Secondary Immunodeficiency and Hypogammaglobulinemia with IgG Levels of <5 g/L in Patients with Multiple Myeloma: A Retrospective Study Between 2012 and 2020 at a University Hospital in China

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Background: Infections are the main cause of mortality and morbidity in multiple myeloma (MM) patients. However, adult immunodeficiency specialists in China are lacking, and the care of secondary immunodeficiency (SID) and the prognostic role of hypogammaglobulinemia in MM is unknown.

Material/Methods: MM patients (295) were retrospectively analyzed between January 2012 and 2020 in Zhejiang Provincial People's Hospital, Hangzhou Medical College. MM patients with immunoglobulin (Ig) G <5 g/L were defined as SID patients. The care of these patients and the prognostic role of IgG <5 g/L were analyzed.

Results: Forty-five of 295 MM patients with IgG <5 g/L were defined as SID patients. These 45 patients mainly had recurrent infections, especially pulmonary bacterial infections; 2 patients had them 5 times/year. The median survival time was significantly shorter in MM patients with SID (24 vs 66 months). More importantly, the multivariate and univariate analysis revealed that IgG <5 g/L was an independent prognostic factor for MM patients.

Conclusions: Ig replacement therapy or prophylactic antibiotics for MM patients with SID were lacking in this single retrospective study. IgG <5 g/L could be a prognostic marker for MM patients.

Keywords: Antibiotic Prophylaxis • Immunoglobulins, Intravenous • Multiple Myeloma

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Background

Multiple myeloma (MM) is a neoplastic plasma cell proliferative disorder and the second most common hematological malignancy [1], accounting for 0.9% of all cancers worldwide in 2018 and 1.1% of cancer deaths [2]. Current treatment options, such as a regimen of vincristine, Adriamycin, and dexamethasone (VAD), and a regimen of bortezomib, cyclophosphamide, and dexamethasone (PCD), have significantly improved the survival rate of patients with MM [3,4]. However, these drugs exert tremendous effects on the immune system, resulting in the impairment of immunity. These patients have a very high risk of developing secondary immunodeficiency (SID) and increased infection risk, and the drugs continue to be a main cause of mortality and morbidity for MM patients [5,6]. Therefore, care is critical for the quality of life and long survival for MM patients with SID [6].

SID patients also present a wide range of special problems and are have an increased risk of infection [6]. Thus, prophylactic antibiotics and immunoglobulin replacement therapy (IgRT) are 2 main strategies for the care of SID patients, especially secondary to hematological diseases [5]. Recent data demonstrated that compared with patients not receiving IgRT, MM patients receiving IgRT had lower infection rates, fewer days of hospitalization, and longer time free of infections [7,8]. Recently, in a European online survey of about 230 physicians responsible for diagnosing SID and administration of IgRT in hematological malignancy patients, 85% of physicians prescribed IgRT for patients with ≥2 severe infections. Additionally, in Italy, the United States, Germany, and Spain, IgRT use was above average in hypogammaglobulinemia patients, whereas considerably fewer patients received IgRT in the UK [9].

Furthermore, because of the scarce and expensive resources of IgRT, failure to respond to a 3-month course of prophylactic antibiotics is required for use of IgRT under the guidelines in the UK [9] and 86% of patients receive a trial of prophylactic antibiotics before consideration for IgRT by Irish and British immunologists [10], although prophylactic antibiotic usage can be controversial in an era of increasing antibiotic stewardship.

On the contrary, in the Chinese mainland, hematologic SID specialists are still lacking, IgRT for SID patients is not covered by health insurance, and the optimal treatment of SID caused by MM is still unknown. In the richest Hong Kong special administrative area, immunology service care for adult immunodeficiency patients was only established in 2016; prognosis and care of MM patients with SID in the Chinese mainland are still lacking. Therefore, we conducted this single-center retrospective study to describe the prognostic role of IgG <5 g/L and care of MM patients with SID in a university hospital in China.

Material and Methods

Study Design

We conducted this retrospective review of all MM patients in our university hospital and laboratory database from January 2012 to January 2020 in Zhejiang Provincial People's Hospital, Hangzhou Medical College. Patients' electronic medical records were reviewed through the hospital and laboratory information system database, including clinical characteristics, laboratory results, treatment, and survival outcomes. This study was conducted after approval by the Zhejiang Provincial People's Hospital Ethics Committee (no. 2020QT138).

