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RESEARCH ARTICLE

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PHD finger protein 19 expression in multiple myeloma: Association with clinical features, induction therapy outcome, disease progression, and survival

Yaqiong Li | **Jichang Gong** | **Lingli Zhang**

Department of Hematology, Dazhou Central Hospital, Dazhou, China

Correspondence
Yaqiong Li, Department of Hematology, Dazhou Central Hospital, No. 56 Nanyue Temple Street, Tongchuan District, Dazhou 635000, Sichuan, China.
Email: nieya612000@163.com

Abstract

Background: PHD finger protein 19 (PHF19), also known as polycomb-like protein 3 (PCL3), promotes the progression of multiple myeloma (MM) and drug resistance; however, its role in the management of MM remains unclear. Therefore, we aimed to elucidate the correlation between PHF19 expression and treatment response, disease progression, and survival of patients with MM.

Methods: Plasma cells derived from the bone marrow of 101 *patients with de novo* MM were collected prior to induction therapy, as were plasma cells derived from the bone marrow of 30 healthy donors. PHF19 expression in plasma cells was analyzed using quantitative reverse transcription polymerase chain reaction. Furthermore, the response to induction therapy, progression-free survival (PFS), and overall survival (OS) were assessed.

Results: PHF19 expression tends to be upregulated more often in MM patients than in healthy donors ($p < 0.001$) and can accurately predict MM risk (area under curve [AUC], 0.916; 95% confidence interval [CI], 0.869–0.962). Furthermore, elevated PHF19 expression was correlated with higher International Staging System (ISS) ($p = 0.036$) and revised ISS stages ($p = 0.035$). In addition, MM patients who achieved complete response (CR) exhibited reduced PHF19 compared to those who did not ($p = 0.028$). Moreover, increased PHF19 expression was correlated with unfavorable PFS ($p = 0.006$) and OS ($p = 0.027$) rates. Furthermore, the results of multivariate Cox analysis also revealed that PHF19 high expression was independently associated with a reduced PFS rate (hazard ratio: 2.025, $p = 0.028$).

Conclusion: Increased PHF19 expression is correlated with poor induction therapy response and unfavorable long-term prognosis of MM.

KEYWORDS
disease risk, multiple myeloma, PHD finger protein 19, survival profile, treatment response

1 | INTRODUCTION

Multiple myeloma (MM) is the second most common hematological malignancy worldwide and claimed the lives of approximately 32,000 individuals in the United States in 2019.[1–3] Treatment for MM has improved greatly over the past several decades, particularly due to the advent of immunomodulatory drugs and proteasome inhibitors.[4] However, the incidence of relapse and refractory MM remains high.[5–7] Because the outcome of MM is still primarily unfavorable,[5] discovering novel biomarkers to improve the overall prognosis of MM patients is crucial.

Polycomb group proteins are chromatin-related gene suppressors that participate in stem cell differentiation and proliferation.[8] PHD finger protein 19 (PHF19), also known as polycomb-like protein 3 (PCL3), a member of the Polycomb group proteins, plays an essential role in several malignancies, including MM.[2,8–10] For instance, PHF19 can promote MM oncogenesis through histone H3 lysine 27 (H3K27me3) and polycomb repressive complex 2 (PRC2).[8] In addition, PHF19 is able to inhibit drug sensitivity in patients with MM by regulating the enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) phosphorylation.[2] Based on the above-mentioned information, we hypothesized that PHF19 may serve as a potential biomarker of induction therapy response, along with long-term prognosis of MM. However, its role in MM remains unclear. Therefore, the aim of this study was to investigate the correlation between PHF19 expression and clinical characteristics, treatment response, and long-term prognosis of MM.

