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ORIGINAL RESEARCH

Identification of BRCA1-Associated RING Domain 1 Mutation as a Novel Indicator for Constructing a Prognostic Nomogram in Multiple Myeloma: A Retrospective Single-Center Study

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Background: This study aims to investigate the prognostic value of BARD1 (BRCA1-associated RING domain 1) in newly diagnosed multiple myeloma (NDMM), which has not been well defined previously.

Methods: This is a retrospective analysis containing 74 NDMM patients. Clinical data, including R2-ISS and BARD1 gene mutation status, were employed to construct a nomogram using Cox's proportional hazards model.

Results: Univariate analysis revealed a significant correlation between R2-ISS, BARD1 gene mutations and both Overall Survival (OS) and Progression-Free Survival (PFS) ($P < 0.01$). Notably, the constructed nomogram models, comprising R2-ISS and BARD1 gene mutations, exhibited excellent predictive performance for PFS and OS in both training and validation sets.

Conclusion: The nomogram, innovatively combining the BARD1 gene with R2-ISS staging, effectively predicts the prognosis of NDMM. Although this study is limited by the relatively small number of patients with BARD1 mutations, the outcome may aid us in comprehending the role of genetic mutations in NDMM and further in the investigation of drugs targeting this gene.

Keywords: BARD1 mutation, nomogram, multiple myeloma, prognosis

Introduction

Multiple myeloma (MM) ranks as the second most frequently diagnosed hematopoietic malignancy in numerous countries.[1,2] Despite advancements in medical practice, this malignancy remains incurable. Recent years have witnessed relentless research efforts, both domestically and internationally, that have shifted therapeutic strategies from conventional chemotherapy to novel non-chemotherapeutic agents. These include immunomodulators, proteasome inhibitors, monoclonal antibodies, and Chimeric Antigen Receptor T-Cell Therapy (CAR-T). While these advancements have extended patient survival, the challenge of relapse remains.

MM's unique characteristics have led researchers to develop various staging systems, including the Durie-Salmon (DS) system,[3] the International Staging System (ISS), the Revised International Staging System (R-ISS),[4] and the Second Revision of the International Staging System (R2-ISS).[5] While these staging systems provide a general framework for prognostic assessment, they fail to encompass all factors influencing patient outcomes. The variability in prognosis among patients within the same stage, as well as the absence of anticipated prognostic differences between different stages, suggests that additional factors are influencing outcomes. The variation of gene expression profiling (GEP) is unquestionably pivotal in influencing the progression and treatment response of newly diagnosed multiple myeloma (NDMM). This can lead to differences in drug sensitivity or resistance, thereby affecting prognosis. SKY92 is a widely

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used commercial GEP-based high-risk signature, with prognostic value validated in the PROMMIS study (NCT02911571) of 251 NDMM patients.[6] Beyond SKY92, emerging signatures include a 22-gene clonal gene signature (CGS) developed through a computational framework selecting genes driven by clonal copy number alterations. Across five independent datasets (2155 MM samples), CGS maintained significant prognostic value after adjusting for cytogenetic abnormalities, ISS, and R-ISS stage.[7] These emphasize the application value of genetic alterations on prognosis evaluation of NDMM.

Currently, gene-targeted therapy stands at the forefront of research into diverse tumor pathologies. Mutations in the BRCA1-Associated RING Domain 1 (BARD1) gene have been closely associated with a range of malignancies, including breast cancer, ovarian cancer, colorectal cancer, and acute myeloid leukemia.[8] In fact, some research efforts have begun to focus on its potential utility as a prognostic biomarker for various tumors and its candidacy for targeted cancer therapy.[9] BARD1 mutations remain understudied in hematologic malignancies compared to solid tumors, yet emerging evidence supports their clinical relevance. Schulz et al identified germline BARD1 mutations within DNA damage response genes as key susceptibility alleles in therapy-related myeloid neoplasms, indicating that BARD1 may contribute to secondary hematologic malignancies following genotoxic exposure.[10] Additionally, it is well-established that a range of gene mutations, including KRAS, NRAS, BRAF, TP53, ATM, ATR, and ZNFHX4, are deeply implicated in the onset and progression of multiple myeloma.[11,12] However, the potential correlation between the BARD1 gene and multiple myeloma has yet to be documented. This underscores the need for further investigation into the connection between the BARD1 gene and multiple myeloma.