Clinical and Laboratory Data

The diagnosis of infection was made via clinical presentation, along with positive radiologic findings and positive microbiological cultures indicative of infection according to standard practice [11]. The complete data on infections, including frequency, location, and type, are listed in **Table 1 and Supplementary Table 1**. Moreover, the details of treatment, including prophylactic antibiotics, antibiotics treatment after infections, IgRT, and chemotherapy regimens, are documented in **Table 2 and Supplementary Table 1**.

Data on demographics and the subtype of MM are summarized in **Table 3**. Additionally, the results of kappa and lambda light chain determinations were measured by immunofixation electrophoresis. The serum IgG level was measured by nephelometry (Beckman Coulter, IMMAGE800) and the IgG reference values were 7.51-15.6 g/L.

End Points and Survival Analysis

Survival data of all MM patients were telephoned in and documented in August 2020. IgG was first measured at diagnosis, monitored at admission, and followed up when MM patients received treatment in our hospital. The start point of survival time correlation with IgG level was based on the first IgG results in our hospital. Notably, SID patients were defined as having IgG <5 g/L at least twice. For the group with IgG <5 g/L, the overall survival (OS) was calculated from the first hypogammaglobulinemia (IgG <5 g/L) event in our hospital until the end point. In the cohort with IgG ≥5 g/L, the start point of OS was from the first occurrence of IgG ≥5 g/L in our hospital.

Statistical Analysis

Statistical tests for data analysis included Cox survival analysis. Multivariate statistical analysis was performed via a Cox regression model. Statistical analysis was performed via the SPSS 19.0 statistical software package. $P<0.05$ was considered statistically significant.

Table 1. Past history of infection of multiple myeloma patients with and without secondary immunodeficiency.

	IgG <5 g/L (n=45)	IgG ≥5 g/L (n=103)
Infection times (per year)		
0	4 (8.89)	33 (32.00)
1	30 (66.67)	56 (54.37)
2	11 (24.44)	18 (17.48)
3	6 (13.33)	4 (3.88)
4	3 (6.67)	2 (1.94)
5	2 (4.44)	2 (1.94)
Localization of infection		
Lung	31 (68.89)	57 (55.34)
Upper respiratory tract	8 (17.78)	11 (10.67)
Genitourinary	5 (11.11)	0 (0.00)
Gingiva	2 (4.44)	0 (0.00)
Others	13 (28.89)	9 (0.87)
Type of infection		
Bacteria	42 (93.33)	82 (79.62)
Proven fungal	2 (4.44)	4 (3.88)
Virus	5 (11.11)	6 (5.83)
Probable fungal	3 (6.67)	5 (4.85)

All data are presented with no. (%).

Table 3. Clinical characteristics of multiple myeloma patients with and without secondary immunodeficiency.

	IgG <5 g/L (n=45)	IgG ≥5 g/L (n=103)
Sex		
Male	34 (75.56)	63 (61.17)
Female	11 (24.44)	40 (38.83)
Age		
≤65 years	23 (51.11)	51 (49.51)
>65 years	22 (48.89)	52 (50.49)
Subtype		
IgA, λ light chain	15 (33.33)	11 (10.68)
IgA, κ light chain	12 (26.67)	3 (2.91)
IgD, λ light chain	5 (11.11)	4 (3.88)
IgG, λ light chain	1 (2.22)	35 (33.98)
IgG, κ light chain	0 (0.00)	25 (24.27)
λ light chain	6 (13.33)	6 (5.83)
κ light chain	4 (8.89)	8 (7.77)
IgA	0 (0.00)	1 (0.97)
IgG	0 (0.00)	1 (0.97)
IgG, IgA, λ light chain	0 (0.00)	1 (0.97)
Unknown	2 (4.44)	8 (7.77)

All the data were presented with no. (%).

Table 2. Effectiveness of antimicrobial prophylaxis in the following 2 weeks or 1 month.

Infection *N (%)	Antimicrobial prophylaxis (n=14)				Nonantimicrobial prophylaxis (n=19)
	Total	Antibiotic prophylaxis	Antifungal prophylaxis	Antivirus prophylaxis	
Total	14 (100.00)	10 (71.43)	2 (14.29)	2 (14.29)	19 (100.00)
Infection within 2 weeks	3 (21.43)	3 (30.00)	0 (0.00)	0 (0.00)	6 (31.58)
Infection within 1 month	6 (42.85)	5 (50.00)	0 (0.00)	1 (50.00)	8 (42.11)

* N=number of patients that developed infections.

