC new sub-variants, all exhibiting higher transmissibility than the BA.2, have become largely prevalent. In addition, the BQ.1.1 and XBB.1 variants are now dominant in Europe and the US. The newly emerged Omicron variants of SARS-CoV-2 harbor multiple novel spike protein mutations that raise concerns about clinical outcome of COVID-19 in MM patients infected by these variants, vaccine efficiency and antiviral efficacy of the available therapeutic monoclonal antibodies. In fact, a recent publication shows the lowest vaccine-elicited neutralisation activity against BA.2.75.2, BQ.1.1, and XBB.1 [53].

The EPICOVIDEHA registry recently updated the outcome of 1221 MM patients with COVID-19 collected between February, 2020 and August, 2022 [54]. At the time of analysis, 414 patients (34%) were vaccinated with one or more doses (mainly with three). Of note, 446 patients (36.5%) were managed as outpatients during SARS-CoV-2 infection, while 775 patients (63.5%) were hospitalized. Over 10%, namely 13.8% ($n = 169$) of patients were admitted to an ICU and 63.3% of them required invasive mechanical ventilation. In 346 (28.3%) patients, specific treatments were reported, including various combinations of antivirals, monoclonal antibodies, corticosteroids and convalescent plasma. With a median follow-up of 52 days for the entire cohort and 83.5 days for survivors, 303 patients died (total mortality rate: 25%). The reported primary reason for death was COVID-19 or a combination of MM and COVID-19 in approximately 90% of patients. OS was significantly higher in vaccinated patients with both stable and active MM versus not vaccinated ones ($p = 0.002$

Table 1. Consensus statements on the management of patients with MM and COVID-19 in the post-pandemic era.

MM and COVID-19
• MM patients present an increased risk for severe COVID-19 infection, breakthrough infections, and poor COVID-19 outcomes including hospitalization and death, even in the era of novel SARS-CoV-2 mutants that produce milder COVID-19.
• Main clinical risk factors for severe outcomes are older age, male sex, uncontrolled disease, multiple comorbidities, race/ethnicity, severe/critical COVID-19, ICU admission and low response to vaccination.
• Specific anti-myeloma therapy, such as anti-CD38 antibodies and BCMA targeted therapy, increases the risk for severe COVID-19.
• Overall, management of myeloma patients with COVID-19 has been improved since the outburst of the pandemic, resulting in lower morbidity and mortality.
MM and COVID-19 vaccination
• Booster vaccines for SARS-CoV-2 should be administered to all patients with MM.
• Variant-specific booster vaccines, such as the bivalent vaccine for the ancestral Wuhan strain and the Omicron BA.4/5 strains, are important for COVID-19 protection, as novel strains emerge and become dominant in the community.
• Boosters should be administered 6–12 months after the last vaccine shot or documented COVID-19 infection (hybrid immunity). A 6–12 month interval between each booster dose is reasonable. It is unknown if boosters with the same vaccine are effective against the new virus strains.
• If possible, vaccination should be performed before the initiation of B-cell depleting therapies (CD38- or BCMA-targeting treatments). Booster shots seem to overcome the negative effect of anti-CD38 monoclonal antibodies, but not of anti-BCMA treatments, on humoral responses.
• Apart from active treatment with B-cell depleting therapies, risk factors for poor response to vaccination include older age, lymphopenia, immunoparesis and uncontrolled relapsed/refractory disease.
• Autologous stem cell transplantation does not seem to exert a negative effect on immune response following vaccination, especially if the vaccine is administered at least 3 months post-transplant.
• Evaluation of the immune response after vaccination may identify a particularly vulnerable subset of patients who may need additional boosters, prophylactic therapies and prevention measures. However, kits for neutralizing antibodies measurement against the new mutants are not commercially available.
• Household members and healthcare professionals caring for patients with MM should be vaccinated according to the guidelines for the general population.
Pre-exposure prophylaxis for COVID-19
• The combination of monoclonal antibodies tixagevimab/cilgavimab (Evusheld®) is no more active against the widely prevalent Omicron subvariants BQ.1, BQ.1.1, BA.4.6. and XBB.1.5. Evidence is therefore lacking that Evusheld can effectively protect vulnerable adults against the current and anticipated variants over the next 6 months of SARS-COV-2 and is therefore not recommended for prophylaxis.
• Immunoglobulin should be considered in patients with multiple episodes of recurrent/persistent infections and IgG levels less than 400 mg/ml.
• Patients with MM are important to follow prevention measures during SARS-CoV-2 outbreaks including mask wearing and avoiding crowded places.
Treatment of patients with MM and COVID-19
• Oral antivirals nirmatrelvir/ritonavir (Paxlovid) or molnupiravir (Lagevrio) can be offered to all MM outpatients with mild to moderate COVID-19 regardless vaccination or disease status, as soon as possible after the positive test for SARS-CoV-2 and within 5 days of COVID-19-related symptom onset. Careful consideration of drug interactions is essential. Nirmatrelvir/ritonavir is preferred over molnupiravir.
• Remdesivir can be administered intravenously both in the outpatient and the inpatient setting. For patients who cannot receive nirmatrelvir/ritonavir, the use of remdesivir is recommended.
• Oral antivirals and remdesivir remain effective against Omicron subvariants BA.2.12.1, BA.4, BA.5, BQ.1.1, XBB and XBB.1.5.
• High-titer convalescent plasma may improve patient outcomes; however, it is extremely difficult to have convalescent plasma against the novel mutants and, thus, its value is debatable in the post-pandemic era.
• Myeloma treatment should be interrupted and re-initiated upon symptom resolution.

