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

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32 Vaccines have been instrumental in reducing incidence and severity of COVID-19 with
33 efficacy rate of about 95% reported in phase 3 clinical data for both the mRNA vaccines
34 (Pfizer and Moderna)¹⁻³. These studies excluded immunocompromised patients,
35 including those with hematologic malignancies. Patients with multiple myeloma (MM)
36 have inferior vaccine efficacy and COVID-19 infections are more severe⁴, especially in
37 patients being treated with anti-CD38 or anti-B-cell maturation antigen (BCMA) directed
38 therapies⁵. Patients with monoclonal gammopathy of undetermined significance
39 (MGUS) are at increased risk of infections from suboptimal immune responses and
40 demonstrate higher risk of infections compared to age-matched controls^{6,7}. The data on
41 clinical course of COVID-19 infections in patients with MGUS is limited and the impact
42 of immune paresis on severity of infection needs additional evaluation.

43 Patients with MGUS evaluated at Mayo Clinic Rochester, Arizona, and Florida between
44 12/01/2019 and 8/31/2021 were screened and patients with a positive polymerase chain
45 reaction (PCR) for SARS-CoV-2 were included in the study population (**Supplementary**
46 **Figure 1**). Severe COVID-19 infection was defined using the original study definition
47 adopted for the mRNA vaccine study [presence of respiratory failure, evidence of shock,
48 significant acute renal, hepatic, or neurologic dysfunction, admission to an intensive
49 care unit, or death]¹. During the timeframe of study, the Center for Disease Control and
50 Prevention (CDC) recommended 2 doses of either the Pfizer or Moderna vaccine or 1
51 dose of the Janssen vaccine to complete the primary vaccine series, which was used to
52 define “fully vaccinated” status. Cardiac comorbidity included structural or ischemic
53 heart disease, and arrhythmias. Pulmonary comorbidities included obstructive airway
54 disease, interstitial lung disease or obstructive sleep apnea.

55 Out of 10,718 patients with MGUS, 290 (2.7%) patients had a documented positive
56 COVID-19 PCR test and were included in this study. Most patients (n=197; 70%) in this
57 study developed COVID-19 between 10/1/2020 to 03/1/2021 (**Supplementary Figure**
58 **2a**), which correlates to the third COVID-19 wave that occurred over the winter months
59 of 2020–21 (**Supplementary Figure 2b**). The median duration of follow-up from
60 COVID-19 diagnosis was 11.2 (95% CI: 11, 12) months. Patient characteristics are
61 depicted in **Table 1**. Quantitative immunoglobulin levels were available for 101 patients
62 at the time of COVID-19 diagnosis and 54 patients (53%) had immunoparesis, defined
63 as suppression of ≥ 1 uninvolved immunoglobulin(s) ⁸. At the time of COVID-19
64 diagnosis, 254 patients (88%) were unvaccinated, 14 patients (5%) were partially
65 vaccinated, and 22 patients (8%) had completed the initial vaccine series
66 (**Supplementary Table 1**). The median time from completion of primary vaccination
67 series to testing positive for COVID-19 was 100 (range: 3–179) days. Twelve fully
68 vaccinated patients (55%) developed COVID-19 greater than 90 days from time of
69 completion of primary vaccination series, while the remaining 10 patients developed
70 COVID-19 within 90 days. Three out of the 22 fully vaccinated patients (14%) developed
71 a severe COVID-19 infection, including 1 COVID-related death (5%). Comparing fully
72 vaccinated versus unvaccinated patients, fully vaccinated patients had a lower risk for
73 severe COVID-19 infection [RR 0.3 (95% CI: 0.08, 0.9); p=0.028]. Data for vaccination
74 status at end of follow-up period is depicted in **Supplementary Table 1**.

75 Data regarding hospitalization was available for 289 patients. Ninety-seven patients
76 (34%) required hospitalization, 22 patients (8%) required ICU admission, and 9 patients
77 (3%) required mechanical ventilation. Seventy-one patients (24%) developed severe