Results

Forty-Five of 266 MM Patients Were Defined as SID Patients

We retrospectively analyzed data from 295 MM patients in Zhejiang Provincial People's Hospital, Hangzhou Medical College from January 2012 to January 2020. Twenty-nine outpatients with incomplete information were excluded (**Figure 1**). On the basis of the criterion of IgG <5 g/L for SID patients [12,13], 266 MM patients were separated into 2 groups: 74 MM patients with SID (IgG <5 g/L) and 192 MM patients without SID (IgG ≥5 g/L). In addition, 29 MM patients with SID and 89 MM patients whose phone numbers were wrong or changed, resulting in lost contact, were also excluded. Thus, data from 45 MM patients with SID and 103 MM patients without SID were analyzed (**Figure 1**).
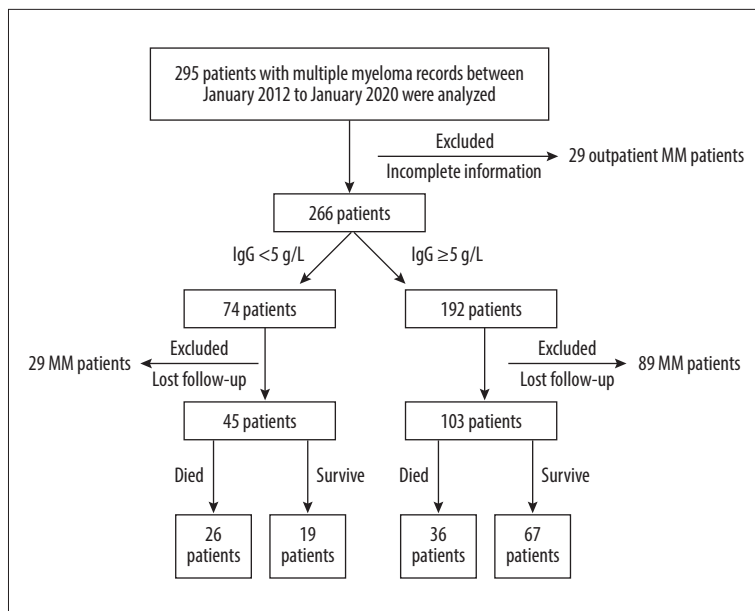
Figure 1. Flow chart of the selection of multiple myeloma (MM) patients with or without secondary immunodeficiency (SID).

Clinical and Laboratory Characteristics of These 148 MM Patients with and without SID

According to the cutoff value IgG <5 g/L, 148 MM patients identified in this study were separated into 2 groups, the IgG <5 g/L group and the IgG ≥5 g/L group. Among these 45 MM patients with SID, 34 (75.56%) patients were men and the other 11 (24.44%) were women. Twenty-three (51.11%) patients were ≤65 years old, and 22 (48.89%) were >65 years old (**Table 1**). In these 45 MM patients with SID, the antibody composition was 15 λ and 12 κ IgA, 5 λ IgD and 1 λ IgG, 6 λ and 4 κ, and 2 unclear types (**Table 3**). Most importantly, on review of the patient history, the SID diagnosis had never been listed for these 45 MM patients. In the IgG ≥5 g/L cohort, 51 (49.51%) patients were ≤65 years and 63 MM patients (61.17%) were men. On the basis of the result of immunofixation electrophoresis, 11, 3, 4, 35, 25, 6, 8, 1, 1, 1, and 8 MM patients were IgA, λ light chain; IgA, κ light chain; IgD, λ light chain; IgG, λ light chain; IgG, κ light chain; λ light chain; κ light chain; IgA; IgG; IgG, IgA, λ light chain, and unknown, respectively (**Table 3**).

MM Patients with and without SID Had Recurrent Infections, Especially Pulmonary Bacterial Infection

Among these 45 MM patients with SID, 41 had at least 1 infection; 11 of these patients had infection twice, 6 patients had it 3 times, 3 patients had it 4 times, and 2 patients had infection 5 times in 1 year (infection time available in Zhejiang Provincial People's Hospital is fully listed in **Table 1 and Supplementary Table 1**). Of these infections, 31 were in the lung, 8 in the upper respiratory tract, 5 in the genitourinary tract, and 2 in the gingiva (**Table 1**). Forty-two patients had bacterial infections, 2 had proven fungal infections, 3 patients had probable fungal

Table 4. Death rate of multiple myeloma patients with or without secondary immunodeficiency at 1 year and 3 years.

