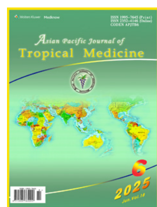

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COVID–19 vaccine hesitancy and acceptance in patients with multiple myeloma: A national multicenter survey in China

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ABSTRACT

Objective: To investigate factors influencing vaccine hesitancy and its effects on SARS-CoV-2 infection in multiple myeloma (MM) patients during the Omicron BA.4/5 subvariant outbreak.

Methods: This cross-sectional study was conducted in mainland China from December 26, 2022, to April 20, 2023. An expert-developed anonymous online questionnaire was distributed *via* WeChat mini-program to several groups of 500 MM patients, each comprising of 500 patients. The questionnaire covered demographic characteristics, MM medical attributes, COVID-19 vaccine status, and clinical manifestations of COVID-19. Data were analyzed to assess the impact of vaccination on COVID-19 infection rates and the disease severity among MM patients.

Results: Among 508 valid responses from 30 provinces, only 34.1% (*n*=173) of MM patients reported receiving COVID-19 vaccination, and the proportions were lower among patients who had undergone autologous stem cell transplantation (20.2% *vs.* 48.4%, $P<0.001$). Vaccine hesitancy was primarily attributed to physician recommendations (52.0%), conflicts with MM treatment (37.8%), and concerns about MM progression (31.3%). Hospitalization due to severe SARS-CoV-2 infections was significantly reduced in the vaccinated group (4.8% *vs.* 12.3%, $P=0.038$).

Conclusions: The lower infection rate in MM patients may be attributed to stringent quarantine measures and self-imposed social restrictions. While vaccination did not directly correlate with fewer SARS-CoV-2 infections, it did afford protection to vulnerable populations. Clinicians are encouraged to recommend vaccines to MM patients to mitigate severe infections and associated mortality during recurrent COVID-19 waves.

KEYWORDS: Questionnaire; Multiple myeloma; Vaccination; SARS-CoV-2; Outbreak infection

1. Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 triggered the global coronavirus disease 2019 (COVID-19) pandemic[1]. Considerable evidence

Summary

Question: Is the COVID-19 vaccine safe and effective in patients with multiple myeloma (MM)?

Findings: In this retrospective cohort study of 508 MM patients, only one-third accepted inactivated COVID-19 vaccines before the Omicron variant emerged. Despite this, approximately 60% of vaccinated patients get COVID-19 infection and had mild infection, and the occurrence of severe outcomes were significantly reduced compared to unvaccinated patients.

Meaning: The vaccination for COVID-19, during the Omicron BA.4/5 subvariant outbreak is critical for MM patients, as it improves the outcome of severe COVID-19, even amid hesitancy.

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shows that cancer patients have a higher risk of infection and severe complications from viral infections, including COVID-19[2-5]. Among the hematological malignancies, multiple myeloma, the second most common type in the elderly, is characterized by malignant plasma cells proliferation primarily in the bone marrow[6]. MM patients are particularly susceptible to COVID-19 due to immune dysfunction from the disease and its treatments[7,8]. This immune compromise may worsen due to MM-related or treatment-induced organ dysfunction, comorbidities, immune senescence from aging[9], and T-cell exhaustion from prolonged therapy[10].

Vaccination is the most cost-efficient way to prevent infectious diseases and a mainstay of public health strategies[11,12]. The success of COVID-19 vaccination depends on achieving high inoculation rates. If a large portion of the population hesitates or refuses vaccination, overall coverage remains low. Vaccine hesitancy has become a major global public health issue over the past decade, influenced by diverse factors such as demographics, disease characteristics, geography, time, and other contextual variables, making it challenging to identify reasons and design interventions[13,14]. The COVID-19 vaccination rate in Chinese MM patients is unclear. Although the impact of the Omicron subvariant pandemic on this vulnerable group was anticipated[15], the extent of benefits MM patients gain from COVID-19 vaccination was largely unknown[16]. Given the recurrence nature of COVID-19 infections, understanding patients' vaccination willingness is crucial. In this study, we conducted a prospective questionnaire survey of MM patients after the outbreak of SARS-CoV-2 Omicron subvariant to identify factors influencing vaccination decisions. Our goal is to develop rational SARS-CoV-2 vaccination strategies for this immunecompromised group.

