Baseline IncRNA PCAT1 high expression and its longitude increment during induction therapy predict worse prognosis in multiple myeloma patients

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Abstract

**Background:** Long noncoding RNA PCAT1 (Inc-PCAT1) involves in the proliferation and drug sensitivity of multiple myeloma (MM), while its prognostic role in MM patients is still obscure. This study aimed to explore the association of Inc-PCAT1 with MM risk, clinical characteristics, treatment response, progression-free survival (PFS), and overall survival (OS).

**Methods:** A total of 83 symptomatic MM patients were enrolled in this study. Additionally, 30 healthy bone marrow donors as health controls were also recruited. Bone marrow plasma cell samples of MM patients and health donors were collected. Lnc-PCAT1 in bone marrow plasma cells was detected by reverse transcription-quantitative polymerase chain reaction.

**Results:** Lnc-PCAT1 was increased in MM patients than in health donors ($p < 0.001$), and receiver operating characteristic (ROC) curve showed that Inc-PCAT1 had excellent capability of discriminating MM patients from health donors (area under curve: 0.932, 95% confidence interval: 0.889–0.976). In MM patients, Inc-PCAT1 was correlated with bone lesion ($p = 0.024$), higher $\beta_2$-MG ($p = 0.005$), LDH ($p = 0.037$), and presence of Del (17p) ($p = 0.029$). Lnc-PCAT1 was also associated with poor ISS stage ($p = 0.013$) and R-ISS stage ($p = 0.005$). Besides, Inc-PCAT1 was reduced after treatment ($p < 0.001$); meanwhile, Inc-PCAT1 before treatment was correlated with lower CR ($p = 0.046$) but not ORR ($p = 0.185$). Additionally, Inc-PCAT1 after treatment was associated with lower CR ($p = 0.003$) and ORR ($p = 0.010$). Furthermore, baseline Inc-PCAT1 high and Inc-PCAT1 increase after treatment were correlated with worse PFS and OS (all $p < 0.05$).

**Conclusion:** Lnc-PCAT1 dysregulation serves as a biomarker for diagnosis and prognosis for MM.

**KEYWORDS**
clinical characteristics, disease risk, Long noncoding RNA PCAT1, multiple myeloma, prognosis
1 | INTRODUCTION

Accounting for approximately 10% of hematologic malignancies, multiple myeloma (MM) is a heterogeneous disease characterized by uncontrolled growth of monoclonal plasma cells in the bone marrow.\(^1,2\) Although there are several therapeutic methods for newly diagnosed MM, many patients still develop refractory or relapsed conditions, especially among elderly patients.\(^3\) Simultaneously, the 5-year survival rate of MM disease is under 50%.\(^4,5\) According to a previous report, there were estimated 16,500 new cases and 10,300 deaths of MM in China in 2016, while its mortality rate increased annually by 4.5% from 2006 to 2014.\(^6\) Therefore, it would be essential to find out more biomarkers for predicting the MM prognosis, which might strengthen the management of MM patients.

Long noncoding RNAs (lncRNAs) are transcripts with more than 200 nucleotides (nts) but with little protein-coding ability.\(^7\) It is reported that some lncRNAs have participated in the progression of MM. For example, knockdown of Incsmall nuclear RNA host gene 16 suppresses MM cell proliferation by sponging miR-342-3p; Incnuclear enriched abundant transcript 1 accelerates MM progression via the Janus kinase 2/signal transducer and activator of transcription 3 pathway; Inc-NR_046683 highly expresses in drug-resistant MM strains, which indicates that it is a potential drug target for MM treatment.

Among the commonly investigated lncRNAs, IncRNA prostate cancer-associated transcript 1 (IncPCAT1) involves in the progression of several malignancies.\(^8\) For example, overexpression of IncPCAT1 expedites cell proliferation and migration in diffuse large B-cell lymphoma through miR-508-3p/NFIB axis\(^9\); IncPCAT1 promotes esophageal squamous cell proliferation by sponging miR-326.\(^10\) Apart from these malignancies, IncPCAT1 also participates in the progression of MM. For instance, a recent study shows that dysregulated IncPCAT1 promotes proliferation in MM cells via p38 and jun N-terminal kinase/mitogen-activated protein kinase (JNK/MAPK) pathways.\(^11\) Additionally, enhanced IncPCAT1 promotes plasma cell proliferation and inhibits apoptosis by downregulating microRNA-129 (miR-129) and further regulating mitogen-activated protein kinase kinase kinase 7/nuclear factor-kappaB (MAP3K7/NF-kB) pathways in MM.\(^12\) Moreover, via modulating the protein kinase B/\(\beta\)-catenin signaling pathway, IncPCAT1 facilitates plasma cell proliferation, thus participating in the occurrence and progression of MM.\(^13\) Based on the above-mentioned information, we hypothesized that IncPCAT1 might be a potential biomarker for MM. However, no previous studies have been performed on this.

