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RESEARCH ARTICLE

COVID-19 Infections and Clinical Outcomes in Patients with Multiple Myeloma in New York City: A Cohort Study from Five Academic Centers

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ABSTRACT

Patients with multiple myeloma have a compromised immune system, due to both the disease and antimyeloma therapies, and may therefore be particularly susceptible to COVID-19. Here, we report outcomes and risk factors for serious disease in patients with multiple myeloma treated at five large academic centers in New York City in the spring of 2020, during which it was a global epicenter of the SARS-CoV-2 pandemic. Of 100 patients with multiple myeloma (male 58%; median age 68) diagnosed with COVID-19, 75 were admitted; of these, 13 patients (17%) were placed on invasive mechanical ventilation, and 22 patients (29%) expired. Of the 25 nonadmitted patients, 4 were asymptomatic. There was a higher risk of adverse outcome (intensive care unit admission, mechanical ventilation, or death) in Hispanics/Latinos ($n = 21$), OR = 4.7 (95% confidence interval, 1.3–16.7), and African American Blacks ($n = 33$), OR = 3.5 (1.1–11.5), as compared with White patients ($n = 36$). Patients who met the adverse combined endpoint had overall higher levels of inflammatory markers and cytokine activation. None of the other studied risk factors were significantly associated ($P > 0.05$) with adverse outcome: hypertension ($n = 56$), OR = 2.2 (0.9–5.4); diabetes ($n = 18$), OR = 0.9 (0.3–2.9); age >65 years ($n = 63$), OR = 1.8 (0.7–4.6); high-dose melphalan with autologous stem cell transplant <12 months ($n = 7$), OR = 0.9 (0.2–5.4); and immunoglobulin G <650 mg/dL ($n = 42$), OR = 0.9 (0.3–2.2). In this largest cohort to date of patients with multiple myeloma and COVID-19, we found the case fatality rate to be 29% among hospitalized patients and that race/ethnicity was the most significant risk factor for adverse outcome.

SIGNIFICANCE: Patients with multiple myeloma are immunocompromised, raising the question whether they are at higher risk of severe COVID-19 disease. In this large case series on COVID-19 in patients with multiple myeloma, we report 29% mortality rates among hospitalized patients and identify race/ethnicity as the most significant risk factor for severe outcome.

See related commentary by Munshi and Anderson, p. 218.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by the SARS-CoV-2 virus, has become a global health crisis since it was first reported in Wuhan, China, in December 2019 (1, 2). COVID-19 has so far caused over 600,000 deaths globally and has spread to the majority of countries around the world (https://coronavirus.jhu.edu/map.html). New York City was one of the global epicenters for the SARS-CoV-2 outbreak in the spring of 2020, and a significant number of individuals have been infected by the virus, including both patients with underlying health conditions as well as healthy individuals (3). Clinical symptoms of COVID-19 include fever, cough, fatigue, diarrhea, headaches, and shortness of breath (1). They range from mild symptoms to severe disease characterized by pneumonia, hypoxia, respiratory failure, acute respiratory disease syndrome (ARDS), immune dysregulation, cytokine storm, thromboembolic events, and multiorgan failure (1). Reported risk factors for severe COVID-19 disease are male gender, advanced age, smoking, and certain comorbidities such as hypertension (1, 4).

Several studies of varying size have suggested that patients with cancer on active therapy or recent surgery have a higher risk of a more severe COVID-19 disease course (2, 5–14). Patients with metastatic disease or hematologic cancers have been among those with the poorest outcomes (10). In addition, recent immunotherapy treatment with checkpoint inhibitors was associated with a poorer outcome (7). Patients with multiple myeloma have an inherently compromised humoral and cellular immunity from the malignant plasma cell disorder itself and its associated hypogammaglobulinemia (15). The immunosuppression seen at presentation can be exacerbated by the standard combination antimyeloma therapies currently in use (16). Among the conventional treatment options for multiple myeloma, the use of high-dose melphalan chemotherapy followed by autologous stem cell transplant is particularly associated with acute and sustained hypogammaglobulinemia and T-cell suppression (17). Here, we report on the largest experience to date from a cohort of patients with multiple myeloma with COVID-19 from five large academic centers in New York City during the height of the COVID-19 outbreak.

RESULTS

We identified a total of 100 patients with multiple myeloma and COVID-19. Median age at the time of COVID-19

Table 1. Patients' characteristics

	Number (%)
All patients	127 (100)
Men	68 (54)
Women	59 (46)
Median age at COVID-19 (years)	68 years
Former/current smoker	34 (27)
Never smoker	92 (73)
Multiple myeloma	100 (79)
Newly diagnosed multiple myeloma	30
Stable multiple myeloma without relapse	35
Relapsed/refractory multiple myeloma	35
MGUS	20 (16)
Smoldering multiple myeloma	3 (2.4)
AL amyloidosis	3 (2.4)
Solitary plasmacytoma	1 (0.8)

Note: Three multiple myeloma patients had concomitant AL amyloidosis.