2. Methods

2.1. Study setting

This cross-sectional study was conducted in mainland China from December 26, 2022, to April 20, 2023, following a COVID-19 outbreak. The study questionnaire was developed based on relevant literature reviews[17,18] and expert group discussions. Our center follows up with a cohort of approximately 1 000 MM patients regularly, adding around 100 newly diagnosed multiple myeloma (NDMM) patients annually, with a dropout rate less than 5%. A pilot study was conducted to assess the questionnaire's feasibility and determine the main study's sample size. It included 50 MM patients with COVID-19: 18 vaccinated (1 hospitalized) and 32 unvaccinated (5 hospitalized). Using a two-proportion comparison formula, we calculated that 145 patients per group were needed to achieve 80% power at a 5% significance level.

Particularly, Mr. Shaohua Xin, a leader of the mainland China MM patient organization, kindly distributed the online questionnaire *via* WeChat mini-program to several groups, each comprising 500 MM patients. We sent the questionnaire to our cohort in groups and requested referrals. The selection was non-random but aimed to maximize geographic and disease subtype diversity. All participants were informed of the study's objectives and assured of data anonymity and confidentiality. The Ethics Committee of Peking Union Medical College Hospital approved this prospective study on February 7, 2023 (protocol number K2751). The study procedures adhered to the ethical guidelines of Declaration of Helsinki.

2.2. Questionnaire design

The questionnaire was divided into four sections: (1) Demographic characteristics, including gender, age, body mass index (BMI; kg/m^2), geographic location, marital status and parenthood status, non-communicable chronic diseases (NCD) status, education, occupation status, annual household income. (2) MM medical attributes, covering Durie-Salmon (DS) stage, International Staging System (ISS), monoclonal (M) protein type, treatment during SARS-CoV-2 infection, history of autologous stem cell transplantation (ASCT), disease status of MM, relapsed/refractory MM. (3) COVID-19 vaccination status, adverse effects after inoculation, and reasons for acceptance or hesitancy. The multiple-choice question provided predefined options and an open-ended choice for unlisted reasons. (4) Clinical manifestations of COVID-19, including infection duration, fever and maximum temperature, treatment, hospitalization, and complications. Appropriate response options were included for categorical variables.

2.3. Statistical analysis

Survey data were exported from the online questionnaire platform (https://www.wenjuan.com/list/) in the form of an Excel file. Descriptive statistics (frequencies, percentages) characterized categorical variables, while the median and interquartile range (IQR) were computed for continuous variables that were in abnormal distribution. Continuous variable comparisons utilized the Mann-Whitney U test, while categorical variables were evaluated using the *Chi*-square test and Fisher's exact test. A two-sided P-value of <0.05 indicated statistical significance. Analyses were performed using the Statistical Package for Social Sciences (SPSS, Version 28.0, IBM Corporation, USA) and GraphPad Prism version 8 (GraphPad Software, USA).

3. Results

3.1. COVID-19 vaccination rate and influencing factors

A total of 508 complete and valid questionnaires were collected from 30 provinces across China (Figure 1), based on participants'

permanent addresses. The median age of participants was 61 years (IQR: 54-68 years), with 51.7% (263/508) male. In terms of BMI, 51.0% (259/508) were in the normal range (18.5-24). Most participants (271/508, 53.3%) reported NCD, 38.4% (195/508) had multiple offspring, 40.8% (207/508) had a college degree, 53.0% (269/508) were retirees, and 75.6% (384/508) had an annual household incomes below 100000 CNY in 2022.