The present study was designed to investigate the association of IncPCAT1 with MM risk and its clinical characteristics. Besides, this study also aimed to explore the correlation of IncPCAT1 with MM prognosis, including treatment response, progression-free survival (PFS), and overall survival (OS).

2 | METHODS

2.1 | Subjects

In this prospective study, 83 symptomatic MM patients admitted to the hospital between March 2017 and September 2020 were consecutively enrolled. All eligible patients were newly diagnosed as

### TABLE 1 Baseline characteristics of MM patients

| Items                                      | MM patients (\(N = 83\)) |
|--------------------------------------------|---------------------------|
| Age (years), mean ± SD                     | 53.9 ± 8.5                |
| >60 years, No. (%)                         | 18 (21.7)                 |
| ≤60 years, No. (%)                         | 65 (78.3)                 |
| Male, No. (%)                              | 51 (61.4)                 |
| Bone lesion, No. (%)                       | 62 (74.7)                 |
| Renal impairment, No. (%)                  | 33 (39.8)                 |
| Immunoglobulin subtype, No. (%)            |                           |
| IgG                                        | 47 (56.6)                 |
| IgA                                        | 15 (18.1)                 |
| Others                                     | 21 (25.3)                 |
| Hemoglobin (g/L), mean ± SD                | 98.5 ± 25.0               |
| Calcium (mg/dl), mean ± SD                 | 9.9 ± 2.0                 |
| Serum creatinine (mg/dl), median (IQR)     | 1.8 (1.2–2.2)             |
| Albumin (g/L), median (IQR)                | 34.0 (28.0–38.0)          |
| \(\beta_2\)-MG (mg/L), median (IQR)        | 5.6 (3.0–9.6)             |
| LDH (U/L), median (IQR)                    | 206.3 (172.9–253.7)       |
| Chromosomal abnormality, No. (%)           |                           |
| t (4; 14)                                  | 8 (9.6)                   |
| t (14; 16)                                 | 4 (4.8)                   |
| Del (17p)                                  | 6 (7.2)                   |
| DS stage, No. (%)                          |                           |
| I                                          | 0 (0.0)                   |
| II                                         | 8 (9.6)                   |
| III                                        | 75 (90.4)                 |
| ISS stage, No. (%)                         |                           |
| I                                          | 12 (14.5)                 |
| II                                         | 28 (33.7)                 |
| III                                        | 43 (51.8)                 |
| R-ISS stage, No. (%)                       |                           |
| I                                          | 7 (8.4)                   |
| II                                         | 38 (45.8)                 |
| III                                        | 38 (45.8)                 |

Abbreviations: DS, Durie-Salmon; 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; \(\beta_2\)-MG, Beta-2-microglobulin.
symptomatic MM according to the International Myeloma Working Group (IMWG) diagnostic criteria and had an age above 18 years old, willing to participate in the study and comply with study follow-up. The patients were ineligible to be included in the study if they were identified as asymptomatic MM or had other malignant tumors. Meanwhile, pregnant patients were also excluded. Moreover, 30 healthy bone marrow donors were also recruited as health controls in the study analysis. Ethical approval for this study was obtained from the Institutional Review Board. Written informed consent was acquired from each recruited subject.

### 2.2 Lnc-PCAT1 determination

For the investigation of Lnc-PCAT1 expression, bone marrow samples of MM patients were collected at diagnosis and at the completion of 3 to 4 cycles of induction therapy, respectively. The bone marrow samples of health donors were collected on their donation. Immediately after collection, CD138-immunomagnetic beads (Miltenyi Biotec) were used to sort out plasma cells from the bone marrow samples. Subsequently, reverse transcription-quantitative polymerase chain reaction (RT-qPCR) was carried out to determine the expression of Lnc-PCAT1 in the plasma cells. The plasma cells were treated by TRIzol™ Reagent (Thermo Fisher Scientific) to extract total RNA, which were then submitted to perform reverse transcription using iScript™ cDNA Synthesis Kit (with random primer) (Bio-Rad). After that, qPCR was carried out with QuantiNova SYBR Green PCR Kit (Qiagen). GAPDH was served as reference gene. The relative quantitative expression of Lnc-PCAT1 was conducted with the use of 2^−ΔΔCt method. Primers were designed referring to a previous study.