Abbreviations: AL, amyloid light-chain; MGUS, monoclonal gammopathy of undetermined significance.

Table 2. Treatment regimens in patients with multiple myeloma at the time of COVID-19 diagnosis

	Number
All patients	100
Patients with ongoing treatment	86
Bortezomib-including regimen	20
Carfilzomib-including regimen	15
Daratumumab-including regimen	24
Ixazomib-including regimen	6
Lenalidomide maintenance	22
Other treatments[a]	10
Prior MEL/ASCT	39
Prior allogeneic transplant	2
Not on treatment	12
Missing information regarding treatment status	2

[a]Other treatments included DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin), low-dose melphalan, panabinostat, iberomid, chlarithromycin, venetoclax, selinexor, and AMG-701.

Abbreviation: MEL/ASCT, melphalan/autologous stem cell transplant.

infection was 68 years (range, 41–91 years). Fifty-eight (58%) of the patients were male, and 24 were current or former smokers (Table 1). Concomitant cardiovascular or pulmonary comorbidities were seen in 74 patients, of which hypertension was the most common (56%). In addition, we identified 27 patients with related plasma cell disorders; 20 with monoclonal gammopathy of undetermined significance (MGUS), 3 with smoldering multiple myeloma (SMM), 3 patients with amyloid light-chain (AL) amyloidosis, and 1 patient with solitary plasmacytoma (Table 1).

Of the 100 patients with multiple myeloma, 28 patients (28%) had newly diagnosed multiple myeloma; 26 were being treated with induction therapy, 1 had not yet started induction, and 1 had opted not to start therapy. There were 35 (35%) patients with stable disease (i.e., nonactive disease); 23 of these were on lenalidomide maintenance, 5 were on other forms of maintenance including ixazomib/dexamethasone and daratumumab/dexamethasone, and 7 patients with stable disease were monitored off therapy. Thirty-five (35%) patients had relapsed/refractory multiple myeloma, of which 31 were on various anti–multiple myeloma treatments—the majority daratumumab- or carfilzomib-based treatments. The remaining 4 relapsed/refractory patients were not on active anti-myeloma therapy due to advance disease stage (hospice) or other more pressing comorbidities. Information on treatment status was missing for 2 patients, who had both been classified as newly diagnosed multiple myeloma (Table 2). Overall, a total of 39 patients had undergone high-dose melphalan followed by autologous stem cell transplant—7 patients within the 12 months prior to contracting COVID-19. Six patients and 1 patient had undergone high-dose melphalan followed by autologous stem cell transplant within 6 months and 3 months, respectively, prior to contracting COVID-19. Two patients had a prior allogeneic stem cell transplant several years before the COVID-19 diagnosis (Table 2). Forty-two patients (42%) had hypogammaglobulinemia [immunoglobulin G (IgG) <650 mg/dL], and 18 patients (18%) had severe hypogammaglobulinemia (IgG <400 mg/dL).

The laboratory findings in this multiple myeloma cohort revealed lymphopenia and elevated C-reactive protein, ferritin, D-dimer, and interleukin 6 (IL-6) levels (Table 3). Patients who met the adverse combined endpoint [i.e., intensive care unit (ICU) admission, invasive mechanical ventilation, or death] had overall higher levels of inflammatory markers, reflecting a more severe infection and cytokine activation (Table 3).

Of the 100 patients with multiple myeloma and a SARS-CoV-2 positive RNA PCR test on this study, 75 (75%) were admitted due to COVID-19; 17 were admitted to the ICU, and 13 of these patients were placed on invasive mechanical ventilation. Twenty-two of the multiple myeloma patients, thus 29% of those admitted, expired during the follow-up time; all reported deaths were from COVID-19.

Regarding treatments used for COVID-19, 52 patients were treated with hydroxychloroquine and 52 with azithromycin; 42 had the combination of the two, and 35 received neither hydroxychloroquine nor azithromycin (Table 4). Twenty-seven patients were treated with steroids, mainly dexamethasone or methylprednisone, for COVID-19. Nine patients received treatment with IL-6 inhibitors, tocilixumab or sarilumab, and 1 patient was treated with the IL-1 inhibitor anakinra and the TNF-alpha inhibitor infliximab. Other treatments included broad-spectrum antibiotics and investigational antiviral therapies such as lopinavir-ritonavir ($n = 4$) and remdesivir ($n = 3$). Two patients were treated with convalescent plasma.