MM multiple myeloma, *COVID-19* coronavirus disease 2019.

and $p = 0.003$, respectively). At multivariate analysis, age, renal failure, active disease, hospital stay and ICU admission were independently associated with poor survival. Notably, a time-dependent analysis revealed that mortality rates progressively and significantly declined throughout the different pandemic waves, from 34% (first wave) to 10.2% (last wave), likely reflecting, along with the already demonstrated usefulness of other general measures, the efficacy of extensive vaccination policies even against new emerging variants of concern, such as BA.2, BA.4, BA.5, B.Q.1.1, and XBB.1.

Another study from the EPICOVIDEHA registry was the first report on clinical data in a large cohort of exclusively Omicron-infected HM patients [55]. In total, 593 HM patients (including 97 MM) infected with documented Omicron VOC starting from June 2021 were analyzed. Overall mortality among hospitalized patients, was 16.5% (51/309), 95.4% of whom was classified as attributable to or contributable by Omicron. Risk factors associated with mortality in hospitalized patients were older age (HR 1.05 [95% CI] 1.02–1.07, $p < 0.001$]) and active malignancy (HR 2.5 [95% CI 1.3–4.8, $p = 0.007$]). Progression to critical infection occurred in 53 (17.0%) of hospitalized patients. A risk factor for progression to critical COVID-19 was pre-existent chronic pulmonary disease (OR 3.2 [95% CI 1.4–7.3, $p = 0.005$]). Baseline lymphocytes of ≥500 cells/mm^3 (OR 0.4 [95% CI 0.18–0.90, $p = 0.027$]) and three doses of vaccine were protective (OR 0.29 [95% CI 0.13–0.64, $p = 0.003$]). Mortality among patients with critical infection was 39.2% (20/53).

The update of EPICOVIDEHA registry showed that the mortality rate in patients with Omicron variants was 7.9%, comparable to other variants, with a significantly lower 30-day mortality rate than in the pre-vaccine era (31%). In the multivariable model, older age, active disease, severe COVID-19, and 2–3 comorbidities were

Table 2. Summary of selected studies reporting COVID-19-related outcomes in patients with MM in the pre-vaccination era.