### 2.3 Data collection and assessment

Baseline clinical features and staging information (Durie-Salmon (DS) stage, International Staging System (ISS) stage, and revised ISS (R-ISS) stage) of MM patients were documented after initial examinations. Induction therapy with regimen of lenalidomide/bortezomib/dexamethasone was administered for patients as recommended in the IMWG guideline. Response to induction therapy was evaluated at the completion of 3 to 4 cycles of induction therapy according to the IMWG criteria. For study analysis, patients with complete response (CR), very good partial response (VGPR), or partial response (PR) were recorded, and objective response rate (ORR) was calculated as the ratio of CR, VGPR, and PR patients in total patients. Patients without induction therapy response evaluation due to early death or loss of follow-up were not included in the final analysis. Follow-up and monitoring of patients were managed as recommended in the IMWG guideline. In the present study, the last follow-up date was 3/31/2021. Progression-free survival (PFS) and overall survival (OS) were evaluated in accordance with IMWG guideline.

### 2.4 Statistical analysis

SPSS 24.0 (IBM Corp.) and GraphPad Prism 7.01 (GraphPad Software Inc.) were used for data analysis and graph plotting, respectively. Categorical data were described as count with percentage. Continuous data distribution was analyzed using Kolmogorov-Smirnov (K-S) test, and median with interquartile range (IQR) or mean with standard deviation (SD) was calculated for descriptive analysis. Wilcoxon rank sum test or Kruskal–Wallis test was used for comparison of Lnc-PCAT1 expression in independent samples. Wilcoxon signed-rank test was used for comparison of Lnc-PCAT1 expression in paired samples. The correlation of Lnc-PCAT1 with disease stage was analyzed by Spearman’s rank correlation test. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to estimate the ability of Lnc-PCAT1 expression in identifying different subjects. Kaplan–Meier curve was plotted to display survival profiles of different subjects. Log-rank test was applied for the determination of PFS and OS difference between subjects. In the survival analysis, “Lnc-PCAT1 decline” was defined as Lnc-PCAT1 expression declined after treatment compared with that before treatment; “Lnc-PCAT1 increase” was defined as Lnc-PCAT1 expression increased after treatment compared with that before treatment. Statistical significance was concluded if there was a \( p \) value < 0.05 in the corresponding analysis.
3 | RESULTS

3.1 | Baseline characteristics of MM patients

A total of 83 symptomatic MM patients were enrolled in this study. The baseline characteristics of MM patients were summarized in Table 1. In detail, the mean age of MM patients was 53.9 ± 8.5 years. There were 18 (21.7%) MM patients >60 years and 65 (78.3%) MM patients ≤60 years. The number of male patients was 51 (61.4%). Besides, the number of patients with bone lesion and with renal impairment was 62 (74.7%) and 33 (39.8%), respectively. Regarding immunoglobulin subtype, there were 47 (56.6%) patients with IgG, 15 (18.1%) patients with IgA, and 21 (25.3%) patients with other immunoglobulin subtypes. Besides, the mean values of hemoglobin and calcium were 98.5 ± 25.0 g/L and 9.9 ± 2.0 mg/dl, respectively. Meanwhile, the median values of serum creatinine, albumin, \( \beta_2 \)-MG, and LDH were 1.8 (1.2–2.2) mg/dl, 34.0 (28.0–38.0) g/L, 5.6 (3.0–9.6) mg/L, and 206.3 (172.9–253.7) U/L, respectively. As for the chromosomal abnormality, there were 8 (9.6%) patients having \( t \)(4; 14), 4 (4.8%) patients having \( t \)(14; 16), and 6 (7.2%) patients having Del(17p). Additionally, 8 (9.6%) patients were at DS stage II and 75 (90.4%) patients were at DS stage III, while no patients were at DS stage I; 12 (14.5%) patients were at ISS stage I, 28 (33.7%) patients were at ISS stage II and 43 (51.8%) patients were at ISS stage III; 7 (8.4%) patients were at R-ISS stage I, 38 (45.8%) patients were at R-ISS stage II and 38 (45.8%) were at R-ISS stage III.