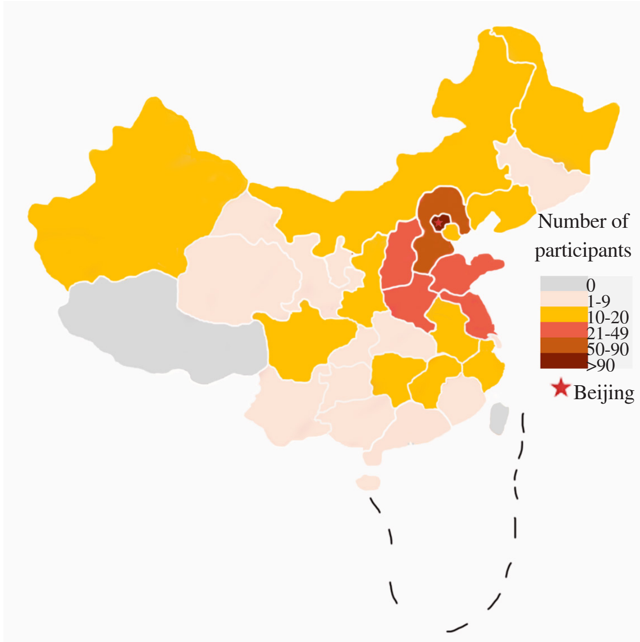

Figure 1. Regional distribution of the participants in the survey.

As shown in Table 1, only 34.1% (173/508) of MM patients received at least one dose of the SARS-CoV-2 inactivated vaccine. In the vaccinated group, 57.8% (100/173) were male, compared to 48.7% (163/335) in the unvaccinated group (P=0.051). The median age of the vaccinated group and unvaccinated group was (range: 53-68 years) and (54-68 years), respectively. About 40% of the participants in both groups were 65 years or above showing no significant difference between the two groups. However, a significant discrepancy in BMI distribution was observed (P=0.01), none of patients with low BMI (BMI<18.5) (0/19) vaccinated. Notably, only 20.2% (35/173) of vaccinated MM patients who had undergone ASCT were vaccinated, significantly lower than the unvaccinated group (48.4%, 162/335). Other factors, including NCDs, multiple offspring, education level, employment status, and income, showed no significant differences between the groups and were not key factors affecting COVID-19 vaccination decisions among MM patients.

3.2. Reasons for COVID–19 vaccine acceptance or hesitancy

To understand the rationale behind COVID-19 vaccine acceptance and hesitancy among MM patients, multiple-choice questions were included in the questionnaire. Figure 2 presents the primary reasons for vaccine acceptance (Figure 2A) and hesitancy (Figure 2B). The top three motives for vaccination were personal discretion (49.0%, 85/173), concern about COVID-19 infection (35.1%, 61/173), and trust in vaccine efficacy (26.5%, 46/173). Conversely, the main reasons for hesitancy were physicians' advice (52.0%, 174/335), concerns about conflicts with MM treatment (37.8%, 127/335), and fears about MM progression (31.3%, 105/335). Overall, MM patients' reluctance toward COVID-19 vaccination was primarily to disease status and anti-myeloma management.