Study	Number of patients [study design]	Region/Time period	Outcomes	Prognostic factors
[46]	58 MM [R]	Mount Sinai Hospital (New Yok City) / March 1, 2020 to April 30, 2020	36 hospitalized	Hospitalization: older age (>70 years), male sex, cardiovascular risk, and patients not in complete or stringent remission; Mortality among hospitalized: elevated inflammatory response to SARS-CoV-2, severe hypogammaglobulinemia, non-White race
[47]	100 MM [R]	Five academic centres in New York City / Spring of 2020	75 hospitalized, 13 invasive mechanical ventilation, 22 died	Intensive care unit (ICU) admission, mechanical ventilation, or death: race/ethnicity (Hispanics/Latinos or African American Blacks vs White), higher levels of inflammatory markers, cytokine activation
[48]	21 MM [R]	10 cancer German centres / March to May 2020	Longer duration to clinical improvement and longer hospitalization time vs healthy	No role of type of chemotherapy prior to COVID-19 diagnosis
[49]	75 MM [P]	UK / until May 2020	72 admitted for clinical care, 41 died	COVID-19-related mortality: higher median age, greater level of comorbidity, Afro-Caribbean compared to Caucasian origin and newly diagnosed patients.
[21]	106 PCD [R]	66 Italian hospitals / February and May, 2020	39 died	Poor outcomes: MM/plasmacytomas, older age, progressive underlying disease, severe or critical COVID-19
[50]	650 PCD [R]	International Myeloma Society / until June 2020	Thirty-three percent of hospitalized patients died, with significant geographic variability, ranging from 27% to 57% within ten different countries	Adverse outcomes: older age, high-risk MM, renal disease, suboptimal MM control
[51]	134 MM [P]	69 cancer hospitals UK Coronavirus Cancer Monitoring Project / March to August, 2020	Mortality rate 49.3%	Mortality for MM OR, 1.53; 95% CI, 1.04–2.26, ($p < 0.03$)
[11]	167 MM [R]	Spanish Myeloma Collaborative Group / March to April, 2020	Moderate/severe COVID-19: 89%; Mortality: 34%	Mortality: males, older than 65, active/progressive MM, renal disease
[12]	684 MM [R]	EPICOVIDEHA international registry / March to December 2020	Mortality rate = 33%, Decreased between the first (March–May 2020) and the second wave (October–December 2020)	Mortality: disease type, age, active malignancy, chronic cardiac disease, liver disease, renal impairment, smoking history, severe and critical SARS-COV-2 infection, ICU stay, low lymphocyte count

MM multiple myeloma, *PCD* plasma cell dyscrasias, *R* retrospective, *P* prospective.

correlated with a higher mortality, whereas monoclonal antibody administration against SARS-CoV-2, alone or combined with antivirals, was protective [54–56].

COVID-19 vaccine effectiveness in patients with MM

The most important strategy to fight COVID-19 is vaccination. The authorized vaccines employ a variety of platforms including mRNA, viral vectors, proteins/peptides, and inactivated viruses. Despite that robust clinical data with direct comparisons among the available vaccines are not available, preclinical results indicate that antibody responses to mRNA vaccines and the Novavax protein subunit vaccine are greater than those to viral-vectored and inactivated virus vaccines [57]. mRNA-based vaccines against SARS-CoV-2 are currently the mainstay of COVID-19 vaccination strategies in Europe and in the USA including booster vaccinations, preferably with the adapted bivalent vaccines [58].

Vaccine effectiveness in the real-world depends on several factors including demographic and host characteristics (age, comorbidities, previous COVID-19 infection, herd immunity), immune factors (humoral and T-cell response to vaccination, immune compromise, immunological disease), viral characteristics (antigenic shift, transmissibility, new variants) and factors related to vaccine access including vaccine type, number of doses and time interval between doses, vaccine availability [56]. In patients with MM, reduced vaccine response is caused by myeloma- and treatment-related immune deregulation, but it is further impacted by advanced age and comorbidities [31, 59]. Although novel SARS-CoV-2 variants are more transmissible than previous strains and they may compromise vaccine effectiveness, booster vaccination is effective against symptomatic infection from the Omicron variants. However, vaccine effectiveness wanes over time [60].

An emerging question, after the application of large vaccination campaigns and the appearance of novel virus mutants, is the incidence and the clinical outcome of breakthrough SARS-CoV-2 infection in vaccinated patients. In this setting, the National COVID Cohort Collaborative program provided real-world evidence on risks and outcomes of breakthrough SARS-CoV-2 infections in vaccinated patients with cancer [13]. A total of 1460 breakthrough cases within cancer patients partially or fully vaccinated with mRNA COVID-19 vaccines and no prior SARS-CoV-2 infection were recorded between December 2020 and May 2021. Solid tumors and HM had significantly higher risks for breakthrough infection (ORs = 1.12, 95% CI, 1.01 to 1.23 and 4.64, 95% CI, 3.98 to 5.38) and severe outcomes (ORs = 1.33, 95% CI, 1.09 to 1.62 and 1.45, 95% CI, 1.08 to 1.95) compared with non-cancer patients, adjusting for age, gender, race/ethnicity, smoking status, vaccine type, and vaccination date. In comparison with solid tumors, HM were at increased risk for breakthrough infections. Non-surprisingly, breakthrough risk was reduced after the second vaccine dose for all cancers (OR = 0.04; 95% CI, 0.04 to 0.05), and for Moderna's mRNA-1273 compared with Pfizer's BNT162b2 vaccine (OR = 0.66; 95% CI, 0.62 to 0.70), particularly in patients with MM (OR = 0.35; 95% CI, 0.15 to 0.72). Medications with major immunosuppressive effects and stem cell transplantation were strongly associated with increased breakthrough risk among the vaccinated population.