Nine patients developed COVID-19-related thromboembolic events: 7 venous thromboembolic events and 2 cerebrovascular events. Six of these patients were on active multiple myeloma therapy prior to the COVID-19 diagnosis—4 on treatment including lenalidomide. The majority of admitted

Table 3. Laboratory findings in patients with multiple myeloma and COVID-19

	All patients $n = 100$			With combined adverse outcome $n = 29$			Without combined adverse outcome $n = 71$				
	Median	Range	*n*	Median	Range	*n*	Median	Range	*n*	Reference range	*P*
ANC	3.2	0.4–17.5	82	4.0	0.4–17.2	26	2.5	0.4–17.5	56	1.5–7.5 ($\times 10^9$/L)	0.025
ALC	0.6	0.1–1.8	82	0.6	0.1–1.2	26	0.7	0.1–1.8	56	0.9–3.2 ($\times 10^9$/L)	0.21
Platelets	152	6–507	82	119	6–350	26	164.5	19–507	56	160–400 ($\times 10^9$/L)	0.037
C-reactive protein	34	2.7–293	65	37	5.5–293	25	25.5	2.7–259	40	<0.50 (mg/dL)	0.25
Ferritin	658	2–40,000	64	2,015	42–40,000	25	476	2–7,174	39	22–415 (ng/mL)	0.001
D-dimer	1.3	0.2–83	59	3.0	0.3–83	24	0.9	0.2–5.5	35	<0.5 (mcg/mL FEU)	0.001
IL-6	71	6–3,238	50	102	7.3–3,238	21	64.5	6.0–532	29	<5.0 (pg/dL)	0.14

Note: Adverse combined endpoint = ICU admission, mechanical ventilation, or death. Wilcoxon rank test was used to compare laboratory values for patients who had the combined adverse outcome versus patients without the adverse outcome.

Abbreviations: ANC, absolute neutrophil count; ALC, absolute lymphocyte count; IL-6, interleukin 6.

patients ($n = 47$) were on thromboprophylaxis with heparin or low molecular-weight heparin prophylaxis, unless there was a contraindication or prophylaxis was not indicated (young, mobile patient with mild disease). Nine patients were on direct anticoagulatory medication; the majority continued while inpatient in lieu of heparin or low molecular-weight heparin prophylaxis. Two patients did not receive thromboprophylaxis and information on prophylaxis was missing for 1 patient who developed thrombosis. Fifteen of the patients with multiple myeloma continued on low-dose aspirin prophylaxis, and the majority of these were outpatients.

Twenty-nine patients (29%) of the 100 patients with multiple myeloma met the combined adverse endpoint (ICU admission, invasive mechanical ventilation, or death). The risk of adverse outcome was highest in Hispanic/Latino patients ($n = 21$), OR = 4.7 (1.3–16.7), and African American Blacks ($n = 33$), OR = 3.5 (1.1–11.5), compared with White patients ($n = 36$; Fig. 1). There was no significant difference between patients who were newly diagnosed, OR = 1.2 (0.4–3.7), or patients with relapsed/refractory disease, OR = 1.3 (0.5–3.8), compared with multiple myeloma patients with stable disease. On the basis of small numbers ($n = 7$), high-dose melphalan chemotherapy followed by autologous stem cell transplant within 12 months prior to COVID-19 diagnosis was not significantly associated with the adverse combined endpoint, OR = 0.9 (0.2–5.4). None of the other studied risk factors were significantly associated ($P > 0.05$) with adverse outcomes, including hypertension ($n = 56$), OR = 2.2 (0.9–5.4); diabetes ($n = 18$), OR = 0.9 (0.3–2.9), age >65 years ($n = 63$), OR = 1.8 (0.7–4.6); or male gender ($n = 58$), OR = 0.9 (0.4–2.0). We did not observe any statistical association between the adverse combined endpoint and hypogammaglobulinemia (IgG <650 mg/dL; $n = 42$), OR = 0.9 (0.3–2.2), or severe hypogammaglobulinemia (IgG <400 mg/dL; $n = 18$)OR = 1.0 (0.3–3.2), respectively (Fig. 1).

In the entire case series of 127 patients with plasma cell disorders, the OR of severe outcome (ICU admission, mechanical ventilation, or death) was significantly elevated for those with hypertension ($n = 72$; OR = 2.9; 1.3–6.4), whereas diabetes, male gender, age >65 years, or chronic obstructive pulmonary disease/asthma were not significantly associated with the adverse combined endpoint.