In our study, we discovered that over half of the MM patient population possesses BARD1 mutations. Consequently, we aim to integrate the BARD1 mutation with additional clinical indices to construct an innovative nomogram designed to predict the Overall Survival (OS) and Progression-Free Survival (PFS) in patients with NDMM. Concurrently, we endeavor to discuss the potential of targeting BARD1 as a novel therapeutic strategy for MM treatment.

Materials and Methods

Ethics

This single-center retrospective study received approval from the institutional review board of Fujian provincial hospital, with an exemption from informed consent requirements. Additionally, this paper adheres to the strengthening the reporting of observational studies in epidemiology guidelines.

Patients

We amassed clinical data from 104 patients newly diagnosed with NDMM spanning December 2018 to August 2022. Of these, 30 patients were excluded from the study due to various reasons: 7 were diagnosed with solitary plasmacytoma, 8 were unable to complete 2 cycles of induction chemotherapy, and 15 were lost to follow-up. Ultimately, 74 patients conforming to the International Myeloma Working Group 2014 criteria were included in this study. Clinical staging was conducted employing the Durie-Salmon (DS) staging system, the International Staging System (ISS), the R-ISS, and the R2-ISS.

Therapeutic Regimen

The inclusion of patients in the study was predicated upon their treatment regimen for NDMM. In light of patient-specific conditions and guideline recommendations, all patients received induction therapies primarily based on guideline-recommended frontline regimens, including BCD (bortezomib, cyclophosphamide, dexamethasone), VRD (bortezomib, lenalidomide, dexamethasone), and PAD (bortezomib, doxorubicin, dexamethasone). Only four patients underwent autologous hematopoietic stem cell transplantation, followed by consolidation therapies such as VRD, VD, and IRD (ixazomib, lenalidomide, dexamethasone). Maintenance regimens for all patients mainly consisted of VRD, BTD (bortezomib, thalidomide, dexamethasone), and IRD. A pivotal criterion for inclusion was that these patients were treated with at least 2 cycles of the mentioned therapy regimens, ensuring a baseline uniformity in treatment exposure among the study participants.

Date Collection and Definition

For this study, we systematically retrieved patient clinical data from the hospital's electronic medical record system. This data encompassed a spectrum of parameters including age, gender, white blood cell count (WBC), platelet count (PLT), total protein (TP), globulin (GLO), beta-2-microglobulin (β2-MG), percentage of bone marrow plasma cells (BMPC), as well as staging according to the DS system, R-ISS, and R2-ISS. Additionally, bone marrow blood fluorescence in situ hybridization (FISH, $CD138^+$ selection) and next-generation sequencing (NGS) data, among others, were collected. Overall survival (OS) was delineated as the elapsed period from diagnosis to the event of death, and progression-free survival (PFS) was determined from the point of diagnosis to either disease progression (PD) or death from any cause. It was imperative for all enrolled patients to undergo diagnostic assessments via FISH and NGS. These tests were executed and reported by Hightrust Diagnostics, Co., Ltd., providing pivotal molecular insights into each patient's myeloma profile.

NGS Data Acquisition

Qualified libraries were enriched using a 393-gene panel and sequenced on the Illumina NovaSeq PE150 platform, generating 15 Gb of data per sample (~10,000 × depth). Clean reads were aligned to the human reference genome (GRCh37/HG19) using Burrows-Wheeler Aligner (BWA v0.7.17). SNP and small fragment insertions/deletions were detected using Mutect2 (GATK v4.1.1.0). Identified variants were annotated with ANNOVAR (v201804) using public databases (COSMIC, dbSNP, 1000 Genomes, ClinVar, gwasCatalog, esp6500si_all, GnomAD_ALL_AF, GnomAD_ALL_AN, GnomAD_EAS_AF, GnomAD_EAS_AN, etc)., covering positional information, variant type, and conservation predictions. Variants with minor allele frequency (MAF) > 1% in East Asian populations (gnomAD, EXAC, etc.) and VAF ≥ 0.001 were excluded. Filtered somatic variants were classified into four clinical tiers (I, II, III, IV) according to the 2017 AMP/ASCO/ACMG/CAP cancer variant interpretation guidelines.

