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TO THE EDITOR:

Risk factors for severe infection and mortality in COVID-19 and monoclonal gammopathy of undetermined significance

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Vaccines have been instrumental in reducing the incidence and severity of COVID-19, with efficacy rates of about 95% reported in phase 3 clinical data for both of the messenger-RNA vaccines (Pfizer and Moderna).[1-3] These studies excluded immunocompromised patients, including those with hematologic malignancies. For patients with multiple myeloma

(MM), vaccine efficacy is inferior and COVID-19 infections are more severe,[4] especially in those being treated with anti-CD38 or anti–B-cell maturation antigen–directed therapies.[5] Patients with monoclonal gammopathy of undetermined significance (MGUS) are at increased risk of infection, owing to suboptimal immune responses, compared to age-matched controls.[6,7] Data on the clinical course of COVID-19 infection in patients with MGUS are limited, and the impact of immunoparesis on the severity of infection needs additional evaluation.

Patients with MGUS evaluated at the Mayo Clinic in Minnesota, Arizona, and Florida, between 1 December 2019 and 31 August 2021, were screened, and those patients with a positive polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 were included in the study population (supplemental Figure 1, available on the *Blood* website). Severe COVID-19 infection was defined using the original study definition adopted for the messenger-RNA vaccine study (presence of respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death).[1] During the timeframe of the study, the Centers for Disease Control and Prevention recommended 2 doses of either the Pfizer or Moderna vaccine, or 1 dose of the Janssen vaccine, to complete the primary vaccine series, which was used to define "fully vaccinated" status. Cardiac comorbidity included structural or ischemic heart disease, and arrythmias. Pulmonary comorbidities included obstructive airway disease, interstitial lung disease, and obstructive sleep apnea.

Of 10 718 patients with MGUS, 290 patients (2.7%) had a documented positive COVID-19 polymerase chain reaction test and were included in this study. Most patients in this study (n = 197; 70%) developed COVID-19 between 1 October 2020 and 1 March 2021 (supplemental Figure 2A), which correlates to the third COVID-19 wave that occurred over the winter months of 2020 to 2021 (supplemental Figure 2B). The median duration of follow-up after a COVID-19 diagnosis was 11.2 months (95% confidence interval [CI]: 11, 12). Patient characteristics are depicted in Table 1. Quantitative immunoglobulin levels were available for 101 patients at the time of COVID-19 diagnosis, and 54 patients (53%) had immunoparesis, defined as suppression of ≥1 uninvolved immunoglobulin(s).[8] At the time of COVID-19 diagnosis, 254 patients (88%) were unvaccinated, 14 patients (5%) were partially vaccinated, and 22 patients (8%) had completed the initial vaccine series (supplemental Table 1). The median time from completion of the primary vaccination series to a positive test for COVID-19 was 100 days (range: 3-179). Twelve fully vaccinated patients (55%) developed COVID-19 at >90 days from the time of completion of the primary vaccination series, whereas the remaining 10 patients developed COVID-19 within 90 days. Of the 22 fully vaccinated patients, 3 (14%) developed a severe COVID-19 infection, including 1 COVID-related death (5%). Fully vaccinated patients, compared with unvaccinated patients, had a lower risk for severe COVID-19 infection (risk ratio [RR] 0.3 [95% CI: 0.08, 0.9]; P = .028). Data for vaccination status at the end of the follow-up period are provided in supplemental Table 1.