	IgG <5 g/L (n=45)	IgG ≥5 g/L (n=103)
Death at 1 year (no./rate)	15 (33.33)	13 (12.62)
Death at 3 years (no./rate)	23 (51.11)	24 (23.30)

All data are presented with no. (%).

infections, and 5 patients had viral infections (**Table 1**). For the group with IgG ≥5 g/L, 70 patients had at least 1 infection 18 patients had infections twice, 4 patients had them 3 times, 2 patients had them 4 times, and 2 patients had 5 infections in 1 year. The most common location of infections was the lung (57 cases) and the upper respiratory tract (11 cases). As shown in **Table 1**, 82 bacterial infections, 4 proven fungal infections, 5 probable fungal infections, and 6 viral infections were documented. Thus, MM patients with IgG <5 g/L and with IgG ≥5 g/L both mainly had pulmonary bacterial infections. Notably, compared with the IgG ≥5g/L group, the proven fungal infection rate and probable fungal infection rate in the IgG <5 g/L group were significantly higher.

Fourteen MM Patients with SID Received Antimicrobial Prophylaxis and Only 3 Patients Received IgRT

As we know, chemotherapy can be the major cause of SID in hematological diseases [6]. Thus, the treatment for these MM patients was systematically analyzed; the most common regimen was VAD and PCD therapy (**Supplementary Table 1**). During the hospitalization, all 41 MM patients with SID were treated with
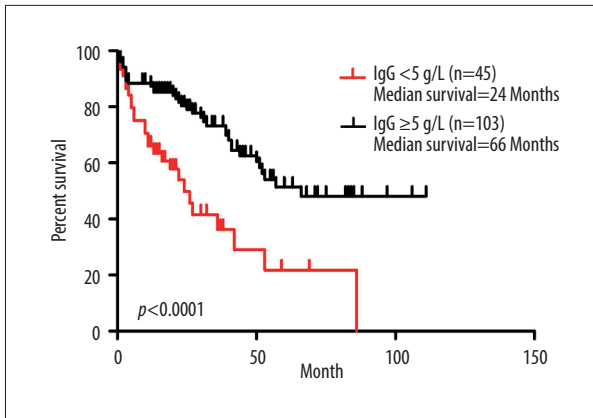
Figure 2. Prognostic role of IgG <0.5 g/L in multiple myeloma (MM) patients. Kaplan-Meier curves of MM patients with IgG <5 g/L (*n*=45) vs IgG ≥5 g/L (*n*=103) (*P*<0.0001, log-rank test, Cox analysis).

antimicrobials when they encountered infection, but only 14 patients received it to prevent these infections. As shown in **Table 4**, 14 MM patients with SID received antimicrobial prophylaxis, including antibiotic, antifungal, and antivirus treatment. Twelve patients with infection at admission were ruled out, and the other 19 MM patients with SID had not received antimicrobial prophylaxis. The results show that the infection rate was lower in the antimicrobial prophylaxis group within 2 weeks (21.43% vs 31.58%), but no significantly different change was seen within 1 month (42.85% vs 42.11%) (**Table 2**). Moreover, only 3 patients had received IgRT among these 45 MM patients with SID.

IgG <5 g/L Predicted Poor Prognosis in MM Patients

To further evaluate the role of hypogammaglobulinemia in the clinical progression of MM patients with SID, we compared the survival status of MM patients with or without SID. Notably, 1-year and 3-year mortality rates of 45 SID patients associated with MM were significantly higher than the 103 MM patients without SID (33.33% vs 12.62% at 1 year; 51.11% vs 23.30% at 3 years) (**Table 4**). To further investigate the prognostic role of SID in MM patients' progression, we performed Cox survival analysis to assess the role of hypogammaglobulinemia in the clinical progression of these MM patients. By using the IgG <5 g/L cutoff value, results revealed that the survival time in MM patients with IgG <5 g/L was notably lower than in the MM patients with IgG ≥5 g/L (*P*<0.0001, **Figure 2**), indicating that IgG<5g/L could be a prognosis marker for MM patients. Moreover, the median survival for the IgG ≥5 g/L group was 66 months, but the median survival for the IgG <5 g/L group was only 24 months (**Figure 2**).