3.2 | Lnc-PCAT1 expression in MM patients and health donors as well as its relation to MM risk

Lnc-PCAT1 expression was higher in the MM patients (\( N = 83 \)) than in the health donors (\( N = 30 \)) (\( p < 0.001 \)) (Figure 1A). Besides, the ROC curve showed that lnc-PCAT1 expression possessed excellent potential in discriminating MM patients from health donors with AUC of 0.932 (95% confidence interval (CI): 0.889–0.976) (Figure 1B).

3.3 | Correlation of lnc-PCAT1 with characteristics of MM patients

As shown in Table 2, lnc-PCAT1 expression had positive association with bone lesion (\( p = 0.024 \)), >5.5 mg/L \( \beta_2 \)-MG (\( p = 0.005 \)), >220 U/L LDH (\( p = 0.037 \)), and presence of Del(17p) (\( p = 0.029 \)) (Table 2). In addition, as suggested in Figure 2, lnc-PCAT1 expression was correlated with elevated ISS stage (\( p = 0.013 \)) (Figure 2B) and R-ISS stage (\( p = 0.005 \)) (Figure 2C). However, no correlations were observed between lnc-PCAT1 expression and other characteristics of MM patients, including DS stage, age, gender, renal impairment, immunoglobulin subtype, hemoglobin, calcium, serum creatinine, albumin, and chromosomal abnormalities except Del(17p) (Figure 2A, Table 2) (all \( p > 0.05 \)).

| Items               | lnc-PCAT1 expression | \( p \) Value |
|---------------------|----------------------|--------------|
| Age                 |                      |              |
| >60 years           | 3.009 (1.290–3.638)  | 0.342        |
| ≤60 years           | 3.084 (2.214–4.639)  |              |
| Gender              |                      |              |
| Male                | 3.024 (2.514–4.535)  | 0.392        |
| Female              | 3.158 (1.636–4.118)  |              |
| Bone lesion         |                      |              |
| Yes                 | 3.237 (2.429–4.709)  | 0.024        |
| No                  | 2.580 (1.602–3.236)  |              |
| Renal impairment    |                      |              |
| Yes                 | 3.242 (2.104–4.862)  | 0.270        |
| No                  | 2.937 (2.069–3.831)  |              |
| Immunoglobulin subtype |                    |              |
| IgG                 | 3.148 (2.537–4.729)  | 0.184        |
| IgA                 | 2.531 (1.643–3.416)  |              |
| Others              | 3.174 (1.598–4.304)  |              |
| Hemoglobin          |                      |              |
| >85 g/L             | 3.031 (2.164–4.703)  | 0.623        |
| ≤85 g/L             | 3.114 (1.801–4.365)  |              |
| Calcium             |                      |              |
| >11.5 mg/dl         | 3.123 (1.773–4.106)  | 0.802        |
| ≤11.5 mg/dl         | 3.031 (2.103–4.574)  |              |
| Serum creatinine    |                      |              |
| >2 mg/dl            | 3.426 (1.719–4.929)  | 0.419        |
| ≤2 mg/dl            | 2.986 (2.103–3.840)  |              |
| Albumin             |                      |              |
| >35 g/L             | 3.237 (2.113–4.448)  | 0.783        |
| ≤35 g/L             | 2.986 (2.103–4.514)  |              |
| \( \beta_2 \)-MG    |                      |              |
| >5.5 mg/L           | 3.573 (2.536–5.008)  | 0.005        |
| ≤5.5 mg/L           | 2.599 (1.677–3.392)  |              |
| LDH                 |                      |              |
| >220 U/L            | 3.242 (2.531–5.387)  | 0.037        |
| ≤220 U/L            | 2.974 (1.570–4.118)  |              |
| Chromosomal abnormality |                    |              |
| \( t \)(4; 14)   | 3.826 (2.775–4.680)  | 0.130        |
| Positive            | 2.986 (1.967–4.422)  |              |
| Negative            | 3.024 (2.043–4.422)  |              |
| \( t \)(14; 16)   | 5.188 (2.662–7.536)  | 0.195        |
| Positive            | 3.024 (2.005–4.211)  |              |
| Negative            | 3.024 (2.005–4.211)  |              |