Data regarding hospitalization were available for 289 patients. A total of 97 patients (34%) required hospitalization, 22 patients (8%) required intensive care unit (ICU) admission, and 9 patients (3%) required mechanical ventilation. A total of 71 patients (24%) developed severe COVID-19, and of these, 68 (96%) were unvaccinated at the time of infection. Multivariable analysis identified age ≥65 years (RR: 3.2; 95% CI: 1.3, 7.5; P = .009), unvaccinated status at the time of COVID-19 infection (RR: 4; 95% CI: 1.1, 13.7; P = .003), underlying pulmonary comorbidity (RR: 2.1; 95% CI: 1.2, 3.7; P = .014), body mass index ≥40 (RR: 1.5; 95% CI: 0.8, 2.9; P = .018), and immunoparesis (RR: 3.6; 95% CI: 1.1, 11.1; P = .029) as significant risk factors for severe COVID-19 infection (Table 2). Results of univariable analysis are shown in Table 2 and supplemental Figure 3. A

Table 1. Patient characteristics

	n (%)
Total number of MGUS patients	290 (100)
Age at time of COVID-19 diagnosis, years	73 (23-99)*
Female sex	112 (39)
Anti-CD38 therapy within 6 months of COVID-19 diagnosis	3/289 (1)
Monoclonal gammopathy of renal significance	2/289 (0.7)
Type 3 cryoglobulinemia	1/289 (0.3)
Immunoparesis within 3 months of COVID-19 diagnosis	54/101 (53)
Severity of COVID-19 infection	
Asymptomatic/Mild	167 (58)
Moderate	52 (18)
Severe	71 (24)
Hospitalization needed during COVID-19 infection	97/289 (34)
ICU admission during COVID-19 infection	22/289 (8)
Mechanical ventilation required	9/289 (3)
VTE during COVID-19 infection	12/289 (4)
Number of COVID infections	
1	277 (96)
2	13 (4)
Deceased at follow-up	30 (10)
COVID-19–associated deaths	16 (6)
Cardiovascular complications	3 (1)
Non-COVID-19 infection	3 (1)
ESRD	2 (0.7)
Fall	2 (0.7)
Bowel perforation	1 (0.3)
COPD exacerbation	1 (0.3)
Dementia	1 (0.3)
Unclear	1 (0.3)

COPD, chronic obstructive pulmonary disease: ESRD, end-stage renal disease. ICU, intensive care unit; MGUS, monoclonal gammopathy of undetermined significance; VTE, venous thromboembolism.

*Median (range).

Table 2. Univariable and multivariable analysis of factors associated with all-cause mortality and severe COVID-19 in patients with monoclonal gammopathy of undetermined significance (MGUS) and COVID-19

Dependent variables	Variables significant on univariable analysis	Univariable analysis		Multivariable analysis	
		Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
Mortality	**Aged ≥65 y at COVID diagnosis**	**11.8 (1.6, 87.9)**	**.016**	**9 (1.2, 68.9)**	**.035**
	Cardiac disease	2.6 (1.2, 6)	.02	1.9 (0.8, 4.4)	.15
	eGFR < 60	2.2 (1, 4.6)	.048	1.8 (0.8, 4)	.13
Severe COVID-19	**Aged ≥65 y at COVID diagnosis**	**3.5 (1.6, 7.8)**	**.002**	**3.2 (1.3, 7.5)**	**.009**
	Unvaccinated	**4 (1.2, 13.5)**	**.025**	**4 (1.1, 13.7)**	**.03**
	Cardiac disease	2 (1.1, 3.4)	.015	1.5 (0.8, 2.9)	.17
	Pulmonary disease	**2.5 (1.5, 4.4)**	**.001**	**2.1 (1.2, 3.7)**	**.014**
	Hypertension	1.9 (1, 3.4)	.041	0.2 (1.5, 0.8, 2.9)	.23
	BMI ≥ 40 kg/m^2	**3.4 (1.4, 8.6)**	**.009**	**1.5 (0.8, 2.9)**	**.018**
	Immunoparesis	**3.2 (1.1, 9.7)**	**.037**	**3.6 (1.1, 11.1)**	**.029**

Boldface indicates statistical significance.

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate.

total of 22 patients (8%) required ICU admission; of these, 21 (95%) were unvaccinated at the time of COVID-19 infection, and 1 (5%) was fully vaccinated (with 1 Janssen vaccine).