Nomogram Prediction Model Construction

The R 4.03 software was used to construct the column-line diagram, and the Cox multiple regression results were imported into R software. The rms package was applied to establish a nomogram prediction model, which was internally validated through 800 bootstrap repeated sampling. The Harrell's C statistic was used to calculate the C-index to assess the discriminative power of the column-line diagram model. The C-index range is 0.50–1.00, with a C-index ≥ 0.70 indicating good discriminative power of the prediction model. A higher consistency index reflects greater precision of the prediction model. The calibration curve was used to verify the consistency between the predicted probability values and actual probability values for tumors within 1–5 years. Scattered points lying on the 45° diagonal indicated good prediction consistency. The X-tile software was employed to identify the optimal cutoff value for the total score of the column-line diagram. Based on this cutoff value, patients were stratified into low-, medium-, and high-risk groups for survival risk. The Log rank test was used, with $p < 0.05$ considered statistically significant.

Statistical Analysis

For data analysis, we utilized SPSS 26.0 statistical software. Survival outcomes were analyzed using the Kaplan-Meier method, and the resulting survival curves were compared via the Log rank test. Univariate and multivariate survival analyses were conducted using the Cox proportional hazards model. A p-value of less than 0.05 was considered statistically significant. Forest plots were utilized to illustrate the impact of various risk factors. Furthermore, the rms package within R software, version 4.03, was used to construct the nomogram prediction model. Harrell's C statistic was employed to compute the Concordance index (C-index), providing a measure of predictive accuracy and discriminative ability. To assess the nomogram's prognostic performance over different time points, time-dependent receiver operating characteristic (time-ROC) curves were plotted using the "timeROC" package in R 4.03. Internal validity of the nomogram model was confirmed through the Bootstrap resampling method, iterated 800 times. The most advantageous cut-off value for the nomogram's total score was determined using X-tile software, classifying patients into low, medium, and high-risk categories. The Kaplan-Meier method was then used to generate survival curves for these distinct risk groups, maintaining a p-value of less than 0.05 as the criterion for statistical significance.

Results

Clinical Characteristics of the Study Population

This study encompassed a cohort of 74 patients with NDMM. The median age of participants was 67.5 years, with a range from 33 to 84 years. The gender distribution comprised 42 males (56.8%) and 32 females (43.2%). By the conclusion of the follow-up period, 33 fatalities had occurred within the patient group. The clinical characteristics of these patients are delineated in Table 1. NGS analysis revealed numerous gene mutations in our cohort (Figure 1A), including NRAS, KRAS, BRAF, and other mutated genes consistent with previous research findings. Notably, we

Table 1 Clinical Characteristics of 74 NDMM Patients

Clinical Data	n (%)
Age (years)	
>65.0	43 (58.1%)
≤65.0	31 (41.9%)
Gender	
Male	42 (56.8%)
Female	32 (43.2%)
WBC (×10 9 /L)	
≥4.8	51 (68.9%)
<4.8	23 (31.1%)
Hb (g/L)	
≥100.0	48 (64.9%)
<100.0	26 (35.1%)
PLT (×10 9 /L)	
≥265.0	55 (74.3%)
<265.0	19 (25.7%)
GLO (mmol/L)	
≥28.0	56 (75.7%)
<28.0	18 (24.3%)
ALB (mmol/L)	
≥35.0	31 (41.9%)
<35.0	43 (58.1%)
TP (mmol/L)	
≥104.0	19 (25.7%)
<104.0	55 (74.3%)
MP (g)	
≥50.5	18 (24.3%)
<50.5	56 (75.7%)
Ca (U/L)	
≥2.6	15 (20.3%)
<2.6	59 (79.7%)
SCr (μmol/L)	
≥177.0	12 (16.2%)
<177.0	62 (83.8%)
β2-MG (mg/L)	
≥5.5	46 (62.2%)
<5.5	28 (37.8%)
LDH (U/L)	
≥250.0	18 (24.3%)
<250.0	56 (75.7%)

(*Continued*)

Table 1 (Continued).