2 | METHODS

2.1 | Subjects

With approval from the appropriate Institutional Review Board, 101 patients with *de novo* symptomatic MM were recruited consecutively between January 2017 and June 2020. Patients who met the following criteria were eligible for inclusion: (a) newly diagnosed symptomatic MM in accordance with the International Myeloma Working Group (IMWG) criteria[11]; (b) over 18 years old; (c) a willingness to participate in the study and provide a bone marrow (BM) sample for research purposes; and (d) the ability to be followed up regularly. Patients were excluded based on the following criteria: (a) secondary or relapsed MM; (b) smoldering (asymptomatic) MM; (c) presentation of plasma cell disorders or immunoglobulin-related disorders besides MM, (d) MM concomitant with other malignant diseases, (e) a history of radiotherapy or chemotherapy, and (f) gestation. In addition to the 101 MM patients, this study also enrolled 30 healthy BM donors as healthy controls. Each eligible subject signed an informed consent form prior to recruitment.

2.2 | Baseline data collection

After diagnostic workup, the patients' demographic and disease characteristics, biochemical indexes, and cytogenetic abnormalities were recorded for analysis. Staging was performed according to the Durie-Salmon staging system, International Staging System (ISS), or revised ISS (R-ISS).[12–14]

2.3 | BM sample collection and processing

Bone marrow samples were acquired from MM patients at diagnosis and from healthy donors at the time of donation, after which they were submitted to the laboratory. Subsequently, plasma cells were obtained from the BM samples using CD138-immunomagnetic beads (Miltenyi Biotec) in accordance with the manufacturer's instructions. The purity of the isolated sample was confirmed, and only samples with >70% plasma cells were subjected to further analysis of PHF19 expression through reverse transcription quantitative polymerase chain reaction.

2.4 | RT-qPCR

In short, total RNA was extracted using the RNeasy Protect Mini Kit (Qiagen) and reverse transcribed using the ReverTra Ace® qPCR RT Kit (Toyobo). qPCR was performed using the KOD SYBR® qPCR Mix (Toyobo). Relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method, and GAPDH was used as an internal reference. In addition, primer sequences were constructed according to the methods of a previous study.[8] The thermal cycle parameters of RT were 37°C for 15 min and 98°C for 5 min. Meanwhile, the thermal cycle parameters of qPCR were as follows: 1 cycle at 98°C for 2 min; 40 cycles at 98°C for 10 s, 61°C for 10 s, and 68°C for 30 s.

2.5 | Follow-up and assessment

All patients underwent combination induction therapy with proteasome inhibitors, immunomodulators, and dexamethasone. The patients' response to induction therapy was assessed in accordance with the International Myeloma Working Group (IMWG) criteria.[11] The objective response rate was calculated as the percentage of patients with complete response (CR), very good partial response, or partial response. In addition, follow-up and surveillance were conducted every 3 months or as clinically indicated. The follow-up deadline for the current study was 2021/1/31, resulting in a median follow-up of 29.0 months with 95% confidence interval (CI) of 25.4–32.6 months (reverse Kaplan-Meier (KM) method). Progression-free survival (PFS) and overall survival (OS) were estimated according to the IMWG guidelines.[11] Patients who died during induction therapy or were not assessed for response to induction therapy due to early loss of follow-up were excluded from the final analysis.

2.6 | Statistical analysis

The Kolmogorov-Smirnov (K-S) test was used to ascertain the normality of continuous variables, which were described as mean and

standard deviation if normally distributed, or as median and interquartile range if not. Differences were analyzed using the Mann-Whitney U or Kruskal-Wallis test. Correlation analysis was performed using the Spearman test. The discrimination performance of the variable was estimated using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). PFS and OS were analyzed using the KM and log-rank tests. Prognostic factors were determined using multivariable Cox proportional hazard regression model analysis. *Statistical significance was set at* $p < 0.05$. SPSS 24.0, IBM Corp., Armonk, New York, USA, was used to analyze data.

