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Risk Factors for Severe Infection and Mortality in COVID-19 and Monoclonal Gammopathy of Undetermined Significance

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Abstract:

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Vaccines have been instrumental in reducing incidence and severity of COVID-19 with efficacy rate of about 95% reported in phase 3 clinical data for both the mRNA vaccines (Pfizer and Moderna)[1-3]. These studies excluded immunocompromised patients, including those with hematologic malignancies. Patients with multiple myeloma (MM) have inferior vaccine efficacy and COVID-19 infections are more severe[4], especially in patients being treated with anti-CD38 or anti-B-cell maturation antigen (BCMA) directed therapies[5]. Patients with monoclonal gammopathy of undetermined significance (MGUS) are at increased risk of infections from suboptimal immune responses and demonstrate higher risk of infections compared to age-matched controls[6,7]. The data on clinical course of COVID-19 infections in patients with MGUS is limited and the impact of immune paresis on severity of infection needs additional evaluation.

Patients with MGUS evaluated at Mayo Clinic Rochester, Arizona, and Florida between 12/01/2019 and 8/31/2021 were screened and patients with a positive polymerase chain reaction (PCR) for SARS-CoV-2 were included in the study population (**Supplementary Figure 1**). Severe COVID-19 infection was defined using the original study definition adopted for the mRNA 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 study, the Center for Disease Control and Prevention (CDC) 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 or obstructive sleep apnea.

Out of 10,718 patients with MGUS, 290 (2.7%) patients had a documented positive COVID-19 PCR test and were included in this study. Most patients (n=197; 70%) in this study developed COVID-19 between 10/1/2020 to 03/1/2021 (**Supplementary Figure 2a**), which correlates to the third COVID-19 wave that occurred over the winter months of 2020–21 (**Supplementary Figure 2b**). The median duration of follow-up from COVID-19 diagnosis was 11.2 (95% CI: 11, 12) months. 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 (**Supplementary Table 1**). The median time from completion of primary vaccination series to testing positive for COVID-19 was 100 (range: 3–179) days. Twelve fully vaccinated patients (55%) developed COVID-19 greater than 90 days from time of completion of primary vaccination series, while the remaining 10 patients developed COVID-19 within 90 days. Three out of the 22 fully vaccinated patients (14%) developed a severe COVID-19 infection, including 1 COVID-related death (5%). Comparing fully vaccinated versus unvaccinated patients, fully vaccinated patients had a lower risk for severe COVID-19 infection [RR 0.3 (95% CI: 0.08, 0.9); p=0.028]. Data for vaccination status at end of follow-up period is depicted in **Supplementary Table 1**.

Data regarding hospitalization was available for 289 patients. Ninety-seven patients (34%) required hospitalization, 22 patients (8%) required ICU admission, and 9 patients (3%) required mechanical ventilation. Seventy-one patients (24%) developed severe

COVID-19 and of these, 68 (96%) were unvaccinated at time of infection. Multivariable analysis identified age ≥65 years (RR: 3.2; 95% CI: 1.3, 7.5; p=0.009), unvaccinated status at time of COVID-19 infection (RR: 4; 95% CI: 1.1, 13.7; p=0.003), underlying pulmonary comorbidity (RR: 2.1; 95% CI: 1.2, 3.7; p=0.014), BMI ≥40 (RR: 1.5; 95% CI: 0.8, 2.9; p=0.018), and immunoparesis (RR: 3.6; 95% CI: 1.1, 11.1; p=0.029) as significant risk factors for severe COVID-19 infection (Table 2). Results of univariable analysis are shown in **Table 2** and **Supplementary Figure 3**. Twenty-two patients (8%) required ICU admission with 21 (95%) of these ICU patients were unvaccinated at time of COVID-19 and 1 patient (5%) was fully vaccinated (Janssen x 1).

Thirty (10%) patients were deceased (all-cause mortality) at the time of follow-up. Overall, 13/30 patients (43%) died within a month of infection, 16/30 (53%) died within 2 months of infection, and 17/30 patients (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), of which 15 patients were unvaccinated and 1 patient was fully vaccinated (Pfizer x 2). The non-COVID-19 causes of mortality are depicted in **Table 1**. Nineteen out of the 97 hospitalized patients (20%) were deceased at time of follow-up. Multivariable analysis identified age ≥65 years (RR: 9; 95% CI: 1.2, 68.9; p=0.035) as a risk factor for mortality after COVID-19 diagnosis (Table 2). Results of univariable analysis are shown in **Table 2** and **Supplementary Figure 4**.

The cross-sectional prevalence of COVID-19 infection was 2.7% with a quarter of the infections being severe. Current data for severity of COVID-19 infection in patients with hematologic malignancies have largely been skewed due to disproportionate reporting of hospitalized patients with mortality rates from COVID-19 reported between 10-34%

[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 included advanced age, unvaccinated status, underlying pulmonary comorbidity and morbid obesity, all of which have been consistently demonstrated 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 the underlying monoclonal gammopathy to be a predictor of hospitalization, ICU admission or mortality [13]. A recent case-control study identified that patients with multiple myeloma and MGUS had higher risk of breakthrough COVID-19 infections compared to a matched cohort of general population, while also demonstration MM-directed treatment increased the risk of severe infection [14]. However, another population-based study did not identify 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 impact of immunoparesis is fraught with multiple limitations including differences in vaccination status, 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 time frame 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 being within 3 months of the completion of primary series of vaccination. Both early and delayed infections after vaccination point

toward possibly a suboptimal response to vaccination as well as a rapidly waning immunity from vaccination, further highlighting 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-fourths 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.

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201 **Table 1: Patient characteristics**

	Median (range) or 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	
One	277 (96%)
Two	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%)

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Table 2: Univariable and multivariable analysis of factors associated with all-cause mortality and severe COVID-19 in patients with MGUS and COVID-19.

Dependent variables	Variables significant on univariable analysis	Univariable analysis		Multivariable analysis	
		Risk ratio (95% CI)	P-value	Risk ratio (95% CI)	P-value
Mortality	**≥65 years at COVID diagnosis**	**11.8 (1.6, 87.9)**	**0.016**	**9 (1.2, 68.9)**	**0.035**
	Cardiac disease	2.6 (1.2, 6)	0.02	1.9 (0.8, 4.4)	0.15
	eGFR < 60	2.2 (1, 4.6)	0.048	1.8 (0.8, 4)	0.13
Severe COVID-19	**≥65 years at COVID diagnosis**	**3.5 (1.6, 7.8)**	**0.002**	**3.2 (1.3, 7.5)**	**0.009**
	Unvaccinated	**4 (1.2, 13.5)**	**0.025**	**4 (1.1, 13.7)**	**0.03**
	Cardiac disease	2 (1.1, 3.4)	0.015	1.5 (0.8, 2.9)	0.17
	Pulmonary disease	**2.5 (1.5, 4.4)**	**0.001**	**2.1 (1.2, 3.7)**	**0.014**
	Hypertension	1.9 (1, 3.4)	0.041	0.2 (1.5, 0.8, 2.9)	0.23
	BMI ≥40	**3.4 (1.4, 8.6)**	**0.009**	**1.5 (0.8, 2.9)**	**0.018**
	Immunoparesis	**3.2 (1.1, 9.7)**	**0.037**	**3.6 (1.1, 11.1)**	**0.029**