78 COVID-19 and of these, 68 (96%) were unvaccinated at time of infection. Multivariable
79 analysis identified age ≥ 65 years (RR: 3.2; 95% CI: 1.3, 7.5; $p=0.009$), unvaccinated
80 status at time of COVID-19 infection (RR: 4; 95% CI: 1.1, 13.7; $p=0.003$), underlying
81 pulmonary comorbidity (RR: 2.1; 95% CI: 1.2, 3.7; $p=0.014$), BMI ≥ 40 (RR: 1.5; 95% CI:
82 0.8, 2.9; $p=0.018$), and immunoparesis (RR: 3.6; 95% CI: 1.1, 11.1; $p=0.029$) as
83 significant risk factors for severe COVID-19 infection (Table 2). Results of univariable
84 analysis are shown in **Table 2** and **Supplementary Figure 3**. Twenty-two patients (8%)
85 required ICU admission with 21 (95%) of these ICU patients were unvaccinated at time
86 of COVID-19 and 1 patient (5%) was fully vaccinated (Janssen x 1).
87 Thirty (10%) patients were deceased (all-cause mortality) at the time of follow-up.
88 Overall, 13/30 patients (43%) died within a month of infection, 16/30 (53%) died within 2
89 months of infection, and 17/30 patients (57%) died within 3 months of COVID-19
90 diagnosis. Of the 17 deaths that occurred within 3 months, 16 (6%) were COVID-19
91 related deaths (Table 1), of which 15 patients were unvaccinated and 1 patient was fully
92 vaccinated (Pfizer x 2). The non-COVID-19 causes of mortality are depicted in **Table 1**.
93 Nineteen out of the 97 hospitalized patients (20%) were deceased at time of follow-up.
94 Multivariable analysis identified age ≥ 65 years (RR: 9; 95% CI: 1.2, 68.9; $p=0.035$) as a
95 risk factor for mortality after COVID-19 diagnosis (Table 2). Results of univariable
96 analysis are shown in **Table 2** and **Supplementary Figure 4**.
97 The cross-sectional prevalence of COVID-19 infection was 2.7% with a quarter of the
98 infections being severe. Current data for severity of COVID-19 infection in patients with
99 hematologic malignancies have largely been skewed due to disproportionate reporting
100 of hospitalized patients with mortality rates from COVID-19 reported between 10-34%

101 ^{9,10}. Our study provides a more balanced representation of data as we have included all
102 patients with a COVID-19 infection rather than restricting the analysis to hospitalized
103 patients. In our study, we identified immunoparesis at the time of COVID-19 infection
104 as an independent predictor of a severe course of COVID-19 infection in patients with
105 MGUS. Other risk factors for a severe infection included advanced age, unvaccinated
106 status, underlying pulmonary comorbidity and morbid obesity, all of which have been
107 consistently demonstrated to be associated with a severe infection ^{11,12}. A small study of
108 91 patients with MGUS and a COVID-19 infection did not identify the underlying
109 monoclonal gammopathy to be a predictor of hospitalization, ICU admission or mortality
110 ¹³. A recent case-control study identified that patients with multiple myeloma and MGUS
111 had higher risk of breakthrough COVID-19 infections compared to a matched cohort of
112 general population, while also demonstration MM-directed treatment increased the risk
113 of severe infection ¹⁴. However, another population-based study did not identify MGUS
114 to be associated with an increased risk of COVID-19 infection ¹⁵. [Additionally, these
115 studies did not clearly address predictors of severe infection in patients with MGUS,](#)
116 which we have established in our study. An age-matched comparison to assess impact
117 of immunoparesis is fraught with multiple limitations including differences in vaccination
118 status, timeframe of infections (different strains) and other medical comorbidities, and
119 hence was not pursued in this study. Most patients in our cohort were unvaccinated at
120 the time of first infection which is expected given the time frame of the study. A small
121 subset of patients were fully vaccinated (8%) and still developed a COVID-19 infection,
122 with approximately half of the infections being within 3 months of the completion of
123 primary series of vaccination. Both early and delayed infections after vaccination point

124 toward possibly a suboptimal response to vaccination as well as a rapidly waning
125 immunity from vaccination, further highlighting need for additional vaccine doses even in
126 patients with MGUS ¹⁶. The lack of correlative neutralizing antibody data after
127 vaccination is a limitation in assessing vaccine efficacy in patients with MGUS. In
128 conclusion, one-fourths of the patient population with MGUS and a COVID-19 infection
129 had a severe infection with immunoparesis being an independent predictor of severe
130 infection. Advanced age was the only independent risk factor for higher risk of mortality.

131

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134 paper. F.B, S.A, J.L, L.B, M.B, A-C-K, D.D, A.D, R.F, M.G, W.G, R.G, S.H, P.K, T.K,
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198 BCMA therapy. *Blood*. 2022;139(9):1409-1412.
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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	

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