3 | RESULTS

3.1 | Baseline characteristics

Among the patients with MM, the mean age was 53.8 ± 8.7 years. We evaluated 63 (62.4%) men and 38 (37.6%) women. Regarding cytogenetics, the patients had the following characteristics: 32 (31.7%) had Amp (1q), 11 (10.9%) patients had t (4; 14), 4 (4.0%) patients had t (14; 16), and 8 (7.9%) patients had Del (17p). There were 13 (12.9%) patients with ISS stage I, 37 (36.6%) patients with stage II, and 51 (50.5%) patients with stage III. In terms of R-ISS stage, 7 (7.0%) patients had stage I disease, 47 (46.5%) had stage II, and 47 (46.5%) had stage III disease. The detailed baseline characteristics of patients with MM are shown in Table 1.

3.2 | Comparison of PHF19 expression between MM patients and health donors

PHF19 expression was elevated in patients with MM [median value: 3.033 (1.968–3.953)] compared to that of healthy donors (median value: 0.981 [0.658–1.487]; $p < 0.001$) (Figure 1A). The ROC curve indicated that PHF19 expression had excellent potential in differentiating patients with MM from healthy donors with an AUC of 0.916 (95%CI: 0.869–0.962). In addition, PHF19 expression was 1.818 at the best cutoff point (the point with the maximum value of the sum of sensitivity and specificity), at which point the values of sensitivity and specificity were 0.782 and 0.967, respectively (Figure 1B).

3.3 | Comparison of PHF19 expression between MM patients with different clinical characteristics

PHF19 expression did not differ among MM patients with different immunoglobulin subtypes (IgG, IgA, and others) or Durie-Salmon stages (stage I, stage II, and stage III) (all $p > 0.05$) (Figure 2A, B). Importantly, PHF19 expression was highest in MM patients with ISS stage III, followed by those with ISS stage II, and lowest in those with ISS stage I ($p = 0.036$) (Figure 2C). Furthermore, PHF19

TABLE 1 Baseline characteristics of MM patients

Items	MM patients ($N = 101$)
Demographic characteristics	
Age (years), mean ± SD	53.8 ± 8.7
Gender, No. (%)	
Male	63 (62.4)
Female	38 (37.6)
Disease characteristics, No. (%)	
Immunoglobulin subtype	
IgG	54 (53.5)
IgA	19 (18.8)
Others	28 (27.7)
Bone lesion	75 (74.3)
Renal impairment	40 (39.6)
Biochemical indexes	
Hb (g/L), mean ± SD	98.3 ± 24.8
Calcium (mg/dl), mean ± SD	9.9 ± 2.0
ALB (g/L), mean ± SD	33.0 ± 6.4
β_2-MG (mg/L), median (IQR)	5.5 (2.9–8.5)
LDH (U/L), median (IQR)	210.7 (173.9–256.4)
Cytogenetics, No. (%)	
Amp (1q)	32 (31.7)
t (4; 14)	11 (10.9)
t (14; 16)	4 (4.0)
Del (17p)	8 (7.9)
Durie-Salmon stage, No. (%)	
Stage I	0 (0.0)
Stage II	10 (9.9)
Stage III	91 (90.1)
ISS stage, No. (%)	
Stage I	13 (12.9)
Stage II	37 (36.6)
Stage III	51 (50.5)
R-ISS stage, No. (%)	
Stage I	7 (7.0)
Stage II	47 (46.5)
Stage III	47 (46.5)
Induction therapy, No. (%)	
BDT	71 (70.3)
BD	30 (29.7)
Allo- HSCT, No. (%)	19 (18.8)

Abbreviations: ALB, albumin; allo-HSCT, allogeneic hematopoietic stem cell transplantation; BD, bortezomib-dexamethasone; BDT, bortezomib-dexamethasone-thalidomide; Hb, hemoglobin; IgA, immunoglobulin A; IgG, immunoglobulin G; IQR, interquartile range; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System; SD, standard deviation; β_2-MG, Beta-2-microglobulin.