Literature data have shown that patients with MM are more likely to have breakthrough infections (13–15%) compared to non-cancer patients (~4%), and that these infections are linked to an increased risk of hospitalization along with significant morbidity and mortality [61–63]. Overall, older patients and those with common and significant comorbidities, as well as patients who received chemotherapy or targeted therapies, were more vulnerable to breakthrough infection [64].

The results of a recent cross-sectional study, including 3555 patients with cancer and 225,272 individuals without cancer, showed that the humoral response following COVID-19 vaccination may enable the identification of vulnerable patients. Patients with suboptimal levels of anti-spike SARS-CoV-2 antibodies had an increased risk for breakthrough COVID-19 infections and hospitalization due to COVID-19 [65]. Taking into consideration that studies addressing the clinical effectiveness of COVID-19 vaccines in patients with MM are rather limited, we may infer protection against COVID-19 by evaluating the kinetics of humoral response following vaccination [66, 67]. We should also consider that the presence of anti-SARS-CoV-2 spike receptor-binding domain (RBD) antibodies does not always correlate with the presence of neutralizing antibodies against SARS-CoV-2. Up to one third of vaccinated MM patients with two doses of mRNA-based vaccines, who have detectable anti-spike RBD antibodies, do not present neutralizing activity against SARS-CoV-2 [68]. Neutralizing antibody levels predict immunological protection against symptomatic SARS-CoV-2 infection [69, 70].

Several studies have evaluated the immune response following the prime complete COVID-19 vaccination in patients with MM [68, 71–110]. Three large meta-analyses have summarized the findings of these studies [32, 33, 111]. Gagelmann et al included data on 1564 patients from 13 studies and showed a pooled antibody response of 76% (95% CI: 67–83%) with significant heterogeneity ($I^2 = 91\%$) [33]. The results were consistent with the meta-analysis by Ito et al, who performed a subgroup analysis on 15 studies with data on MM and found a pooled seropositivity rate of 78% (95% CI: 69%-86%) with significant heterogeneity ($I^2 = 92\%$) [111]. Expectedly, patients with smoldering MM (SMM; 5 studies), similarly as presumed for MGUS patients, showed a high pooled seroconversion rate of 94% (95% CI: 76–100%; $I^2 = 87\%$), which was not statistically different from healthy individuals (random effects RR 0.96, 95% CI: 0.75–1.24) [111]. Active treatment with CD38-targeting drugs was associated with inferior humoral responses compared to other therapeutic combinations (random effects RR 0.86, 95% CI: 0.76–0.96) [111]. Overall, the neutralizing antibody response rate was 62.7% (range 53.3–68.6%) after two doses of mRNA SARS-CoV-2 vaccines. Patients who did not receive any treatment at the time of vaccination were more likely to seroconvert with a pooled odds ratio (OR) of 2.42 (95% CI: 1.10–5.33, low heterogeneity $I^2 = 7\%$). Patients on active treatment with anti-CD38 monoclonal antibodies had inferior humoral responses (pooled OR 0.42, 95% CI: 0.22–0.79, $I^2 = 14\%$) against the Wuhan strain but also against the Alpha and Delta SARS-CoV-2 variants [68, 90]. Patients who were vaccinated more than 30 days from the last anti-CD38 drug infusion seem to have enhanced humoral responses [94]. A longer time interval of 3 months from the last treatment dose to vaccination may further enhance seroconversion rates [112]. Patients with high-risk cytogenetics were also less likely to respond to vaccination (pooled OR of two studies 0.36, 95% CI: 0.18–0.69, $I^2 = 0\%$) [32].

Studies have also reported that older age, lymphopenia and active treatment with BCMA-targeting agents are associated with low rates of antibody response following prime two-dose COVID-19 vaccination [71, 72, 74, 76–78, 81, 86, 88, 89, 94, 96]. Recent ASCT does not seem to impair humoral responses to COVID-19 vaccination, thus most SCT-center recommend re-boosters post ASCT [84, 100, 107, 108]. Furthermore, mRNA1273 seems to induce greater neutralizing antibody responses compared with BNT162b2 in patients with MM [68].