Table 4. Treatment administered for COVID-19 in patients with multiple myeloma

Treatment for COVID-19	Number
Total number of patients	100
Patients receiving therapy for COVID-19	65
Hydroxychloroquine	52
Azithromycin	52
Combination hydroxychloroquine and azithromycin	40
Corticosteroids	27
IL-6 blockade	9
Lopinavir-ritonavir	4
Remdisivir	3
Convalescent plasma	2

DISCUSSION

COVID-19 is a disease caused by the SARS-CoV-2 virus where, in the general population, the most severe outcomes are observed among elderly patients and patients with cardiovascular comorbidities (3, 18). Limited data are available on outcomes in patients with cancers, particularly patients with hematologic malignancies. Here, we present a large case series of COVID-19 in patients with multiple myeloma, a plasma cell malignancy associated with a compromised immune system, due to both disease biology and anti-myeloma therapies (15). Consecutive patients with multiple myeloma and related precursor diseases with confirmed presence of SARS-CoV-2 between March 1, and April 30, 2020, from five large academic centers in New York City were included in this study. In the

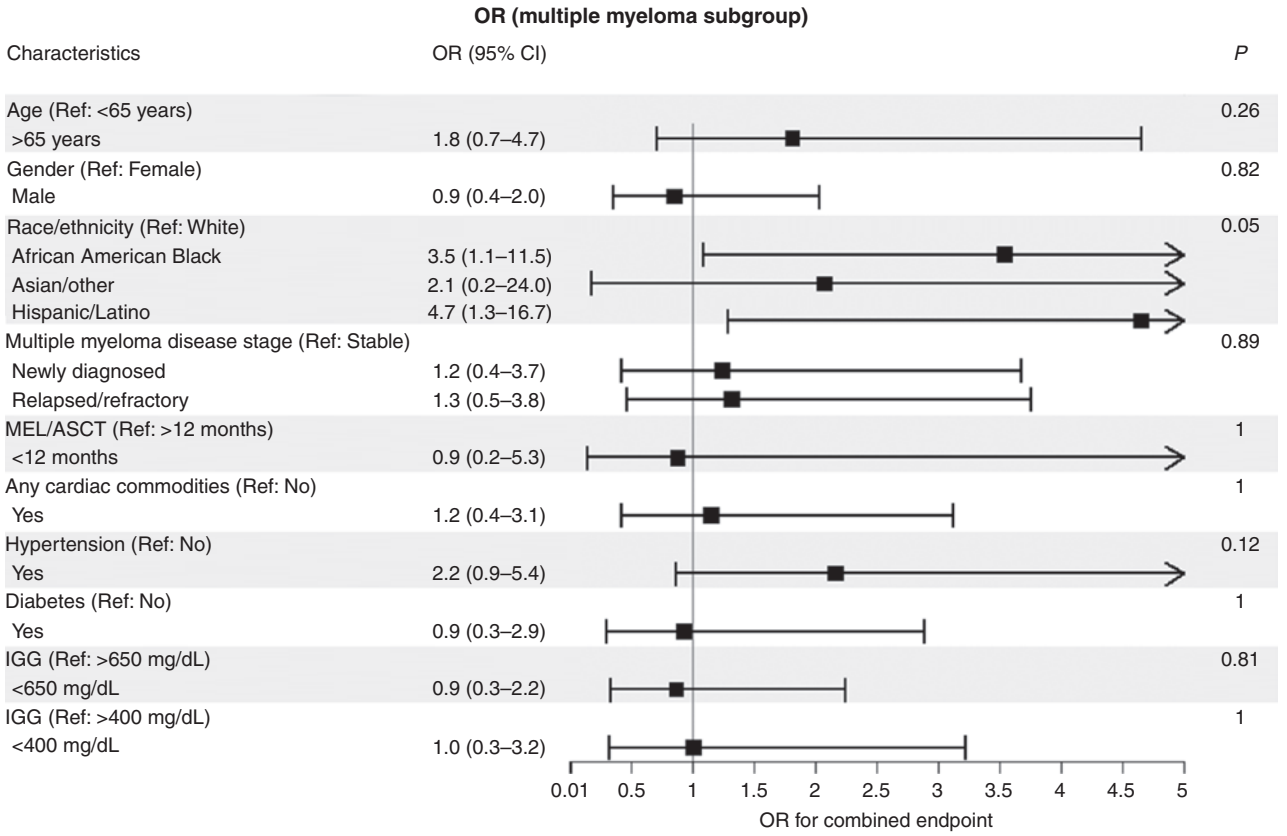

Figure 1. ORs of the combined adverse endpoint (ICU admission, invasive mechanical ventilation, or death). Fisher exact test was used to estimate ORs for the combined adverse endpoint in relation to clinical characteristics. CI, confidence interval; IGG, IgG level.

general population, the probability of dying from COVID-19 has been reported to be between 1% and 6% including all COVID-19–positive cases, and between 6% and 26% for patients hospitalized due to the virus (1, 3, 18–20). Here, we show that among 75 patients with multiple myeloma admitted due to COVID-19, the mortality rate was 29%, which is thought to be on the high end of what has been reported in the general population.