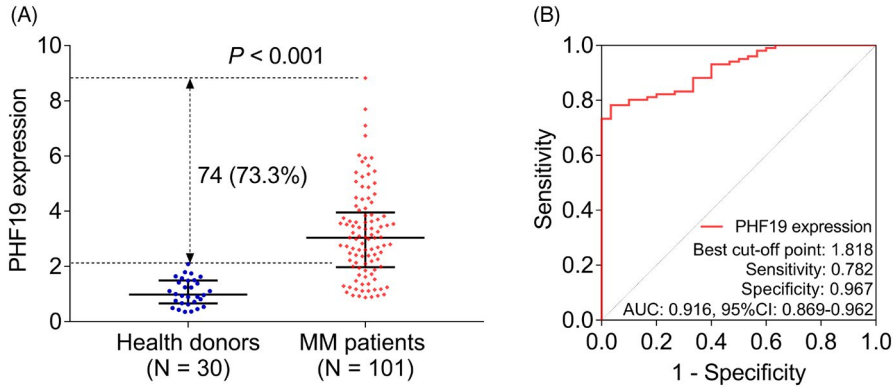

FIGURE 1 PHF19 in MM patients and healthy donors. Comparison of PHF19 between MM patients and healthy donors (A); the ability of PHF19 to discriminate MM patients from health donors (B). PHF19, PHD finger protein 19; MM, multiple myeloma; AUC, area under curve; CI, confidence interval

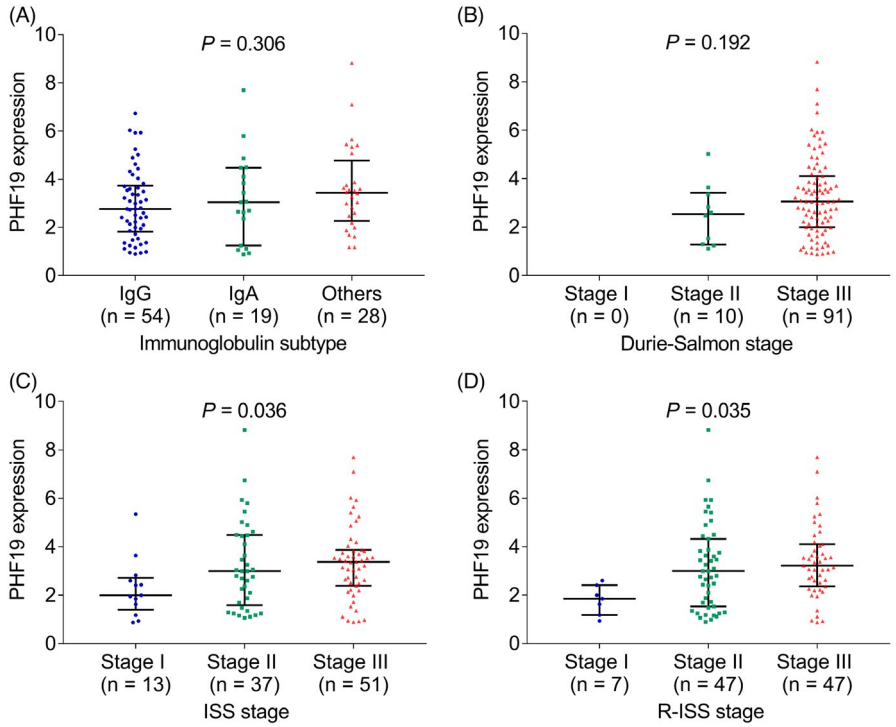

FIGURE 2 PHF19 expression in patients with MM with distinct clinical features. Association of PHF19 with immunoglobulin subtypes (A), Durie-Salmon stages (B), ISS stages (C), and R-ISS stages (D). PHF19, PHD finger protein 19; MM, multiple myeloma; ISS, International Staging System; R-ISS, revised International Staging System