Humoral immunity against SARS-CoV-2 declines over time and, thus, booster vaccination with mRNA-based vaccines has been implemented at 6 months following the completion of the prime vaccination. Terpos et al showed that booster vaccination significantly improves neutralizing antibody response against the Wuhan strain of SARS-CoV-2 with a median neutralization activity of 96.7% (interquartile range 52.6–97.8%) in a prospective study on 167 patients with symptomatic MM [39]. Importantly, almost half of the non-responders after the initial vaccination did respond following the booster vaccine shot. Of course, responders to

complete vaccination were more likely to mount robust antibody responses to booster vaccination. A third vaccine shot may also overcome the negative effect of anti-CD38 treatment, but not that of anti-BCMA agents [39]. Furthermore, a booster shot with mRNA-1273 may induce more robust antibody responses compared with the BNT162b2 booster [36].

Aleman et al. evaluated the immune response to booster vaccination in 261 patients with MM [113]. The booster vaccine shot (BNT162b2 or mRNA-1273) significantly increased the anti-spike RBD antibodies, including patients with antibody levels below the positivity threshold before the administration of the third dose, which is in line with other studies [36–38, 113–118]. Enssle et al. evaluated the neutralizing activity against SARS-CoV-2 variants in 100 patients with MM; the booster shot led to sufficient neutralization titers against Delta and Omicron in 64% and 29% of the patients, respectively [118]. Azeem et al. also reported that the third vaccine shot increased the neutralizing antibodies against Omicron in only one third of 187 patients with MM [119]. Breakthrough COVID-19 infections post booster were documented in 24 patients (13%), who also had lower neutralization titers against Omicron subvariants compared with the others [119].

Patients with relapsed/refractory disease (RRMM) may show attenuated neutralizing responses against Omicron even after the third vaccine shot, in comparison to newly-diagnosed patients who show an increase in neutralizing titers against both the Wuhan strain and variants of concern (Omicron, Delta, Gamma, Beta, Alpha) [120]. Active treatment, especially with B-cell depleting drugs, at the time of booster vaccination seems to have an adverse impact on the neutralizing activity against immunologically divergent SARS-CoV-2 variants, such as the Omicron BA.4/5 [121]. The levels of anti-spike antibodies have been correlated with neutralization capacity against Omicron; however, particularly higher levels were necessary to reach the neutralization threshold against Omicron as compared with Delta and Wuhan [113, 118, 121].

Furthermore, Ntanasis-Stathopoulos et al. evaluated the neutralizing humoral response against the ancestral strain of SARS-CoV-2 after the second booster vaccination (fourth vaccine dose against the initial Wuhan strain) in 201 patients with MM [41]. The fourth dose was administered 6 months after the third vaccine and restored the neutralizing activity against the Wuhan strain to the levels achieved after the first booster (median 96%). Although treatment with anti-CD38 did not impair humoral responses post second booster, anti-BCMA targeted therapy, with belantamab mafodotin, remained a negative predictive factor for antibody response [41]. Faustini et al. confirmed that multiple booster vaccine doses can provide effective protection from COVID-19, even with intensive anti-CD38 therapy for high-risk MM [122].

In addition, patients with MM present defective cellular responses to COVID-19 vaccination. Studies have shown that the initial two-dose vaccination scheme results in reduced levels of SARS-CoV-2-specific CD4 + T-cells, but not CD8 + T-cells, compared with healthy individuals [123]. A pooled analysis of three studies has shown that, on average, the rate of positive functional T-lymphocyte response was 44.2% (34.2–48.5%) after two doses of mRNA-based SARS-CoV-2 vaccines [32]. Following booster vaccination, patients with MM show remarkable CD4 + T cell-mediated cytokine responses against the Wuhan, Delta and Omicron strains [113, 118–120]. Spike-specific CD8 + T-cell responses to booster vaccination are more variable and may depend on the immune status of each patient [120]. Type of treatment at the time of vaccination seems to exert an important effect on cellular responses. Patients receiving anti-CD38 monoclonal antibodies or anti-BCMA bispecific T-cell engagers showed inferior CD4 + T-cell responses against SARS-CoV-2 compared with other therapeutic agents [99, 124]. Interestingly, a subset of patients on anti-CD38 directed treatments may present a delayed antibody response, which has been correlated with low counts of regulatory T-cells [125]. T-cell responses against SARS-CoV-2 variants of concern may be important to attenuate the disease severity in breakthrough infections [126]. Another point to consider is that spike-specific T-cell responses may become evident even in seronegative patients following vaccination [97, 119, 127], which underlines the importance of booster vaccination for supporting cellular immunity in these patients.