Recent publications on COVID-19 in patients with cancer have reported case fatality rates between 11% and 28% and for hematologic malignancies up to 37% (2, 7, 10). Robilotti and colleagues reported on 423 patients with cancer with COVID-19 diagnosed at Memorial Sloan Kettering Cancer Center (MSKCC); of these, 40% were admitted, and 12% expired within the first 30 days after diagnosis (7). Symptomatic COVID-19 in patients with multiple myeloma has been indicated to have a high mortality—as high as 55% in patients undergoing systemic anticancer therapy for multiple myeloma (9). In larger studies from hospitalized COVID-19 patients in the United Kingdom ($N = 20{,}133$) and in one of the hospital systems in the New York area ($N = 5{,}700$), the case fatality rate has been between 21% and 26% for hospitalized patients (3, 18). According to the Johns Hopkins Coronavirus Resource Center, on April 30, New York state had 299,000 cases and 18,100 deaths, indicating an approximate case fatality rate of 6% (https://coronavirus.jhu.edu/map.html, accessed on July 14, 2020). The variation between studies may be caused by study design (inpatient vs. all patients), access to testing, and whether screened patients, likely capturing more asymptomatic patients, were included. Our findings on COVID-19–related mortality, 22% in the whole cohort of patients with myeloma and 29% of those admitted, are in line with recent reports on a high mortality in patients with hematologic malignancies in relation to the general population (Table 5; refs. 2, 10).

We were motivated to better understand risk factors associated with severe outcomes from COVID-19–positive patients with multiple myeloma. Specifically, we studied host characteristics as well as available variables related to the disease and treatment. We found that racial and ethnical background was significantly associated with increased risk of severe outcome, where the highest risks were seen in Hispanics/Latinos and in African American Blacks (21, 22). Underlying reasons for this may be differences in preexisting comorbidities and socioeconomic factors, including the possibility to work from home and to practice social distancing (21, 22). It is possible that disparities in level of care (i.e., health insurance coverage) may have affected the outcome; however, we were unable to address these aspects further within the scope of this study. Similar to reports from the general population, there was a tendency toward a higher OR for adverse outcome (ICU admission, invasive mechanical ventilation, or death) in patients with preexisting hypertension (3). In the analysis of

Table 5. Case fatality rates in this study in relation to published reports

	Patient cohort	Number of patients	Setting	Case fatality rate
Current study	Multiple myeloma	100	Inpatient and outpatient	22%
Lee et al. (11)	All cancer patients	800	Inpatient and outpatient	28%
Robilotti et al. (7)	All cancer patients	423	Inpatient and outpatient	12%
Miyashita et al. (13)	All cancer patients	334	Inpatient and outpatient	11%
Mehta et al. (10)	All cancer patients	218	Inpatient and outpatient	28%
Mehta et al. (10)	Hematologic malignancy subcohort	54	Inpatient and outpatient	37%
Dai et al. (2)	All cancer patients	105	Inpatient and outpatient	11%
Cook et al. (9)	Multiple myeloma	75	Inpatient and outpatient	54.7%
Malard et al. (12)	Hematologic malignancy	25	Inpatient	36%
Docherty et al. (18)	All patients	20,133	Inpatient	26%
Richardson et al. (3)	All patients	5,700	Inpatient	21%
Goyal et al. (19)	All patients	393	Inpatient	10%
Deng et al. (20)	All patients	82,719	All	1%–8%
Guan et al. (1)	All patients	1,099	All	1.4%
Johns Hopkins University CSSE COVID-19 map[a]	All COVID-19–positive cases	~299,000	All	6%

[a]Center for Systems Science and Engineering (CSSE) at Johns Hopkins University COVID-19 map for cumulative number of cases and deaths on April 30, 2020 (https://coronavirus.jhu.edu/map.html).

the entire series of COVID-19–positive patients with multiple myeloma and related plasma cell disorders ($n = 127$), similar to the general population, cardiovascular risk factors were significantly associated with adverse outcome (3).