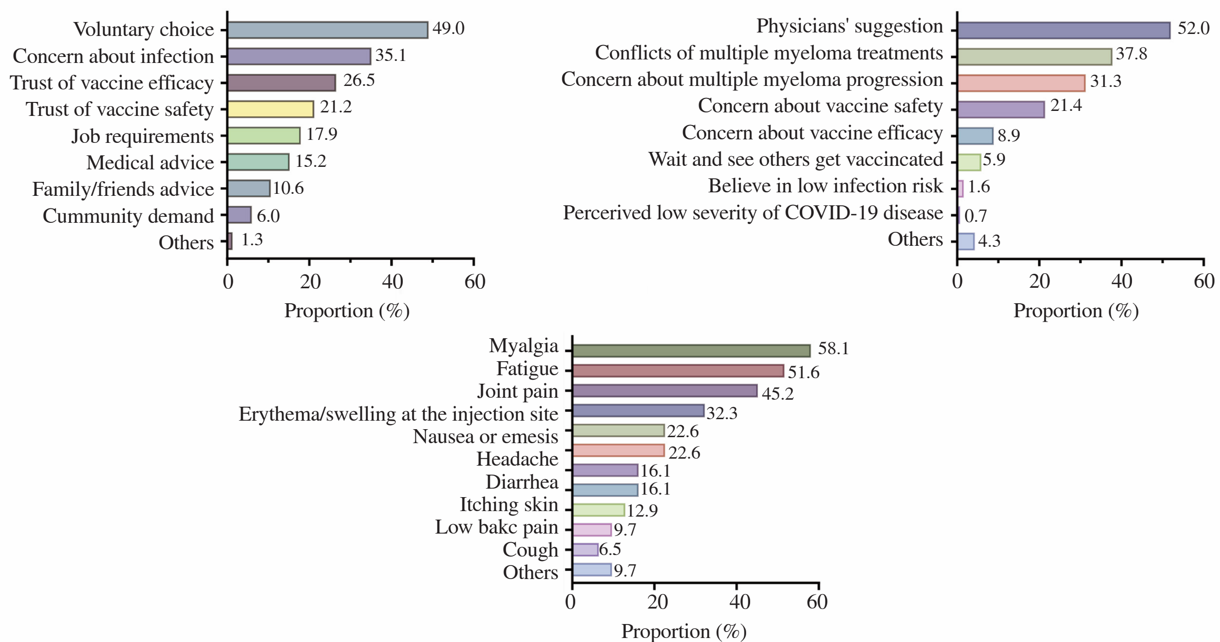

Figure 2. Reasons for COVID-19 vaccine acceptance or hesitancy and frequencies of adverse events. (A) Reasons for COVID-19 vaccine acceptance. (B) Reasons for COVID-19 vaccine hesitancy. (C) Frequencies of adverse events after vaccination.

Table 1. The baseline characteristics of all participants [*n* (%)].

Parameters	All (*n*=508)	Vaccinated (*n*=173)	Unvaccinated (*n*=335)	*P*-value
Sex				0.051
Male	263 (51.7)	100 (57.8)	163 (48.7)	
Female	245 (48.3)	73 (42.2)	172 (51.3)	
Age, years				
<65	305 (60.0)	104 (60.1)	201 (60.0)	
≥65	203 (40.0)	69 (39.9)	134 (40.0)	
BMI, kg/m^2				0.010
<18.5 (thin)	19 (3.7)	0 (0)	19 (5.7)	
18.5 to <24 (normal weight)	259 (51.0)	91 (52.6)	168 (50.2)	
24 to <28 (overweight)	188 (37.0)	70 (40.5)	118 (35.2)	
≥28 (obese)	42 (8.3)	12 (6.9)	30 (8.96)	
History of ASCT				<0.001
Yes	197 (38.8)	35 (20.2)	162 (48.4)	
No	311 (61.2)	138 (79.8)	173 (51.6)	
NCD				0.148
None	237 (46.7)	73 (42.2)	164 (49.0)	
1 or more	271 (53.3)	100 (57.8)	171 (51.0)	
Number of children				0.281
≤1	313 (61.6)	101 (58.4)	212 (63.3)	
>1	195 (38.4)	72 (41.6)	123 (36.7)	
Education				0.313
Primary school and below	51 (10.0)	19 (11.0)	32 (9.6)	
Middle or high school	250 (49.2)	77 (44.5)	173 (51.6)	
Associate/bachelor and above	207 (40.8)	77 (44.5)	130 (38.8)	
Occupation status				0.357
Employed	101 (19.9)	41 (23.7)	60 (17.9)	
Retired	269 (53.0)	84 (48.6)	185 (55.2)	
Farming	64 (12.6)	23 (13.3)	41 (12.2)	
Others	74 (14.5)	25 (14.4)	49 (14.6)	
Annual household income in 2022				0.070
<CNY 100000	384 (75.6)	122 (70.5)	262 (78.2)	
CNY 100000-200000	89 (17.5)	34 (19.7)	55 (16.4)	
>CNY 200000	35 (6.9)	17 (9.8)	18 (5.4)	

BMI: body mass index; ASCT: autologous hematopoietic stem cell transplantation; NCD: non-communicable chronic diseases; CNY: Chinese Yuan.

3.3. Adverse events of COVID-19 vaccines in patients with MM

COVID-19 vaccine-related adverse events (AEs) were investigated in this study (Figure 2C). Among 173 vaccinated patients, 419 doses were administered, with 48 adverse events reported (48/419, 11.5% of total doses) reported. Common AEs included myalgia, fatigue, joint pain, erythema or swelling at the injection sites, and nausea or vomiting, similar to those in the general population. All AEs were mild and manageable, with no vaccine-associated adverse events specific to MM reported.