Univariate analysis revealed that IgG <5 g/L, sex, and albumin were related to MM patients' prognostic factors. The multivariate analysis further corroborated that IgG <5 g/L was a significant independent prognostic factor for MM patients (hazard ratio: 0.335; 95% confidence interval: 0.197-0.571; *P*<0.001, **Tables 5, 6**).

Table 5. Univariate analysis of secondary immunodeficiency in patients with multiple myeloma (MM) and matched MM patients.

Variable	Hazard ratio	95% Confidence interval	P value
Hypogammaglobulinemia (IgG <5 g/L vs IgG ≥5 g/L)	0.369	0.220-0.618	<0.001
Sex (Male vs Female)	0.529	0.298-0.936	0.029
Age (≤65 years vs >65 years)	1.393	0.817-2.373	0.223
Calcium (normal vs abnormal) (141 cases available)	1.220	0.788-1.890	0.372
Hemoglobin (≤90 g/L vs >90 g/L) (145 cases available)	0.679	0.433-1.067	0.093
Creatinine (≤110 µmol/L vs>110 µmol/L)	1.447	0.873-2.399	0.152
Albumin (≤3.5 g/dL vs >3.5 g/dL) (146 cases available)	0.538	0.294-0.984	0.044
β_2-Microglobulin (≤3.5 mg/L vs >3.5 mg/L) (103 cases available)	0.834	0.628-1.108	0.210
Lactate dehydrogenase (≤250 U/L vs >250 U/L) (141 cases available)	1.046	0.418-2.619	0.923

Table 6. Multivariate analysis of secondary immunodeficiency in patients with multiple myeloma (MM) and matched MM patients.

Variable	Hazard ratio	95% Confidence interval	P value
Hypogammaglobulinemia (IgG <5 g/L vs IgG ≥5 g/L)	0.335	0.197-0.571	<0.001
Sex (Male vs Female)	0.516	0.288-0.922	0.026
Albumin (≤3.5 g/dL vs >3.5 g/dL) (146 cases available)	0.443	0.241-0.815	0.009

CLINICAL RESEARCH

Discussion

With the introduction of novel agents, including bortezomib and lenalidomide, the overall survival and progression-free time for MM patients significantly improved [14]. However, current evidence suggests that chemotherapy is significantly associated with myelosuppression or deoxyribonucleic acid synthesis inhibition, further reducing B or T cell proliferation and impairing humoral or cellular immunity. These chemotherapies significantly reduced Ig production and resulted in SID in MM patients [6]. Given these results, MM patients treated with chemotherapies are at a high infection risk. Infections are still the main cause of mortality and morbidity in MM patients [15,16]. A study in Sweden based on 9253 MM patients confirmed that infection represented MM patients' main threat [15]. Additionally, a Danish nationwide retrospective cohort study revealed that risk factors for pneumonia were male sex, International Staging System (ISS) II and ISS III, and elevated lactate dehydrogenase in MM patients who were newly diagnosed [16]. Therefore, the infectious risk assessment should be defined before and during the active treatment of MM patients [17].

Among all sorts of treatment for infection in patients with SID, antimicrobial prophylaxis and IgRT are commonly used to prevent infections [18]. In this study, 41 patients were admitted to the hospital at least 1 time per year because of infections; 2 patients had infections 5 times in a year, including infectious fever and pneumonia. When comparing the infection rate in patients with or without antimicrobial prophylaxis, the antimicrobial prophylaxis significantly decreased the infection rate within 2 weeks, but had no change within 1 month. Notably, no MM patient developed fungal infections after administration of antifungal prophylaxis. Moreover, of these infections, the 4.44% proven invasive fungal disease (IFD) and 6.67% possible IFD in MM patients with IgG <5 g/L were relatively higher than previously reported (<2%) [19]. In addition to the conventional chemotherapy, we speculate that high frequency of immunomodulatory drug administration may be associated with this high rate and further impair the immune system in these MM patients [20].