A total of 30 patients (10%) were deceased (all-cause mortality) at the time of follow-up. Overall, of these 30 patients, 13 (43%) died within a month of infection, 16 (53%) died within 2 months of infection, and 17 (57%) died within 3 months of COVID-19 diagnosis. Of the 17 deaths that occurred within 3 months, 16 (6%) were COVID-19 related deaths (Table 1), and of these, 15 patients were unvaccinated and 1 patient was fully vaccinated (with 2 Pfizer vaccine doses). The non-COVID-19 causes of mortality are given in Table 1. A total of 19 of the 97 hospitalized patients (20%) were deceased at the time of follow-up. Multivariable analysis identified age ≥65 years (RR: 9; 95% CI: 1.2, 68.9; *P* = .035) as a risk factor for mortality after COVID-19 diagnosis (Table 2). Results of the univariable analysis are shown in Table 2 and supplemental Figure 4.

The cross-sectional prevalence of COVID-19 infection was 2.7%, with one-quarter of the infections being severe. Current data for severity of COVID-19 infection in patients with hematologic malignancies have been skewed due to disproportionate reporting of hospitalized patients, with mortality rates from COVID-19 reported to be between 10% and 34%.[9,10] Our study provides a more balanced representation of data, as we have included all patients with a COVID-19 infection rather than restricting the analysis to hospitalized patients. In our study, we identified immunoparesis at the time of COVID-19 infection as an independent predictor of a severe course of COVID-19 infection in patients with MGUS. Other risk factors for a severe infection include advanced age, unvaccinated status, underlying pulmonary comorbidity, and morbid obesity, all of which have been demonstrated consistently to be associated with a severe infection.[11,12] A small study of 91 patients with MGUS and a COVID-19 infection did not identify immunoparesis from the underlying monoclonal gammopathy to be a predictor of hospitalization, ICU admission, or mortality.[13] A recent case-control study identified that patients with MM and MGUS had a higher risk of breakthrough COVID-19 infections, compared to a matched cohort of the general population, while also demonstrating that MM-directed treatment increased the risk of severe infection.[14] However, another population-based study did not find MGUS to be associated with an increased risk of COVID-19 infection.[15] Additionally, these studies did not clearly address predictors of severe infection in patients with MGUS, which we have established in our study. An age-matched comparison to assess the impact of immunoparesis is fraught with multiple limitations, including differences in vaccination status, the timeframe of infections (different strains), and other medical comorbidities, and hence was not pursued in this study. Most patients in our cohort were unvaccinated at the time of first infection, which is expected given the timeframe of the study. A small subset of patients were fully vaccinated (8%) and still developed a COVID-19 infection, with approximately half of the infections occurring within 3 months of the completion of a primary vaccination series. Both early and delayed infections after vaccination may indicate a suboptimal response to vaccination as well as a rapidly waning immunity from vaccination, further highlighting the need for additional vaccine doses even in patients with MGUS.[16] The lack of correlative neutralizing antibody data after vaccination is a limitation in assessing vaccine efficacy in patients with MGUS. In conclusion, one-fourth of the patient population with MGUS and a COVID-19 infection had a severe infection, with immunoparesis being an independent predictor of severe infection. Advanced age was the only independent risk factor for higher risk of mortality.

Authorship

Contribution: M. Ho, S.Z., and S.K. conceived the project and contributed to the design of the study; M. Ho, S.Z., and S.K. collected the data, performed the analysis, and wrote the paper; and F.K.B., S.A., J.L., L.B., M.B., A.C.K., D.D., A.D., R.F., M.A.G., M. Hobbs, W.G., R.S.G., S.H., P.K., T.K., M.Q.L., N.L., Y.L., E.M., V.R., T.S., R.W., A.F., M. Ho, Y.L.H., R.A.K., S.V.R., and S.K. contributed data and reviewed the paper.

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Footnotes

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