3.4. Comparison of infection rates between vaccinated and unvaccinated groups

In our analysis of SARS-CoV-2 infection rates in MM patients, the overall infection rate was slightly higher in vaccinated recipients (60.1%, 104/173) than in the unvaccinated group (55.8%, 187/335). Subgroup analysis revealed that in patients aged 65 or older, the vaccinated group had a lower infection rate (49.3%, 34/69) than the unvaccinated group (55.2%, 74/134), though this difference was not statistically significant (*P*=0.421). In contrast, among participants younger than 65, the vaccinated group had a higher infection rate (67.3%, 70/104) than the unvaccinated group (56.2%, 113/201), with a *P*-value of 0.061. Infection rates were comparable across different BMI levels . In the obese subgroup (BMI 28), the infection rate was lower in vaccinated patients (50.0%, 6/12) than in unvaccinated patients (63.3%, 19/30), though not statistically significant (*P*=0.426). For relapsed/refractory MM patients, the protective effects of vaccines were more pronounced, with infection rates of 42.2% (19/45) in the vaccinated group versus 66.7% (72/108) in the unvaccinated group (*P*=0.005).

3.5. Effect of inactivated vaccines on the severity of SARS-CoV-2 infection in MM patients

Although inactivated vaccines did not significantly reduce COVID-19 infection rates in the MM population, vaccination was associated with less severe clinical manifestations and improved outcomes. Among infected patients, the incidence of fever was lower

Table 2. Characteristics of infected patients in vaccinated group *vs.* unvaccinated group [*n* (%)].

Parameters	Vaccinated		Unvaccinated		*P*-value
	Total (*n*=173)	Infected (*n*=104)	Total (*n*=335)	Infected (*n*=187)	
Sex					
Male	100	59 (59.0)	163	82 (50.6)	0.17
Female	73	45 (61.6)	172	105 (61.0)	0.93
Age					
<65 years	104	70 (67.3)	201	113 (56.2)	0.061
≥65 years	69	34 (49.3)	134	74 (55.2)	0.421
BMI, kg/m^2					
<18.5 (thin)	0	0	19	9 (47.4)	-
18.5 to <24 (normal)	91	59 (64.8)	168	96 (57.1)	0.228
24 to <28 (overweight)	70	39 (55.7)	118	63 (53.4)	0.757
≥28 (obese)	12	6 (50.0)	30	19 (63.3)	0.426
Paraprotein type					
IgG	48	31 (64.6)	150	88 (58.7)	0.466
IgA	33	16 (48.5)	51	26 (51.0)	0.823
IgD	7	6 (85.7)	23	18 (78.3)	0.666
LC	43	33 (76.7)	78	40 (51.3)	0.006
DS stage					
Ⅰ	21	13 (61.9)	40	23 (57.5)	0.74
Ⅱ	25	16 (64.0)	58	35 (60.3)	0.754
Ⅲ	81	51 (63.0)	170	96 (56.5)	0.329
ISS stage					
Ⅰ	25	14 (56.0)	56	32 (57.1)	0.924
Ⅱ	38	22 (57.9)	81	40 (49.4)	0.386
Ⅲ	66	44 (66.7)	134	82 (61.2)	0.451
Completed ASCT	35	19 (54.3)	161	90 (55.9)	0.862
Immunotherapy*	23	16 (69.6)	51	35 (68.6)	0.936
Active MM	18	13 (72.2)	62	46 (74.2)	0.867
R/RMM	45	19 (42.2)	108	72 (66.7)	0.005
Comorbidities					
NCD	100	61 (61.0)	172	93 (54.1)	0.859
Lung diseases	9	6 (66.7)	22	13 (59.1)	0.694
Autoimmune diseases	5	2 (40.0)	11	4 (36.4)	0.889
Other cancers	3	1 (33.3)	11	5 (45.5)	0.707

*Underlying immunotherapy when infection. -: not analyzed. BMI: body mass index; LC: light chain; DS: Durie-Salmon; ISS: International Staging System; ASCT: autologous hematopoietic stem cell transplantation; MM: multiple myeloma; R/R MM: relapsed and/or refractory multiple myeloma; NCD: non-communicable chronic diseases.