Compared with patients not receiving IgRT, patients receiving IgRT can reduce the use of antibiotics, the number of infections, and the days of hospitalization, which is of benefit in terms of conserving hospital resources, and can dramatically improve the quality of life for MM patients [7,18], although IgRT is not routinely recommended for MM patients [17]. A recent randomized trial study showed that using the prophylactic administration of subcutaneous Ig improved both adherence to chemotherapy and health quality of life and was cost effective by reducing the need for hospitalization and the use of antibiotics among MM patients [7]. However, in this

single-center Chinese university hospital retrospective study, only 3 patients had received IgRT. Without the IgRT, the survival of MM patients with SID was significantly lower than in the MM patients without SID. Moreover, compared with the MM patients without SID, the mortality rate of MM patients with SID was significantly higher in the first year and third year after diagnosis. Also, the multivariate analysis of different prognostic factors in MM patients revealed that IgG <5 g/L was an independent prognostic factor of MM.

Currently, updated criteria or guidelines on IgRT use for SID patients with hematological diseases have been issued in the UK, United States, and Australia [13,21-23]. IgRT is taken into consideration by hematologists when the indicators fulfill the criteria and guidelines on hypogammaglobulinemia associated with MM [9]. Physicians often prescribe prophylactic IgRT after any infection occurs, after lower respiratory infection, after the first severe infection, and even before any infection occurs [24]. However, no specific criteria have been issued for the treatment of MM patients with SID in China, and the IgRT or prophylactic antibiotic for the care of the MM patients with SID is still lacking [25,26]. In the present study, 41 patients were admitted to the hospital at least 1 time per year because of infections. Two patients had infections 5 times in a year, including infectious fever and pneumonia. Therefore, great attention should be focused on the care of MM patients with SID, which could significantly improve the life quality and prolong survival of MM patients.

With excellent tolerability of IgRT treatment, IgRT was feasible in SID patients to reduce infection rates and improve life quality [24]. In a noninterventional prospective French longitudinal study, data also confirmed the efficacy of IgRT in reducing infection risks in hematological malignancies associated with SID, which fulfilled physicians' main expectations [8]. In the United States, use of IgRT should be considered in chronic lymphoid leukemia (CLL) or MM patients who had hypogammaglobulinemia with pneumococcal infection or recurrent bacterial infections [27]. In the UK, the Department of Health's selection criteria for IgRT of hypogammaglobulinemia were recommended, particularly with MM, non-Hodgkin lymphoma, CLL, or other relevant B cell malignancy in combination with recurrent or severe bacterial infections, despite patients receiving continuous antibiotic treatment for 3 months [13]. In contrast, the present study revealed discrepancies in the use of prophylactic antibiotics and IgRT in a Chinese university hospital, which shows that more attention should be paid to MM patients with SID and then optimize the treatment regimens to allow those patients to benefit from IgRT.

Notably, MM is characterized by impaired immune surveillance mechanisms, such as altered antibody production, disruption of antigen presentation processes of dendritic cells,

dysregulation of natural killer and T cell proliferation and activation, and upregulation of checkpoint and immunosuppressive mediators, thereby creating a suppressive microenvironment allowing the malignant cells to evade immune control [28,29]. New and emerging immunotherapeutic agents, such as cellular (chimeric antigen receptor T cell, vaccine, and allogeneic stem cell transplantation) therapies and antibody-based therapies (anti-CD38 daratumumab, anti-SLAMF7 elotuzumab, anti-CD28 antibody, or checkpoint inhibitor) have been developed to target evasion tactics of MM [29-31]. However, the present study revealed that evaluation of the immunodeficiency status by using the index of hypogammaglobulinemia (IgG <5 g/L) should be consistently monitored and administration of IgRT could significantly improve the survival and life quality of MM patients.

The strength of this study is that the serum IgG levels were consistently measured by the Beckman Coulter IMMAGE800 nephelometerin at this university hospital and the reference value never changed, which helped in reducing interlaboratory variation in technique and reporting methods. Also, only 3 MM patients with SID had received IgRT. Without IgRT treatment, this study further corroborated the critical and prognostic role of hypogammaglobulinemia in the survival of MM patients.

However, our study had limitations. β_2-microglobulin data of patients were incomplete, and some baseline characteristics, such as ISS stage, were also missing. Moreover, 29 outpatients and 118 MM inpatients of a total of MM 295 patients were excluded and this may have resulted in selection bias of the MM cohort patients. Additionally, only 1 IgG-type MM patient was documented in the IgG <5 g/L group of this study when using the IgG <5 g/L cutoff value to define the SID patients [32], whereas the polyclonal, not monoclonal, IgG was detected in these guidelines. However, MM patients with IgG-type antibody were in a special condition; their IgG was monoclonal. Current quantitative IgG detection methods cannot differentiate the polyclonal or monoclonal IgG concentration; they can only examine total polyclonal IgG and monoclonal IgG. Therefore, when using the IgG <5 g/L for IgG-type MM patients, the inclusion of some MM patients with high monoclonal IgG concentrations and low polyclonal IgG concentrations in the IgG ≥5 g/L group may have resulted in bias.