Moreover, recent studies have suggested that hybrid immunity, following recovery from earlier Omicron SARS-CoV-2 subvariants and vaccination, may be more protective against infection from novel subvariants compared to vaccination-only immunity [128]. The breadth of immune response against SARS-CoV-2 variants is also wider following infection than after vaccination [129]. Studies have shown mixed results regarding the serological response following COVID-19 in patients with plasma cell dyscrasias [130, 131]. Interestingly, SARS-CoV-2 infection may induce superior humoral responses compared to the initial two-dose vaccination scheme in patients with MM on active treatment [132]. Patients who had been infected with SARS-CoV-2 prior to COVID-19 immunization showed more robust antibody responses than COVID-19-naive patients [71]. Recovery from COVID-19 before the booster dose was also associated with enhanced humoral responses [118]. Therefore, hybrid immunity is important in patients with MM and those who have recovered from COVID-19 should follow the recommendations for booster vaccinations [133].

Last but not least, seasonal influenza has returned to the foreground and may lead to severe respiratory disease, especially in immunocompromised patients including those with MM. Tandem high-dose influenza vaccination separated by 30 days leads to higher serologic hemagglutinin inhibition titer responses and more durable influenza-specific immunity in patients with plasma cell dyscrasias compared to single-dose standard-of-care vaccination [134]. Therefore, two doses of flu vaccines separated by one month are recommended for patients with MM. Simultaneous administration of COVID-19 and influenza vaccines is feasible [9].

Pre- and post-exposure prophylaxis for COVID-19

Vaccination and everyday preventive measures against SARS-CoV-2 are the cornerstones of preventing COVID-19. Pre-exposure prophylaxis with monoclonal antibodies targeting SARS-CoV-2 has been found effective especially in the pre-Omicron era [135].

The emergence and dominance of new SARS-CoV-2 Omicron subvariants such as XBB and XBB.1.5 raises severe concerns on the neutralizing ability of tixagevimab/cilgavimab against these subvariants [136]. Due to lack of activity against the new omicron variants, the monoclonal antibodies tixagevimab/cilgavimab, sotrovimab and bebtelovimab are no longer authorized for clinical use by the FDA and EMA.

Immunoglobulin administration, either as IVIG or as subcutaneous IG, is not a SARS-CoV-2-specific treatment. It could be considered in patients with multiple episodes of recurrent/persistent infections and low IgG levels less than 400 mg/ml [9].

Treatment of patients with MM and COVID-19

The administration of oral antivirals including nirmatrelvir/ritonavir (Paxlovid) and molnupiravir (Lagevrio) in outpatients with COVID-19 and high risk for severe disease has improved patient outcomes in terms of hospitalization and death at 1 month [137, 138]. They should be administered as soon as possible after the positive SARS-CoV-2 test and within 5 days post symptoms onset.

However, a recent analysis of the PANORAMIC trial in the UK showed that the addition of molnupiravir in the standard care of patients with COVID-19 during the first 5 days did not improve patient outcomes in terms of hospitalization and death due to COVID-19, although a statistical non-significant tendency for shorter time to recovery was noted in the molnupiravir exposed group. More than 90% of the patients had received at least three

vaccine shots and all of them had increased risk of severe outcomes [139]. A recent study showed that the risk of viral rebound after receiving oral antivirals is small and it is not associated with excess mortality [140]. In vitro studies have shown that nirmatrelvir/ritonavir and molnupiravir remain effective against Omicron subvariants BA.2.12.1, BA.4, and BA.5, while nirmatrelvir/ritonavir is also effective against XBB and XBB.1.5 [141, 142].

A prospective study evaluated the efficacy and safety of oral antivirals in 169 patients with MM and COVID-19 [143]. All patients had received three doses of mRNA-based vaccines and were diagnosed with COVID-19 during the initial Omicron waves (first half of 2022). A total of 139 patients was treated with ritonavir-nirmatrelvir, while the remaining 30 patients were treated with molnupiravir. In total, 149 patients (88.2%) had a mild infection, 15 (8.9%) had moderate infection, and five (3%) had severe COVID-19. No differences in the severity of COVID-19-related outcomes were observed between the two antivirals. Patients with severe disease had lower neutralizing antibody levels before the COVID-19 infection compared to patients with mild disease ($p = 0.04$). Regarding treatment, it was observed that patients receiving belantamab mafodotin had a higher risk of severe COVID-19 ($p < 0.001$) [143]. Similar results have been reported in a case series of 15 patients with MM and COVID-19 who received antivirals [144].