Independent of COVID-19, typically, patients with multiple myeloma are at an increased risk of infections due to both disease- and treatment-associated immunosuppression (15, 23). Examples of these associations are the immunomodulatory and conventional chemotherapy drugs, which cause myelosuppression, and the targeted mAbs such as anti-CD38 associated with suppression of the humoral immune system (24–28). In this series, we did not identify an association between anti-myeloma treatment or hypogammaglobulinemia and adverse outcome; however, due to the lack of detailed biomarker data, we were unable to rule out associations involving other immunologic mechanisms (such as T-cell suppression) that are important in the immune response toward viral and other infections. In patients with multiple myeloma undergoing high-dose melphalan chemotherapy followed by autologous stem cell transplant, it is well-known that there is severe acute as well as sustained long-term immunosuppression, including broad aspects of the immune system (29, 30). In this study, 39 of the 100 patients with multiple myeloma included had been treated with autologous stem cell transplant. On the basis of small numbers ($n = 7$), the OR for the adverse combined endpoint was not significantly elevated in patients who had high-dose melphalan chemotherapy with autologous stem cell transplant within 12 months prior to contracting COVID-19. Despite not seeing an increased mortality associated with high-dose melphalan chemotherapy with autologous stem cell transplant, we note the concerns of the American Society of Hematology, the European Myeloma Network, and the International Myeloma Society, whose recommendations state that for transplant-eligible patients, high-dose melphalan chemotherapy followed with autologous stem cell transplant should be postponed, if possible, until the pandemic abates (ref. 31; American Society of Hematology; COVID-19 and Multiple Myeloma; 2020 at https://www.hematology.org/covid-19/covid-19-and-multiple-myeloma; May 8, 2020; International Myeloma Society Recommendations for the Management of Myeloma Patients During the COVID-19 Pandemic. 2020; https://cms.cws.net/content/beta.myelomasociety.org/files/IMS%20recommendations%20for%20Physicians%20Final.pdf; accessed May 8, 2020). Given that it is unknown whether there could be additional SARS-CoV-2 outbreaks as the lockdown eases or seasonal outbreaks in following years, it is good clinical practice to have this discussion with every patient. When a safe and efficacious SARS-CoV-2 vaccine becomes available, it should be recommended to patients with multiple myeloma and should be added to reimmunization programs for melphalan-induced inactivation of prior vaccines.

To minimize the risk for exposure, management of multiple myeloma including the use of infusions, injections, and oral drugs has been adjusted to favor fewer visits, fewer injections/infusions, and a preference for oral drugs [refs. 31–33; NCCN Coronavirus Disease 2019 (COVID-19) Resources for the Cancer Care Community 2020 at https://www.nccn.org/covid-19/, accessed May 8, 2020, American Society of Clinical Oncology Coronavirus Resources; 2020, https://www.asco.org/asco-coronavirus-information, accessed May 8, 2020, American Society of Hematology. COVID-19 and Multiple Myeloma; 2020 at https://www.hematology.org/covid-19/covid-19-and-multiple-myeloma, accessed May 8,

2020, International Myeloma Society Recommendations for the Management of Myeloma Patients During the COVID-19 Pandemic; 2020. https://cms.cws.net/content/beta.myelomasociety.org/files/IMS%20recommendations%20for%20Physicians%20Final.pdf, accessed May 8, 2020, European Society for Medical Oncology. Cancer Patient Management During the COVID-19 Pandemic. 2020 at https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic, accessed May 8, 2020). All five academic centers limited the use of high-dose melphalan and autologous stem cell transplant, and only a few high-risk patients have been transplanted during the outbreak. In addition, in our experience, patients with multiple myeloma have been particularly adherent to the general recommendations for social distancing (34, 35). This may have contributed to the relatively low number of patients with multiple myeloma and COVID-19 in this cohort given the population of New York City (8.4 million), the overall number of confirmed cases (~300,000 at time of data cutoff), and the large catchment area covered by the five included hospital centers.

In prior reports from the general population, the immune response in patients with severe COVID-19 shows a unique pattern with high IL-6, low HLA-DR expression, and dysregulation of lymphocytes characterized by CD4 lymphopenia and, subsequently, B-cell lymphopenia (36). In the current series of patients with multiple myeloma, we found high levels of IL-6, elevated ferritin, and low absolute lymphocyte levels. Furthermore, COVID-19 can lead to a hypercoagulable state, and patients with severe COVID-19 have an increased risk of venous thromboembolism and stroke (4, 37). In this series, 9 patients had thromboembolic events, and D-dimer levels were significantly elevated in patients with severe outcomes. The biological underpinnings of these observations remain to be further explained in functional studies.

Few treatments have so far shown an unequivocal beneficial effect for treatment of COVID-19. Hydroxychloroquine in combination with azithromycin was initially suggested to be an effective treatment combination; however, validation trials have been unable to confirm beneficial effects. Importantly, the World Health Organization recently expressed concern over cardiac arrhythmias and other potentially serious effects with the hydroxychloroquine–azithromycin combination, and several of the initial publications have now been retracted (38–41). Twenty-seven patients in this cohort were treated with steroids, and dexamethasone has subsequently shown to reduce mortality in hospitalized patients with COVID-19 (42). A few patients in our series were treated with lopinavir-ritonavir; however, clinical trials have not shown a clinical benefit of these antiretroviral drugs (43). Recent reports on remdesivir as well as treatment with convalescent plasma therapy have shown promising results, and there are case reports on successful treatment of COVID-19 with IL-6 blockade (44–49). In addition, there are indications that the Bruton tyrosine kinase inhibitor acalabrutinib can reduce the excessive inflammatory response in patients with severe COVID-19 (50).