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; IQR, interquartile range; LDH, lactate dehydrogenase; Inc-PCAT1, long noncoding RNA prostate cancer-associated transcript 1; MM, multiple myeloma; \( \beta_2 \)-MG, Beta-2-microglobulin.
3.4 | Lnc-PCAT1 expression after induction treatment in MM

Lnc-PCAT1 expression was decreased after treatment (median value: 1.804 (1.076–3.302)) compared with before treatment (median value: 3.031 (2.103–4.514)) (p < 0.001). Besides, Lnc-PCAT1 expression was declined in 61 (73.5%) patients and increased in 22 (26.5%) patients after treatment (Figure 3). In this study, MM patients mainly received bortezomib, cyclophosphamide, and dexamethasone (BCD) as well as bortezomib, lenalidomide, and dexamethasone (BLD) regimens as treatment methods. No difference was observed in Lnc-PCAT1 expression between patients received BCD and BLD before treatment or after treatment (both p > 0.05) (Figure 4A and B). Besides, no difference was observed in the change in Lnc-PCAT1 expression before and after treatment between MM patients received BCD and BLD (p > 0.05) (Figure 4C). However, in both patients received BCD (p = 0.002) and BLD regimens (p < 0.001), Lnc-PCAT1 expression was decreased after treatment (Figure 4D and E).

3.5 | Correlation of Lnc-PCAT1 expression with treatment response in MM

Lnc-PCAT1 expression before treatment in the CR patients (n = 23) was lower than that in the non-CR patients (n = 60) (p = 0.046) (Figure 5A). Otherwise, Lnc-PCAT1 expression before treatment was similar between the ORR patients (n = 59) and the non-ORR patients (n = 24) (p = 0.185) (Figure 5B). In addition, Lnc-PCAT1 expression after treatment was reduced in the CR patients (n = 23) than the non-CR patients (n = 60) (p = 0.003) (Figure 5C). Moreover, Lnc-PCAT1 expression after treatment was declined in the ORR patients (n = 59) compared with that in the non-ORR patients (n = 24) (p = 0.010) (Figure 5D). Additionally, Lnc-PCAT1 expression showed a more predominant reduction in CR patients. In detail, Lnc-PCAT1 expression was greatly decreased in both CR patients (p = 0.010) (Figure 6A) and non-CR patients (p < 0.001) (Figure 6B) after treatment compared with before treatment. No obvious difference was found in the change in Lnc-PCAT1 expression before and after treatment between CR and non-CR patients (p > 0.05) (Figure 6C). In addition, Lnc-PCAT1 expression was declined in both ORR (p < 0.001) patients and non-ORR patients (p = 0.013) after treatment compared with before treatment (Figure 6D and E). No obvious difference was found in the change in Lnc-PCAT1 expression before and after treatment between ORR and non-ORR patients (Figure 6F) (p > 0.05).

3.6 | Correlation of Lnc-PCAT1 expression with accumulating PFS and OS in MM

Baseline Lnc-PCAT1 high expression (defined as Lnc-PCAT1 expression exceeded 3.031, which was the median value of Lnc-PCAT1 expression in MM patients before treatment) was correlated with shorter accumulating PFS (p = 0.009) (Figure 7A) and accumulating OS (p = 0.046) (Figure 7B). What is more, Lnc-PCAT1 increase (vs. Lnc-PCAT1 decline) after treatment was associated with worse accumulating PFS (p = 0.002) (Figure 7C) and accumulating OS.
In addition, by multivariable Cox's proportional hazard regression model analysis, Inc-PCAT1 high (vs. low) (before treatment) \((p = 0.011, HR (95\% CI) = 2.383 (1.218-4.660))\), t(14; 16) \((p = 0.049, HR (95\% CI) = 4.502 (1.003-20.201))\), and R-ISS stage \((p = 0.004, HR (95\% CI) = 2.395 (1.321-4.343))\) were all independent predictive factors for shorter PFS; meanwhile, Inc-PCAT1 decline (vs. increase) (after treatment) was an independent predictive factor for longer PFS \((p = 0.001, HR (95\% CI) = 0.353 (0.189-0.659))\) (Figure 8A). Moreover, \(\beta_2\)-MG >5.5 mg/L \((p = 0.002, HR (95\% CI) = 6.753 (1.972-23.121))\) and t(14; 16) \((p = 0.049, HR (95\% CI) = 4.528 (1.008-20.336))\) were independent predictive factors for worse OS (Figure 8B).
In this study, we aimed to explore the correlation of lnc-PCAT1 with MM risk, clinical characteristics, and prognosis, which observed that (1) lnc-PCAT1 expression was increased in the MM patients; (2) lnc-PCAT1 expression was correlated with bone lesion, higher β2-MG, LDH, and presence of Del (17p) in MM; meanwhile, lnc-PCAT1 expression was associated with poor prognostic risk stratification, including ISS stage and R-ISS stage; and (3) baseline lnc-PCAT1 high expression and its longitude increase during treatment were correlated with worse CR, PFS and OS.