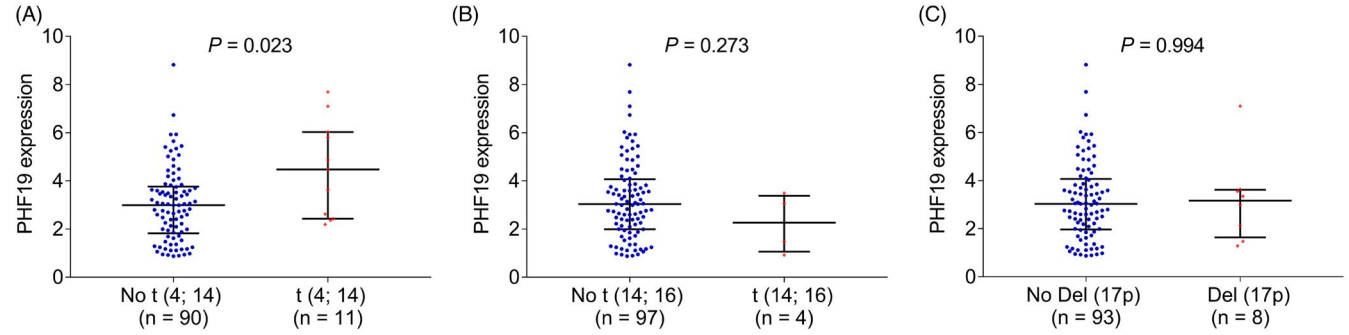

FIGURE 3 PHF19 expression in patients with MM with different cytogenetics. Association of PHF19 with t (4; 14) vs. non-t (4; 14) (A), t (14; 16) vs. non-t (14; 16) (B), Del (17p) vs. non-Del (17p) (C). PHF19, PHD finger protein 19; MM, multiple myeloma

expression was highest in MM patients with R-ISS stage III, followed by R-ISS stage II, and lowest in those with R-ISS stage I ($p = 0.035$) (Figure 2D). In addition, PHF19 expression was potentially enhanced in MM patients with t (4; 14) compared to MM patients without t (4; 14) ($p = 0.023$) (Figure 3A). Moreover, no difference was found in PHF19 expression between MM patients with vs. MM patients without t (14; 16), or MM patients with versus MM patients without Del (17p) (all $p > 0.05$) (Figure 3B, C).

3.4 | Comparison of PHF19 expression between CR patients and non-CR patients, as well as objective response rate (ORR) patients and non-ORR patients

PHF19 expression was reduced in patients who achieved CR compared to those who did not ($p = 0.028$) (Figure 4A). Meanwhile, the ROC curve illustrated that PHF19 expression could somewhat differentiate CR patients from non-CR patients with an AUC of 0.643 (95%CI: 0.515–0.770), even though its effect might be relatively poor. The PHF19 expression value was 2.667 at the best cutoff point, at which point the sensitivity and specificity values were 0.630 and 0.662, respectively (Figure 4B). However, PHF19 expression did not differ between ORR patients and non-ORR patients ($p = 0.092$) (Figure 4C). In addition, PHF19 expression did not differentiate ORR patients from non-ORR patients and had an AUC of 0.613 (95%CI: 0.488–0.738) (Figure 4D). In addition, the results of multivariate logistic regression analysis showed that t (4;14) was independently correlated with a decreased ORR (odds ratio: 0.028, $p = 0.006$) (Table S1).

3.5 | Association of PHF19 expression with accumulating PFS and OS

Patients with MM were divided into PHF19 high expression and PHF19 low expression groups based on the median value of PHF19 expression in patients with MM [median value: 3.033 (1.968–3.953)]. The PFS rate was attenuated in the PHF19 high expression group compared to that of the PHF19 low expression group ($p = 0.006$) (Figure 5A). Moreover, the OS accumulation of the PHF19 high expression group was lower than that of the PHF19 low expression group ($p = 0.027$) (Figure 5B). Furthermore, the results of multivariate Cox proportional hazard regression analysis showed that PHF19 high expression was independently associated with poor PFS (hazard ratio [HR]: 2.025, $p = 0.028$) (Table 2). However, PHF19 high expression was not independently associated with poor OS (HR, 1.395; $p = 0.535$) (Table 2).