Clinical Data	n (%)
BMPC (%)	
≥14.0	54 (73.0%)
<14.0	20 (27.0%)
D-S Stage	
I	3 (4.1%)
II	6 (8.1%)
III	65 (87.8%)
ISS Stage	
I	13 (17.6%)
II	12 (16.2%)
III	49 (66.2%)
R-ISS Stage	
I	13 (17.6%)
II	45 (60.8%)
III	16 (21.6%)
R2-ISS Stage	
I	8 (10.8%)
II	11 (14.9%)
III	37 (50.0%)
IV	18 (24.3%)
ASCT	
Yes	4 (5.4%)
No	70 (94.6%)
1q21 Amplification	
Yes	29 (39.2%)
No	45 (60.8%)
RB1 Deletion	
Yes	26 (35.1%)
No	48 (64.9%)
D13S319 Deletion	
Yes	25 (33.8%)
No	49 (66.2%)
P53 Deletion	
Yes	7 (9.5%)
No	67 (90.5%)
P53 Amplification	
Yes	5 (6.8%)
No	69 (93.2%)
CEP17 Amplification	
Yes	5 (6.8%)
No	69 (93.2%)
CCND1 Amplification	
Yes	4 (5.4%)
No	70 (94.6%)
MAF Deletion	
Yes	2 (2.7%)
No	72 (97.3%)
FGFR3 Amplification	
Yes	2 (2.7%)
No	72 (97.3%)

(*Continued*)

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Table 1 (Continued).

Clinical Data	n (%)
CEP17 Deletion	
Yes	3 (4.1%)
No	71 (95.9%)
CCND3 Amplification	
Yes	1 (1.4%)
No	73 (98.6%)
t (4;14)	
Yes	9 (12.2%)
No	65 (87.8%)
t (6;14)	
Yes	2 (2.7%)
No	72 (97.3%)
t (11;14)	
Yes	3 (4.1%)
No	71 (95.9%)
t (14;16)	
Yes	1 (1.4%)
No	73 (98.6%)

identified two high-frequency mutated genes, KMT2C and BARD1, which diverge from other studies. The mutation frequencies for these genes were 82.0% (60/74) and 72.0% (53/74), respectively. Additional high-frequency mutated genes are illustrated in Figure 1B. Mutations in genes not depicted occurred at frequencies below 50%. To elucidate the functions of these mutated genes, we conducted Kyoto Encyclopedia of Genes and Genomes (KEGG) (Figure 1C) and gene ontology (GO) (Figure 1D) enrichment analysis. Our findings indicate that these genes are primarily involved in cell cycle signaling analysis and DNA binding, transcription, and repair processes.

Patients with BARD1 Mutations and Classified as High-Risk (R2-ISS) Had a Poor Prognosis

Univariate analysis was performed on clinical indicators and mutations in the KMT2C and BARD1 genes. The results revealed that the BARD1 were associated with a increased risk of OS (hazard ratio [HR], 3.889; 95% CI, 1.467–10.309) and PFS (hazard ratio [HR], 3.818; 95% CI, 1.451–10.047) (Figure 2). As shown in Figure 3, the R2-ISS IV group exhibited a substantial reduction in 3-year OS (18.3%) and PFS (12.2%) compared to the R2-ISS I, II, and III groups (OS: 87.5%, 80.8%, 59.6%, respectively, $P = 0.002$; PFS: 87.5%, 80.8%, 59.6%, respectively, $P < 0.001$). Similarly, the group with the BARD1 mutation demonstrated significantly lower 3-year OS at 33.7% ($P = 0.004$) and PFS at 38.9% ($P = 0.004$) compared to the wild-type group, which had an OS of 82.4% and PFS of 75.5%. The multivariate Cox regression analysis indicated that both the R2-ISS stage and BARD1 gene mutation status independently predict OS and PFS in patients with NDMM, as detailed in Table 2. Given the extremely limited number of transplant patients and the significant heterogeneity in treatment regimens due to individual patient factors, treatment-related variables and hematopoietic stem cell transplantation were not included in the multivariate COX regression analysis.