As to lnc-PCAT1 expression in the hematological malignancies, lnc-PCAT1 is enhanced in acute myeloid leukemia patients. Our study found that lnc-PCAT1 was increased in the MM patients than the health donors. A possible explanation could be that lnc-PCAT1 promotes malignant cell growth via different pathways,
including NF-κB pathway, MAPK-κ, and Wnt/β-catenin signaling pathways, which influences the development and pathogenesis of MM.\textsuperscript{11,12,20,21}

In terms of the association of IncRNA expression with clinical characteristics of MM, an interesting study shows that Inc-PCAT1 is positively correlated with β2-MG concentration of MM.\textsuperscript{22} In our study, Inc-PCAT1 was positively correlated with bone lesion, higher β2-MG, LDH, and presence of Del (17p) in MM; moreover, it was associated with poor risk stratification in ISS stage and R-ISS stage. The possible reasons could be that (1) Inc-PCAT1 promotes plasma cell growth, resulting in MM progression,\textsuperscript{12} which might contribute to the bone lesion and develop some forms of renal impairment, then further cause higher β2-MG and LDH concentration\textsuperscript{23,24}; (2) Inc-PCAT1 was positively associated with higher β2-MG (above-mentioned), which was a feature of the poor ISS stage; thus, Inc-PCAT1 was related to the poor ISS stage; meanwhile, Inc-PCAT1 was positively associated with higher LDH, which exceeded the normal level of LDH constituting the most advanced subtype of R-ISS stage, thus Inc-PCAT1 was correlated with poor R-ISS stage.

Regarding the correlation of Inc-PCAT1 expression with prognosis in patients with MM, previous studies elucidate that high expression of NIMA-related kinase 2, a target gene of Inc-PCAT1, is related to poor prognosis and inferior survival in MM.\textsuperscript{20,25} Previous studies also show that other IncRNAs can be served as potential biomarkers in MM. For instance, high Inc-CCTA1 correlates with poor OS in MM patients and serves as a potential biomarker for the prognosis of MM patients\textsuperscript{26}; in our study, we observed that baseline Inc-PCAT1 high expression was correlated with worse CR, PFS, and OS. Possible reasons might be (1) according to a previous study, Inc-PCAT1 expression inhibits bortezomib sensitivity in MM\textsuperscript{12}; thus, it was related to unfavorable treatment response and further affected PFS and OS; (2) Inc-PCAT1 expression was associated with poor risk stratification as mentioned above, including poor ISS stage and R-ISS stage, which might indirectly result in worse PFS and OS. Our study also found that longevity increase in Inc-PCAT1 during treatment had correlation with poor CR, PFS, and OS. The explanation might be that elevated Inc-PCAT1 promotes plasma cell proliferation and inhibits apoptosis through downregulating miR-129 and further modulating MAP3K7/NF-κB pathways in MM.\textsuperscript{12} Therefore, its elevation after treatment might cause deteriorate MM disease condition, then resulting in poor treatment response and subsequently bringing in worse PFS and OS.

Although a lot of findings were identified in this study, there were still some limitations. First, with a small sample size, this study might have low statistical power. Further validation in the more and same number of patients and health controls might be needed. Second, our study evaluated the correlation of Inc-PCAT1 expression with clinical characteristics and prognosis of patients having symptomatic MM, while the correlation of Inc-PCAT1 expression with asymptomatic MM, might be further evaluated. Third, this study did not investigate the molecular mechanism of Inc-PCAT1 involved in MM progression; thus, in vivo and in vitro experiments might be necessary to be further conducted.

Conclusively, Inc-PCAT1 associates with elevated disease risk and unfavorable ISS stage, R-ISS stage, treatment response, and survival of MM. It may potentially serve as a biomarker to predict MM prognosis, further improving the management of MM patients.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

1. Rajkumar SV. Multiple myeloma: every year a new standard? Hematol Oncol. 2019;37(Suppl 1):62-65.
2. Brigle K, Rogers B. Pathobiology and diagnosis of multiple myeloma. Semin Oncol Nurs. 2017;33(3):225-236.