Limitations of this study includes it being a case series from tertiary cancer centers with a selected patient population in which patients who were treated at local hospitals in the outpatient setting were less likely to be included. Nevertheless, we estimate the level of reporting to be high for patients with multiple myeloma given the potential severity of COVID-19 and the high compliance among these patients. However, given the study design, asymptomatic patients may be underrepresented as in many of the published COVID-19 studies. There were missing data for certain laboratory results for some of the patients, primarily those who were treated as outpatients where not all were tested for C-reactive protein, ferritin, D-dimer, or IL-6 levels.

In summary, we present data on a large case series of COVID-19–positive patients with multiple myeloma and related precursor diseases showing case fatality of 29% among hospitalized patients. We comprehensively investigated the role of other comorbidities and found that the strongest risk factors for severe outcome were race/ethnical background and cardiovascular comorbidities similar to those in the general population. In this cohort, multiple myeloma disease stage, type of treatment, and immunoglobulin levels were not significantly associated with adverse outcome. Ongoing larger studies with a wide range of hematologic malignancies will provide additional information on important risk factors in these patients. Nevertheless, given that patients with multiple myeloma are at an increased risk of various other infections due to both disease- and treatment-associated immunosuppression (23), current recommendations by the American Society of Hematology, the European Myeloma Network, and the International Myeloma Society state that high-dose melphalan chemotherapy followed by autologous stem cell transplant should be postponed, if possible, until the pandemic levels off (31). Going forward, until there is a vaccine or effective treatment for COVID-19, clinical management and treatment of patients with multiple myeloma has to be carefully considered and adjusted to reduce the risk of exposure and minimize immunosuppression while aiming to achieve deep remissions in the era of COVID-19.

METHODS

This is a retrospective multiple center study including five large academic centers in New York: MSKCC, New York University Langone Health, Mount Sinai, Weill Cornell Medicine, and Columbia University Medical Center.

Consecutive patients with multiple myeloma and related plasma cell disorders and confirmed COVID-19 either in the inpatient or outpatient setting were included in this study. Patients were identified through automated hospital database searches using ICD-10 codes (C90.0 and D47.2) among those who tested positive for SARS-CoV-2 during the peak of the outbreak between March 10, and April 30, 2020. In addition, all clinical faculty were requested to report if they had patients with multiple myeloma diagnosed at outside clinics. Patients were followed until time of event or until July 6, 2020, by which time all patients had either recovered or expired from COVID-19. A total of 127 patients were included from the following centers: MSKCC (n = 52), New York University Langone Health (n = 30), Mount Sinai (n = 23) (51). Weill Cornell Medicine (n = 13), and Columbia University Medical Center (n = 9). Patient characteristics are presented in the Supplementary Table 1.

The presence of SARS-CoV-2 was determined using nasopharynx swabs and real-time PCRs targeting viral RNA. Patients were admitted if they had shortness of breath, decreased oxygen saturation, or other clinical symptoms such as high fever, fatigue, or failure to thrive based on the treating or admitting physicians' assessment. We obtained data on patient characteristics such as age, gender, race/ethnicity as well as comorbidities including cardiovascular comorbidities (e.g., hypertension and diabetes). We manually extracted

data on multiple myeloma stage, ongoing treatment, and previous autologous or allogeneic stem cell transplant. Laboratory findings, for example, blood counts and inflammatory markers from testing performed at the time of COVID-19, were included. If immunoglobulin levels were not obtained at COVID-19 diagnosis, results from up to 30 days prior were used. COVID-19–related outcomes were assessed regarding the need for admission, ICU admission, invasive mechanical ventilation, and whether the patient expired from COVID-19 or other causes. We also obtained information on treatments used for COVID-19: hydroxychloroquine, azithromycin, dexamethasone, antiviral agents, IL-6 inhibitors, or convalescent plasma.

Descriptive statistics were used to characterize the patient cohort and to present information on outcomes. The primary composite endpoint for adverse outcome was defined as admission to the ICU, need for invasive mechanical ventilation, or death. The assessed risk factors were categorized into clinically relevant thresholds. Hypogammaglobulinemia was defined as IgG levels <650 mg/dL (lower limit of normal), and severe hypogammaglobulinemia was defined as IgG levels <400 mg/dL. Associations between continuous laboratory measurements (absolute neutrophil count, absolute lymphocyte count, platelet count, C-reactive protein, ferritin, D-dimer, IL-6 level) and the adverse combined endpoint were tested by the Wilcoxon rank-sum test, and associations between the combined endpoint and discrete patient characteristics (age >65 years, gender, race/ethnicity, presence of comorbidities, multiple myeloma disease stage, high-dose melphalan and autologous stem cell transplant within 12 months, hypogammaglobulinemia) were tested by Fisher exact test. Univariate logistic regression was used to estimate ORs with 95% confidence intervals (CI) for these risk factors associated with adverse outcomes. In general, the group absence of risk factor under study was used as the reference group. Separate analyses were performed for patients with multiple myeloma ($N = 100$) and for all patients with plasma cell disorders ($N = 127$). This study was approved under the MSK Myeloma Service, and informed consent was waived under the retrospective research protocol (Institutional Review Board protocol 18-143).