4 | DISCUSSION

In our study, we found several notable results, including the following: (1) PHF19 expression was enhanced in MM patients and could accurately differentiate patients with MM from healthy donors; (2) elevated PHF19 expression was correlated with higher ISS and R-ISS stages; and (3) elevated PHF19 expression was associated with treatment response failure and unfavorable long-term prognosis of MM.

PHF19 plays a role in several biological processes, including cell proliferation and differentiation, and abnormal expression has been observed in hematologic malignancies.[4,8,15] In particular, its expression is elevated in patients with B-cell-derived malignancies, including MM.[8] Furthermore, a previous study demonstrated that the expression of PHF19 is notably high in cases of relapsed and refractory MM.[2] In our study, we discovered that PHF19 expression was elevated in patients with MM; furthermore, it can accurately

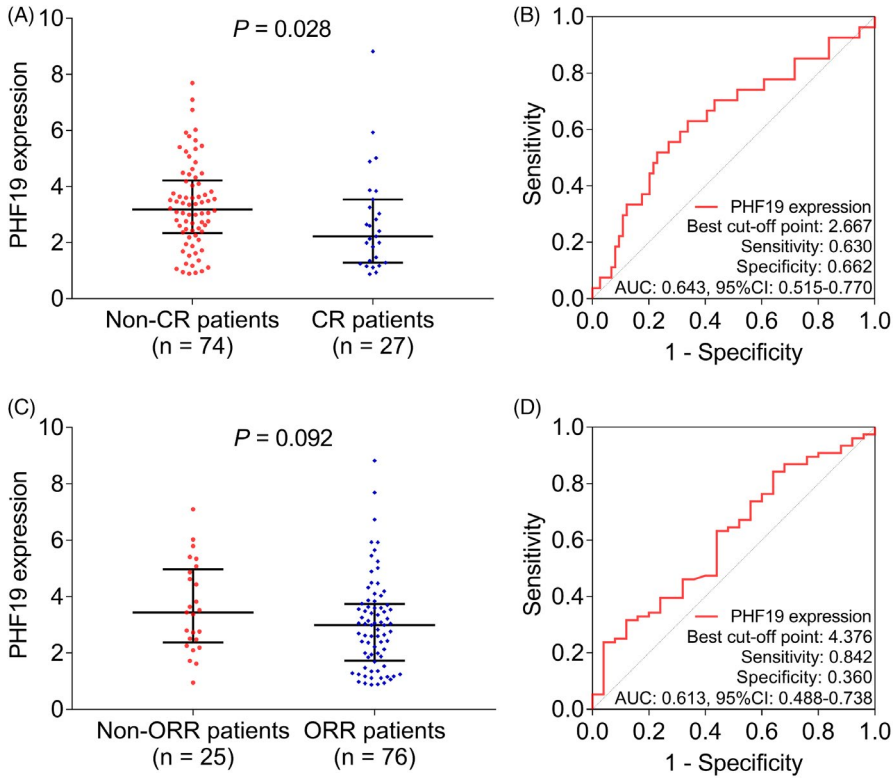

FIGURE 4 PHF19 in CR patients vs. non-CR patients, ORR patients vs. non-ORR patients. Comparison of PHF19 expression between CR patients and non-CR patients (A); the ability of PHF19 expression to discriminate CR patients from non-CR patients (B); comparison of PHF19 expression between ORR patients and non-ORR patients (C); the ability of PHF19 expression to discriminate ORR patients from non-ORR patients (D). PHF19, PHD finger protein 19; CR, complete response; AUC, area under curve; CI, confidence interval; ORR, objective response rate