Construction and Validation of the Nomogram Based on BARD1 Mutation and R2-ISS Stage

BARD1 gene mutation status and R2-ISS score were incorporated into Cox proportional hazards regression models to develop a comprehensive nomogram for predicting 1-year, 3-year, and 5-year OS and PFS rates. The model assigns scores to these two variables, which are summed to yield a total score. This total score corresponds to the probability of

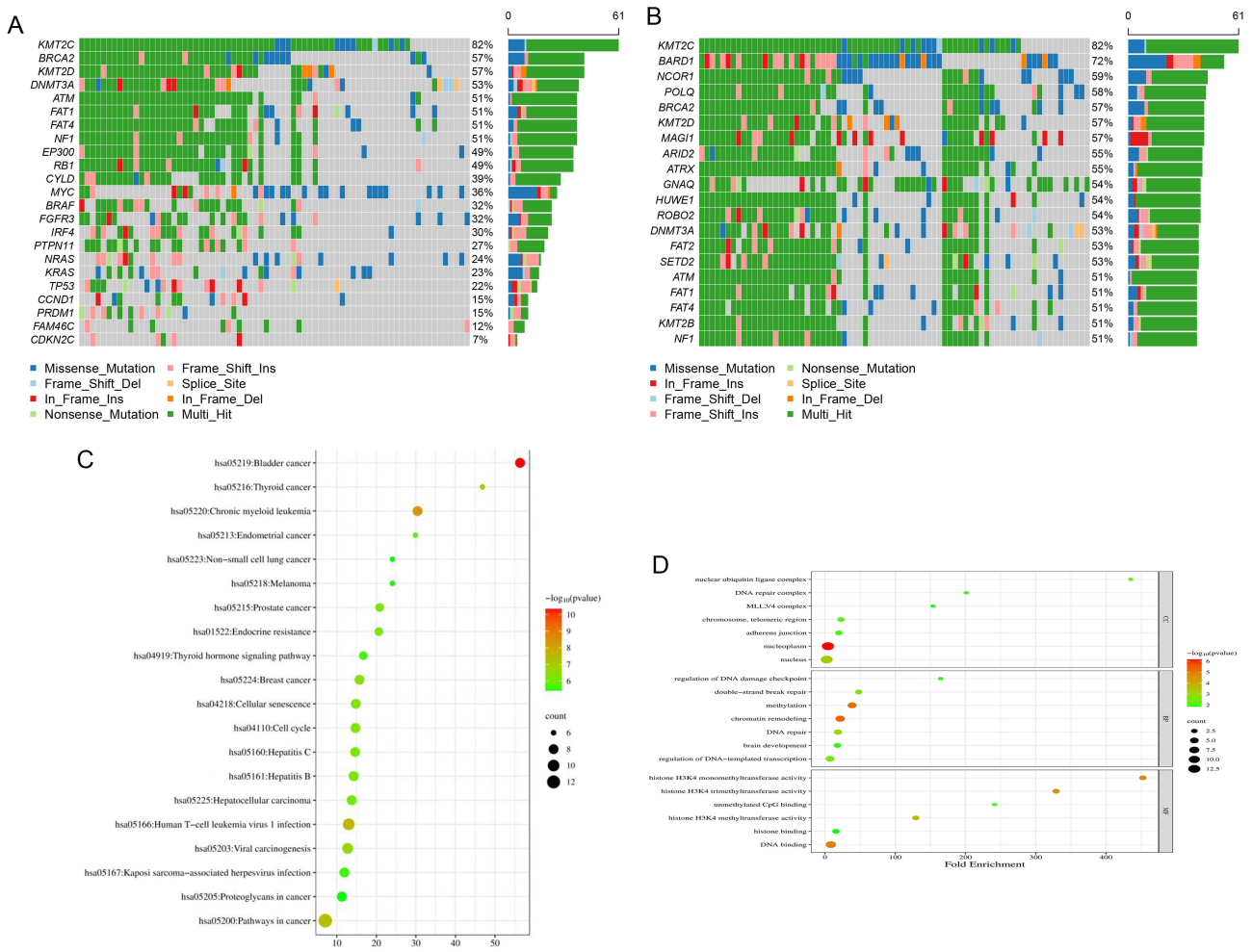

Figure 1 Gene mutations in NDMM. (**A**) The detection status of common myeloma mutation genes in our research (Altered in 72 (97.3%) of 74 samples). (**B**) The frequently mutated genes in our research (Altered in 74 (100%) of 74 samples). (**C**) KEGG and (**D**) GO enrichment of the top 38 mutated genes.

disease progression or mortality (Figure 4A and B). ROC curve analysis demonstrated the model's robust predictive capability for 1-year, 3-year, and 5-year OS and PFS, with area under curve (AUC) values of 0.713, 0.845, 0.961 and 0.749, 0.829, 0.956, respectively (Figure 4C and D). Internal validation of the nomogram's accuracy and reliability was performed using a calibration curve, C-index, and AUC. The calibration curves demonstrated good agreement between predicted and observed outcomes for both 1-year and 3-year OS and PFS rates (Figure 4E and F). Moreover, the C-index values for OS and PFS were 0.687 (95% CI: 0.639–0.734) and 0.697 (95% CI: 0.651–0.743), respectively, indicating strong predictive performance of the model.