3. Lei M, Kim EB, Branagan A, Lou U, Zemel M, Raje N. Current management and emerging treatment strategies for multiple myeloma. Rinsho Ketsueki. 2019;60(9):1243-1256.

4. Fraz MA, Warraich FH, Warraich SU, et al. Special considerations for the treatment of multiple myeloma according to advanced age, comorbidities, frailty and organ dysfunction. Crit Rev Oncol Hematol. 2019;137:18-26.

5. Kosmala A, Bley T, Petritsch B. Imaging of multiple myeloma. Rofo. 2019;191(9):805-816.

6. Liu J, Liu W, Mi L, et al. Incidence and mortality of multiple myeloma in China, 2006–2016: an analysis of the Global Burden of Disease Study 2016. J Hematol Oncol. 2019;12(1):136.

7. Murillo-Maldonado JM, Riesgo-Escovar JR. The various and shared roles of lncRNAs during development. Dev Dyn. 2019;248(11):1059-1069.

8. Liu W, Xu J. LncRNA PCAT-1 in gastrointestinal cancers: a meta-analysis. Medicine (Baltimore). 2018;97(48):e13429.

9. Tian M, Li Y, Zheng W, et al. LncRNA PCAT1 enhances cell proliferation, migration and invasion by miR-508-3p/NFIB axis in diffuse large B-cell lymphoma. Eur Rev Med Pharmacol Sci. 2021;25(6):2567-2576.

10. Huang L, Wang Y, Chen J, et al. Long non-coding RNA PCAT1, a novel serum-based biomarker, enhances cell growth by sponging miR-326 in oesophageal squamous cell carcinoma. Cell Death Dis. 2019;10(7):513.

11. Shen X, Shen P, Yang Q, et al. Knockdown of long non-coding RNA PCAT-1 inhibits myeloma cell growth and drug resistance via p38 and JNK MAPK pathways. J Cancer. 2019;10(26):6502-6510.

12. Shen X, Kong S, Yang Q, et al. PCAT-1 promotes cell growth by sponging miR-129 via MAP3K7/NF-kappaB pathway in multiple myeloma. J Cell Mol Med. 2020;24(6):3492-3503.

13. Chen Y, Hao J, Zhao J, et al. Long non-coding RNA PCAT1 facilitates cell growth in multiple myeloma through an MTDH-mediated AKT/β-catenin signaling pathway by sponging miR-363-3p. RSC Adv. 2019;9(58):33834-33842.

14. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-548.

15. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-3420.

16. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer. 1975;36(3):842-854.

17. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-2869.

18. Ludwig H, Miguel JS, Dimopoulos MA, et al. International Myeloma Working Group recommendations for global myeloma care. Leukemia. 2014;28(5):981-992.

19. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.

20. Xia J, He Y, Meng B, et al. NEK2 induces autophagy-mediated bortezomib resistance by stabilizing Beclin-1 in multiple myeloma. Mol Oncol. 2020;14(4):763-778.

21. van Andel H, Kocemba KA, Spaaargaren M, Pals ST. Aberrant Wnt signaling in multiple myeloma: molecular mechanisms and targeting options. Leukemia. 2019;33(5):1063-1075.

22. Shen X, Zhang Y, Wu X, et al. Upregulated IncRNA-PCAT1 is closely related to clinical diagnosis of multiple myeloma as a predictive biomarker in serum. Cancer Biomark. 2017;18(3):257-263.

23. Panaroni C, Yee AJ, Raje NS. Myeloma and bone disease. Curr Osteoporos Rep. 2017;15(5):483-498.

24. Rysava R. Renal failure in multiple myeloma and its treatment. Vnitr Lek. 2020;66(7):425-431.

25. Liu XL, Liu HM, Han N, et al. PCAT1 promotes the proliferative and migratory potentials of ovarian cancer via targeting NEK2. Eur Rev Med Pharmacol Sci. 2019;23(19):8239-8248.

26. Chen L, Hu N, Wang C, Zhao H, Gu Y. Long non-coding RNA CCAT1 promotes multiple myeloma progression by acting as a molecular sponge of miR-181a-5p to modulate HOXA1 expression. Cell Cycle. 2018;17(3):319-329.

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