Conclusions

IgG <5 g/L appears to be a reliable prognostic marker for MM patients, and the use of IgRT or prophylactic antibiotics should be seriously considered for these SID patients. Our study revealed that IgG <5 g/L could be a prognostic marker for survival in MM patients. The use of IgRT or prophylactic antibiotic for the care of these MM patients with SID was lacking in this single-center Chinese university study. Therefore, it is important to pay more attention to the screening and management of MM patients with SID.

Conflicts of Interest

None.

Supplementary Data

Supplementary Table 1. Details of the clinical characteristics of 45 multiple myeloma patients.

Case	Sex	Age (years)	Live status	Date of death	Survival time (month)	Subtype	Localization of infection	Infection time	Infectious episodes	Prophylactic antibiotics	Other treatment	Treatment options
1	F	79	Died	2019-08	86	IgA, λ	Upper respiratory tract	2012	1	+	—	PD/MP
2	F	74	Died	2019-01	53	IgA, λ	Lung	2014	1	—	—	Velcade + MP
3	F	51	Died	2019-07	42	λ	Lung	2016/2017	1/1	+	—	VAD/CVAD/VADT
4	F	53	Died	2016-06	36	IgA, κ	Upper respiratory tract	2013/2016	3/2	+	—	VAD/ PD+Pirarubicin
5	M	52	Died	2015-07	27	IgD, λ	Lung,skin	2013/2014/2015	2/4/4	+	—	VAD/CTD/CVAD
6	M	47	Died	2014-02	26	IgG, λ	Lung	2012/2016	1/1	—	—	PD/VBAP
7	M	72	Died	2018-09	24	Unclear	Lung, gingiva, skin	2016/2017/2018	1/2/3	—	—	PD/PCD
8	M	52	Died	2014-03	22	IgA, λ	Lung, urinary tract, bronchi	2012/2013/2014	4/1/1	+	HSCT	VASD/PD/ PCD
9	M	49	Died	2015-03	19	IgA, λ	Crissum, upper respiratory tract	2013/2014	3/2	—	—	VAD/MPT
10	M	62	Died	2018-01	16	IgA, λ	Lung	2016/2017	1/2	—	—	Cyclophosphamide +GC
11	F	34	Died	2017-12	11	λ	Lung, gingiva, bladder	2017	5	—	CAR-T/ HSCT	P*AD/ DTPACE+Velcade
12	M	73	Died	2019-02	11	IgA, λ	Lung	2017/2018	1/1	—	—	VAD/MPTC
13	M	78	Died	2013-01	10	IgA, κ	Upper respiratory tract	2012	2	—	—	VAD
14	M	67	Died	2019-08	10	IgD, λ	Lung	2019	1	—	—	DT
15	M	84	Died	2019-02	6	IgA, λ	Skin	2018	2	+	—	PD
16	M	86	Died	2016-10	6	IgD, λ	Fever	2016	1	—	—	—
17	M	62	Died	2013-06	5	IgD, λ	Fever	2013	1	—	—	VAD/MP+ Velcade
*18	M	74	Died	2019-07	5	Unclear	—	—	—	—	—	PD
19	M	58	Died	2016-03	4	IgA, λ	Lung	2015	1	—	—	VAD
20	M	59	Died	2016-06	3	l	Lung	2015/2016	1/2	—	—	DT
*21	M	71	Died	2012-12	3	IgA, κ	—	—	—	—	—	MP/VAD/DT
22	M	73	Died	2014-07	2	λ	Lung	2014	1	—	—	VADT
23	M	77	Died	2014-06	1	IgA, κ	Lung	2011/2012/2014	1/1/1	—	—	DL
24	F	67	Died	2017-07	1	IgA, κ	Upper respiratory tract	2015/2016/2017	1/2/1	+	—	PCD
25	M	83	Died	2017-10	1	IgA, λ	Lung	2017	2	—	—	PD
26	M	45	Died	2020-06	13	IgA, κ	Fever	2020	1	+	CAR-T	DECP/TCD/IRD
27	M	70	Survival	—	59	IgA, λ	Lung	2020	1	+	—	PCD/RD

Supplementary Table 1 continued. Details of the clinical characteristics of 45 multiple myeloma patients.