Table 3. The clinical manifestations of SARS-CoV-2 infection in MM patients [*n* (%)].

Parameters	Total (*n*=291)	Vaccinated (*n*=104)	Unvaccinated (*n*=187)	*P*-value
Asymptomatic infections				0.263
Yes	57 (19.6)	24 (23.1)	33 (17.6)	
No	234 (80.4)	80 (76.9)	154 (82.4)	
Fever				0.188
Yes	191 (81.6)	69 (86.3)	122 (79.2)	
No	43 (18.4)	11 (13.7)	32 (20.8)	
Hospitalization				0.038
Yes	28 (8.6)	5 (4.8)	23 (12.3)	
No	263 (91.4)	99 (95.2)	164 (87.7)	
Duration of COVID-19 symptoms, days				0.350
≤7	29 (20.6)	12 (25.0)	17 (18.3)	
>7	112 (79.4)	36 (75.0)	76 (81.7)	

in the vaccinated group (13.7%, 11/80) than in the unvaccinated group (20.8%, 32/154), though this difference was not statistically significant (*P*=0.188). The vaccinated group also had a lower proportion of clinical manifestation durations within seven days compared to the unvaccinated group (25.0%, 12/48 *vs.* 18.3%, 17/93), though this was not statistically significant (*P*=0.35). While the proportion of asymptomatic infections did not differ significantly between the two groups, the proportion of hospitalized patients with severe COVID-19 was significantly lower in the vaccinated group (4.8%, 5/104) than in the unvaccinated group (12.3%, 23/187) (*P*=0.038).

4. Discussion

Our national survey of 508 MM patients across 30 provinces in China. Notably, it revealed that only about one-third had received inactivated COVID-19 vaccines, despite approximately 60% being infected during the pandemic. This suggested that stringent quarantine policy and self-restriction of social activities contributed to relatively fewer infections in MM patients. However, the vaccines proved effective in reducing severe symptoms and hospitalizations among this immunocompromised group.

Subgroup analyses suggested vaccination benefits in specific scenarios. Elderly MM patients (aged 65 or older) who were vaccinated showed lower infection rates, highlighting vaccination's protective role in this vulnerable group[17]. Similar trends were observed in obese patients and those with relapsed/refractory MM, who were more susceptible to complications. Additionally, vaccination appeared to mitigate COVID-19 symptoms, particularly fever. Notably, although the median time since the last vaccine shot was around one year, vaccination was associated with a significantly reduced hospitalization rate, which was consistent with the results of several retrospective studies[7,8,19–21]. Our data show a significant reduction in hospitalization rate among vaccinated patients (4.8% *vs.* 12.3%, P=0.038), highlighting the vaccine impact on mitigating the severity of COVID-19 in this vulnerable population. However, the proportion of severe COVID-19 patients in both vaccinated and unvaccinated groups was higher than those reported by other countries[19,22–24]. This discrepancy was likely related to the strict quarantine and the long gap between vaccination and the pandemic in December 2022.

Our study involved collaboration with a patient organization leader who himself is a MM patient. This approach helped us comprehensively assess demographic, medical, and socioeconomic factors influencing vaccination decisions, which unveiled insights into MM patients' perspectives on vaccination. We found that gender influenced vaccination intent, with more male patients opting for vaccination. Moreover, no patients with a BMI <18.5 had been vaccinated, which, along with smaller sample sizes for specific subgroups like those who underwent ASCT, may limit the statistical power of our findings. Apart from the potential bias introduced by a small sample size, it is also essential to consider that these patients might have concerns about their clinical status and physical condition. Our insights suggest tailored intervention strategies are needed to address the diverse factors affecting vaccination decisions among MM patients. Future studies with larger cohorts should confirm our preliminary observations and further explore impacts on these high-risk populations.