However, it is known that almost 15% of patients cannot receive ritonavir-nirmatrelvir due to their concomitant medication. In this case, remdesivir is recommended; it is administered either in the outpatient setting for 3 consecutive days starting within 7 days of symptoms onset or in the inpatient setting for 5 consecutive days [145, 146]. Preclinical data have shown that remdesivir remains effective against Omicron subvariants, including XBB and XBB.1.5 [141]. However, Remdesivir usage is limited in patients with severe chronic kidney failure.

COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease such as MM or those receiving immunosuppressive treatment in inpatient or outpatient settings [147, 148]. Patient selection and time of convalescent plasma administration are important factors to consider [149]. However, there are no studies for the use of convalescent plasma in MM patients, especially in the era of Omicron subvariants, and thus the use of convalescent plasma is not recommended for use in MM patients.

Taking into consideration that most symptomatic COVID-19 infections last for less than 10 days, MM therapy may be postponed for 7 to 10 days from COVID-19 diagnosis, similar to the management of other infections [3]. Severe and complicated COVID-19 cases may necessitate longer treatment interruptions, prolonged hospitalization and intensive care [150].

CONCLUSIONS

MM patients are at high risk of severe COVID-19 and related mortality in the post-pandemic era; this risk is reduced compared to the initial Wuhan and Delta strains. According to different studies, risk factors for poor survival after COVID-19 in MM include older age, male sex, uncontrolled/active and/or high-risk disease, multiple comorbidities (mainly cardio-vascular, pulmonary and renal), inflammatory response, race/ethnicity, severe/critical COVID-19, ICU stay, lymphocyte count, vaccination status and recent systemic anticancer therapies (especially targeting BCMA). At least some of these parameters seem to have reduced their importance after the start of vaccination era (i.e. racial or ethnic disparities).

The rapid appearance of new and more diffusive viral mutants has maintained the incidence of COVID-19, although its poor clinical outcome appears to be mitigated. However, there are specific MM populations (i.e. those who receive anti-BCMA therapies) who remain minutely responsive to vaccines and at risk of severe and potentially life-threatening breakthrough infections. These data confirm the possible immune-escape of at least some Omicron variants and thus support calls for rapid approval of second-generation vaccines adapted to both the initial strains, but also to novel SARS-CoV-2 dominant mutants.

Currently available recommendations and detailed decision-making algorithms for the management of patients with MM during COVID-19 pandemic remain based on consensus and are lesser "evidence based", although important information have been implemented during the last three years (Table 1). Therefore, advocacy to include immune-compromised people in pivotal vaccine trials, in prospective cohort studies, and an effort to systematically test strategies to boost vaccine response will help to protect patients with HM (including MM) against COVID-19 and future outbreaks.

On the other hand, preventive measure must be strictly continued, even in the vaccination (and post-vaccination) phases, to maintain virus mitigation strategies in MM patients. MM patients should be vaccinated with an updated booster, preferably mRNA-based, omicron-adapted vaccines such as the Spikevax bivalent Original/Omicron BA.4–5 or the Comirnaty Original/Omicron BA.4–5, either in a treatment-free interval or when deep remission is achieved. Novel monoclonal antibodies targeting the novel SARS-CoV-2 variants for prophylactic use are highly anticipated by the MM community. In case of COVID-19 infection, MM patients should be offered oral antivirals or remdesivir, since they remain effective against Omicron subvariants.

New possibilities, such as the use of artificial neural networks (ANN) based on simple laboratory indices [151] are promising in order to generate useful models to predict the clinical outcome of COVID-19 and these methods could be applied to MM patients in the near future.

DATA AVAILABILITY

No data to deposit in a repository; further data available upon request from the corresponding author.

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AUTHOR CONTRIBUTIONS

ET, PM, ME, IN-S and HL reviewed the literature; ET, PM and HL drafted the first draft of the manuscript. All authors revised and approved the final version of the manuscript.

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ADDITIONAL INFORMATION

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