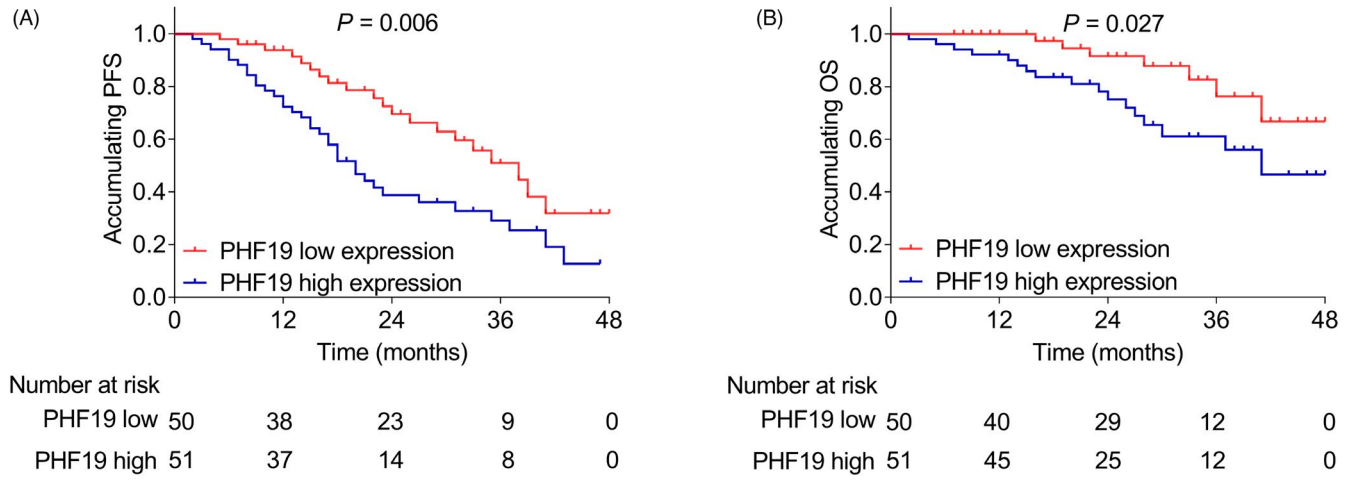

FIGURE 5 The PFS and OS rates in patients with different PHF19 expression. Comparison of accumulating PFS between PHF19 low expression and PHF19 high expression (A); comparison of OS between the PHF19 low expression and PHF19 high expression groups (B). PHF19, PHD finger protein 19; PFS, progression-free survival; OS, overall survival

distinguish patients with MM from healthy donors. This finding was partially consistent with that of previous studies.[2,8] Possible reasons include (1) PHF19 overexpression may accelerate PRC2 activation, which is thought to play a crucial role in the oncogenesis of MM[8]; (2) PHF19 may promote EZH2 phosphorylation by activating the protein kinase B signaling pathway, which may be correlated with the pathogenesis of MM.[2] Therefore, PHF19 expression is enhanced in patients with MM.

In terms of the association between PHF19 expression and MM clinical characteristics, PHF19 expression is reportedly enhanced in MM patients with translocation t (4,14).[16] In our study, we found that PHF19 expression was correlated with higher ISS and R-ISS stages, as well as with the presence of t (4; 14). A possible explanation might be that t (4; 14) may be a critical factor related to higher R-ISS stage; meanwhile, PHF19 overexpression was correlated with the gain of t (4,14) (above-mentioned); thus, PHF19 expression was associated with higher R-ISS stage.[14]

As for the association between PHF19 expression and prognosis of hematologic malignancy, PCL patients with elevated PHF19 expression may exhibit worse clinical outcomes.[8] However, information on the prognostic value of PHF19 in patients with MM is limited. In our study, we discovered that elevated PHF19 expression was associated with poor CR and unfavorable PFS and OS rates. This may be because: (1) PHF19 expression may reduce drug sensitivity in MM, which can result in treatment response failure in patients with MM[2]; (2) furthermore, PHF19 overexpression was associated with a higher ISS and R-ISS stage (as mentioned previously), which could indirectly result in a poor treatment response among patients with MM[14,17]; (3) in addition, PHF19 expression was correlated with both higher ISS and R-ISS stages and the treatment response of MM, which could result in poor long-term prognosis, as reflected by EFS and OS.