Case	Sex	Age (years)	Live status	Date of death	Survival time (month)	Subtype	Localization of infection	Infection time	Infectious episodes	Prophylactic antibiotics	Other treatment	Treatment options
28	M	56	Survival	__	1	κ	Lung	2016/2017/2020	1/1/1	__	__	VAD/DECP/PCD
29	M	65	Survival	__	12	κ	Skin, esophagus	2019/2020	1/1	__	__	PD
30	M	84	Survival	__	15	IgA, κ	Lung	2019	1	__	__	PD
*31	M	67	Survival	__	17	IgA, λ	__	__	__	__	__	PCD/IRD
32	M	77	Survival	__	12	IgA, λ	Lung	2019	1	__	__	PD
33	M	62	Survival	__	12	λ	Lung	2019	4	__	__	PAD/PD
*34	M	79	Survival	__	21	IgA, λ	__	__	__	+	__	DI
35	F	50	Survival	__	21	λ	Lung, urinary tract	2019	3	+	CAR-T	PCD/DECP/FC
36	F	52	Survival	__	20	IgA, κ	Lung, urinary tract, Skin	2019	5	+	HSCT	PD/PDT
37	M	76	Survival	__	30	IgA, κ	Lung, skin	2019/2020	3/1	+	CAR-T	FC/DECP
38	F	58	Survival	__	22	IgD, λ	Lung, upper respiratory tract	2018/2019	1/1	__	IVIG	PAD
39	F	70	Survival	__	38	IgA, λ	Lung	2017	1	__	__	PD
40	M	48	Survival	__	20	IgA, κ	Lung, upper respiratory tract	2018/2019	3/1	__	IVIG	PAD/PADT
41	M	54	Survival	__	32	κ	Lung	2019	1	__	__	PCD/P*AD/DTPACE
42	M	27	Survival	__	37	κ	Lung, upper respiratory tract	2017/2018	2/2	+	IVIG/HSCT	P*AD/DTPACE+Velcade
43	F	66	Survival	__	14	IgA, κ	Lung	2019	1	__	__	DECP/FC/PCD
44	M	58	Survival	__	69	IgA, κ	Lung	2014/2015	1/1	__	__	VADT
45	M	40	Survival	__	20	IgA, λ	Lung	2019	1	__	__	PCD

No infection episode was documented in cases*18, *21, *31, and *34 during one-time hospitalization in Zhejiang Provincial People's Hospital. Infection time available in Zhejiang Provincial People's Hospital is fully listed in Supplementary Table 1. F – Female; M – Male; + – Yes; __ – No. HSCT – hematopoietic stem cell transplant; GC – glucocorticoid; CAR-T – chimericantigenreceptor T cell; IVIG – intravenous immunoglobulin; VAD – vincristine + adriamycin + dexamethasone; VADT – vincristine + adriamycin + dexamethasone + thalidomide; DECP – dexamethasone + etoposide + cyclophosphamide + cisplatin; DTPACE – dexamethasone + thalidomide + cisplatin + adriamycin + cyclophosphamide + etoposide; P*AD – bortezomib + epirubicin + dexamethasone; PAD – bortezomib + adriamycin + dexamethasone; MP – melphalan + prednisone; DT – dexamethasone + thalidomide; DL – dexamethasone + lenalidomide; PD – bortezomib + dexamethasone; PCD – bortezomib + cyclophosphamide + dexamethasone; VBAP – vinblastine + bleomycin + adriamycin + prednisone; PADT – bortezomib + adriamycin + dexamethasone + thalidomide; TPACE – thalidomide + cisplatin + adriamycin + cyclophosphamide + etoposide; FC – fludarabine + cyclophosphamide; CVAD – cyclophosphamide + vincristine + adriamycin + dexamethasone; CDT – cyclophosphamide + dexamethasone + thalidomide; MPTC – melphalan + prednisone + thalidomide + cyclophosphamide; MPT – melphalan + prednisone+thalidomide; TCD – thalidomide+cyclophosphamide+dexamethasone; IRD – ixazomib+lenalidomide+dexamethasone; RD – lenalidomide+dexamethasone; DI – dexamethasone+ixazomib; PDT – bortezomib+dexamethasone+thalidomide.

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