This study explored COVID-19 vaccine acceptance and hesitancy among MM patients, recognizing vaccination as a cost-efficient and effective tool against infectious diseases[25,26]. The success of vaccination programs hinges on high inoculation rates to achieve herd immunity[27]. However, vaccine hesitancy remains a significant challenge[28]. In China, despite available COVID-19 vaccines, rollout challenges persist, with vaccine hesitancy being a major hurdle[29,30]. The complex interplay of demographic, disease-related, geographical, and temporal factors necessitates comprehensive strategies to address these challenges[31]. Reasons for vaccine acceptance, such as voluntary choice and concerns about COVID-19 infection, highlight the importance of personal choice and perceived vulnerability. Conversely, reasons for hesitancy, including concerns about the MM progression and conflicts with ongoing treatment regimens, underscore the complexity of medical decision-making Physicians' recommendations significantly influenced patients' perceptions of vaccination benefits and risks.

Adverse events (AEs) from COVID-19 vaccination have drawn widespread attention. While prior studies have reported severe vaccine-induced AEs in cancer patients, such as immune thrombocytopenia, thrombosis, and breakthrough infections[5,24,32], our study showed AEs in vaccinated MM patients, consistent with observations in healthy populations. This suggests COVID-19 vaccines are safe for MM patients and may encourage wider adoption. The low vaccination rate among patients receiving ASCT may stem from concerns about post-ASCT immunosuppression and vaccine-related AEs. Strict self-quarantine likely contributed to fewer infections in the non-ASCT subgroup. Notably, a refusal rate exceeding 10% of inoculation could weaken population immunity[33]. In China, despite adequate COVID-19 vaccines, rollout remains challenging, with vaccine hesitancy being a primary obstacles[34–36]. Prior studies have highlighted the prevalence of COVID-19 vaccine hesitancy among the general population and medical staff[35]. Given MM patients' advanced age and susceptibility to severe COVID-19 outcomes, they are a priority group for vaccination. Their health status and socioeconomic factors may lead to distinct acceptance or concerns about COVID-19 vaccination compared to the general population[30,37].

The dynamic nature of the COVID-19 pandemic and the emergence of new variants necessitate ongoing evaluation of vaccination strategies. Our findings, specific to December 2022 to April 2023, emphasize this need. Vaccine efficacy against new strains is crucial for shaping future public health policies, particularly for immunocompromised populations like MM patients. It is worthy of providing our recent valuable data to the evolving context. The first study highlights the significant T cell dysregulation in MM patients with severe COVID-19, particularly within the first month post-infection, emphasizing the need for close surveillance of reinfection[38]. Another study identifies risk factors for hospitalization and shows an initial severe impairment of humoral immunity, especially in unvaccinated patients even with relatively intact T-cell responses[39]. Although Omicron BA.4/5 was the main sub-strain during the outbreak, inactivated vaccines reveals the protective impact and a booster shot is suggested 14–16 weeks after to maintain immunity in high-risk MM patients. These findings, combined with our study, emphasize the importance of vaccination

that consider the pandemic's evolution and the specific immune dynamics in MM patients.

While our study provided valuable insights, it has certain limitations. The cross-sectional design restricts causal relationships establishment, and the findings may not apply to MM populations in different regions or healthcare systems. Longitudinal studies with larger, diverse patient populations are needed for a more comprehensive understanding of COVID-19 vaccination's impact on MM patients.

In conclusion, this nationwide survey comprehensively addresses the pressing concern of COVID-19 vaccination among MM patients in China. Despite the pandemic's widespread last December, inactivated COVID-19 vaccines did protect this immunocompromised population from severe infections, particularly in elderly, obese, or relapsed patients. As COVID-19 has evolved into a chronic and recurrent infection, understanding of vaccine acceptance and hesitancy among MM patients will provide valuable evidence for inoculation strategies. Our study proves the efficacy and safety of inactivated COVID-19 vaccines in MM patients. It deserves further well-designed studies for the recommendation of vaccine schedules in other vulnerable populations.

Conflict of interest statement

The authors disclosed no potential conflict of interest.

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Data availability statement

Data are available upon request from the corresponding author.

Authors' contributions

Zhuang JL, Chen WM, Li YZ, Sun WL, Hua BL contributed to the study conception and design. Material preparation, data collection, and analysis were performed by He HW, Jin XH, Li ZP. Liu SJ was responsible for patients' follow-ups. The first draft of the manuscript was written by Jin XH and He HW. Zhuang JL critically revised the manuscript. All authors read and approved the final manuscript.

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