Some aspects are important to note, including the following: (1) In our study, the mean age was relatively low, which might be because the median and mean age of Chinese patients with MM is relatively young, according to clinical features of Chinese MM patients reports.[18,19] Furthermore, in China, some elderly patients would go to the geriatric department instead of the hematology department. In addition, because our sample size was relatively small, outliers may have affected our results. (2) We found that β2-MG was correlated with reduced PFS and OS rates using multivariate Cox analysis for PFS and OS; however, the correlation was not significant ($p = 0.052$, $p = 0.093$, respectively, whose value was <0.1), indicating that it might be independently correlated with PFS and OS. In addition, because β2-MG was not statistically significant according to the multivariate Cox analysis for PFS and OS, this might be explained by the effect of other confounding factors on its prognostic value; additionally, our follow-up duration was relatively short and progression/death events were limited, which might have resulted in less statistical power. (3) Only 19 (18.8%) patients were treated with allogeneic hematopoietic stem cell transplantation, which might be due to the limited number of voluntary donors in China.

Our study had several limitations, such as (1) the sample size was too small and might result in decreased statistical power in the analyses; (2) the clinical value of PHF19 expression in patients with relapsed or refractory MM requires further analysis; (3) the follow-up period was too short; thus, the correlation between PHF19 expression and the long-term survival profile of patients with MM should be investigated in the future; and (4) only 11 patients had translocation t (4,14), which may make it difficult to explore the correlation between PHF19 and t (4,14).

In conclusion, overexpression of PHF19 high expression is correlated with poor induction therapy response and unfavorable long-term prognosis of patients with MM.

TABLE 2 Multivariate Cox's proportional hazards regression analysis for PFS and OS

Items	Multivariate Cox's analysis for PFS		Multivariate Cox's analysis for OS	
	p value	Adjusted HR (95%CI)	*p* value	Adjusted HR (95%CI)
PHF19 high expression	**0.028**	2.025 (1.078–3.804)	0.535	1.395 (0.487–3.996)
Age >60 years	0.791	0.908 (0.446–1.850)	0.756	0.838 (0.275–2.552)
Male	0.713	0.874 (0.425–1.794)	0.443	1.512 (0.526–4.349)
Immunoglobulin subtype				
Others	Reference		Reference	
IgG	0.948	0.974 (0.438–2.165)	0.198	0.442 (0.127–1.535)
IgA	0.240	0.470 (0.133–1.656)	**0.007**	0.027 (0.002–0.367)
Bone lesion	0.558	1.319 (0.522–3.333)	0.565	1.802 (0.242–13.425)
Renal impairment	0.659	0.857 (0.432–1.701)	0.164	2.177 (0.728–6.510)
Hb >100 g/L	**0.006**	0.403 (0.210–0.773)	0.236	0.534 (0.189–1.508)
Calcium >12 mg/dl	0.412	0.654 (0.237–1.804)	0.274	2.318 (0.513–10.461)
ALB >35 g/L	0.494	0.770 (0.364–1.630)	0.120	2.629 (0.778–8.888)
β_2-MG >3.5 mg/L	0.052	2.524 (0.994–6.411)	0.093	5.379 (0.755–38.323)
LDH >220 U/L	0.160	1.592 (0.832–3.045)	0.059	2.835 (0.960–8.373)
t (4; 14)	**0.005**	4.286 (1.567–11.725)	**0.003**	11.581 (2.311–58.023)
t (14; 16)	**0.014**	7.655 (1.522–38.501)	**0.003**	49.841 (3.913–634.834)
Del (17p)	0.138	0.381 (0.106–1.364)	0.683	0.682 (0.109–4.280)

Abbreviations: ALB, albumin; CI, confidence interval; Hb, hemoglobin; HR, hazard ratio; IgA, immunoglobulin A; IgG, immunoglobulin G; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; PHF19, PHD finger Protein 19; β_2-MG, Beta-2-microglobulin. Bold values indicates statistical significance.

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None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Yaqiong Li https://orcid.org/0000-0002-2151-6618

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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