Disclosure of Potential Conflicts of Interest

M. Hultcrantz reports personal fees from Curio Science (consulting) and Intellisphere, LLC (consulting), and grants from the Swedish Blood Cancer Foundation and Karolinska Institute Foundations outside the submitted work. J. Richter reports personal fees from Celgene, Bristol-Myers Squibb, Janssen, Oncopeptides, X4 Pharmaceuticals, Sanofi, Secura Bio, Adaptive Biotechnologies, Antengene, Karyopharm, and AstraZeneca outside the submitted work. C.A. Rosenbaum reports other from Amgen (research funding), Akcea (honoraria), and Celgene (honoraria) outside the submitted work. E.L. Smith reports personal fees from Bristol-Myers Squibb (consultant), Fate Therapeutics (consultant), and Precision Biosciences (consultant) outside the submitted work, as well as patents for CAR T cells for the treatment of multiple myeloma pending, issued, licensed, and with royalties paid from Bristol-Myers Squibb. N. Korde reports personal fees from AstraZeneca (advisory board) and other from Amgen (research funding) outside the submitted work. S. Mailankody reports other from Allogene Therapeutics (research support to institution), Juno/Bristol-Myers Squibb (research support to institution), Janssen (research support to institution), Takeda Oncology (research support to institution), Physician Education Resource [honoraria for continuing medical education (CME) activity], and Plexus Education (honoraria for CME activity) during the conduct of the study. U.A. Shah reports grants from Parker Institute for Cancer Immunotherapy and Celgene, and personal fees from Physicians's Education Resource outside the submitted work. C. Tan reports personal fees from Janssen outside the submitted work. A. Rossi reports other from Bristol-Myers Squibb (advisory board), Janssen (advisory board), and Amgen (advisory board) outside the submitted work. D. Madduri reports other from Foundation Medicine (consultant), Janssen (consultant), Legend (consultant), GlaxoSmithKline (consultant), Sanofi (consultant), Kinevant (consultant), Bristol-Myers Squibb (consultant), and Celgene (consultant) outside the submitted work. A. Chari reports grants and personal fees from Janssen (research funding, advisory board, consultant), Celgene (research funding, advisory board, consultant), Novartis Pharmaceuticals (research funding, advisory board, consultant), Amgen (research funding, advisory board, consultant), Seattle Genetics (research funding, advisory board), and Millenium/Takeda (research funding, consultant); grants from Pharmacyclics (research funding); and personal fees from Bristol-Myers Squibb (consulting), Karyopharm (advisory board, consultant), Sanofi Genzyme (advisory board), Oncopeptides (advisory board), Antengene (consultant), GlaxoSmithKline (advisory board), and Secura Bio (consultant/advisory board) outside the submitted work. M.J. Braunstein reports grants and personal fees from Janssen (research funding, advisory board) and personal fees from Celgene (advisory board), Takeda (advisory board), Karyopharm (advisory board), Amgen (advisory board), and AstraZeneca (advisory board) outside the submitted work. R. Reshef reports personal fees from Gilead, Atara, Magenta, Novartis, Bristol-Myers Squibb, and Pfizer outside the submitted work. F.E. Davies reports personal fees from Adaptive Biotech Roche, Takeda, Sanofi, and Amgen, and grants and personal fees from Bristol-Myers Squibb/Celgene and Janssen outside the submitted work. S. Jagannath reports other from Bristol-Myers Squibb (consulting), Janssen Pharmaceuticals (consulting), Karyopharm Therapeutics (consulting), Legend Biotech (consulting), Sanofi (consulting), and Takeda (consulting) outside the submitted work. S. Lentzsch reports personal fees from Caelum Biosciences (shareholder, patent holder, and scientific advisor), Sorrento, Janssen, and Celularity, and grants from Karyopharm and Sanofi outside the submitted work. O. Landgren reports grants from Amgen, Janssen, and Takeda; personal fees from Amgen (scientific talks), Janssen (scientific talks), and Bristol-Myers Squibb (scientific talks); and other from Janssen (independent data monitoring committee, IDMC), Takeda (IDMC), and Merck (IDMC) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

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