Discussion

Multiple myeloma is a remarkably heterogeneous malignancy, with its pathogenesis intricately associated with genetic mutations, immune dysregulation, and the bone marrow microenvironment.[13] Despite the development of various prognostic frameworks for NDMM, these methodologies exhibit limitations at different disease stages. In this rapidly advancing genomic era, there is a compelling need to integrate genetic mutation data to predict disease prognosis with greater precision and efficiency, thereby informing targeted therapeutic approaches. A growing body of research supports the premise that the incidence, progression, and prognosis of multiple myeloma are closely linked to specific gene mutations. In a study by Xie et al the top ten genes exhibiting the highest mutation frequency among 50 NDMM patients were MUC16, MUC4, TTN, AHNAK2, MUC17, OBSCN, OR4C3, MUC2, MKI67, and PRUNE2, all presenting with

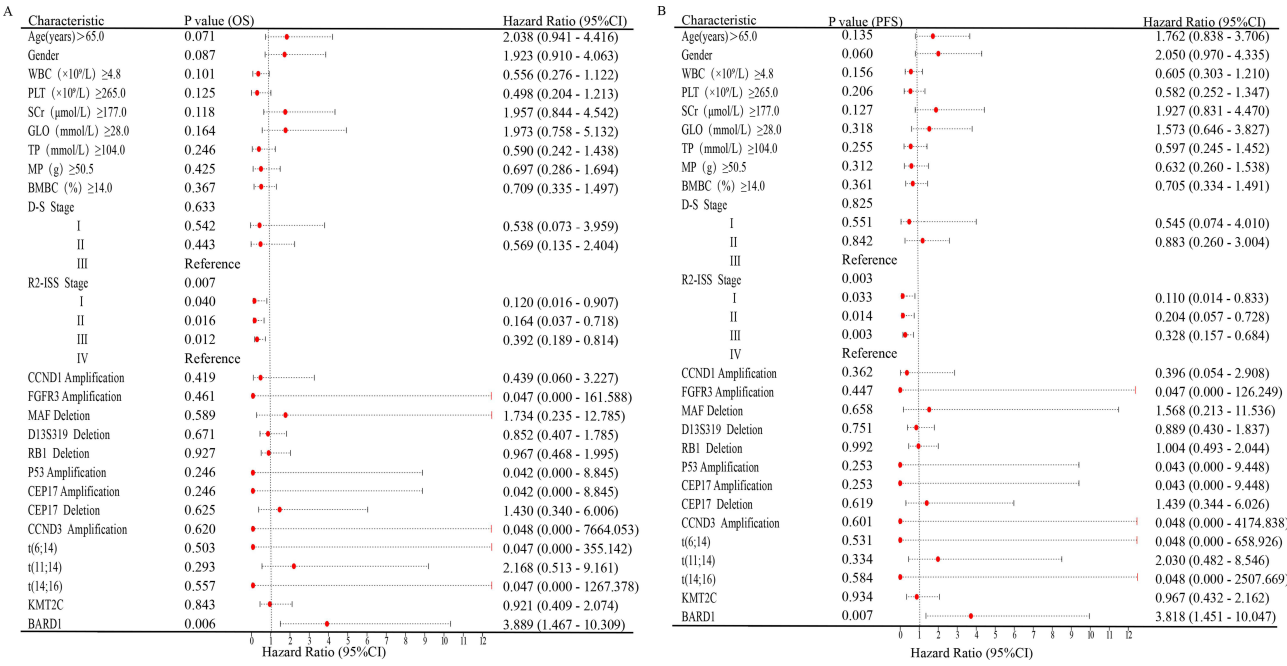

Figure 2 Forest plots of Cox regression analysis. (**A**) Forest plots showing multivariate analysis of OS in patients. (**B**) Forest plots showing multivariate analysis of PFS in patients.

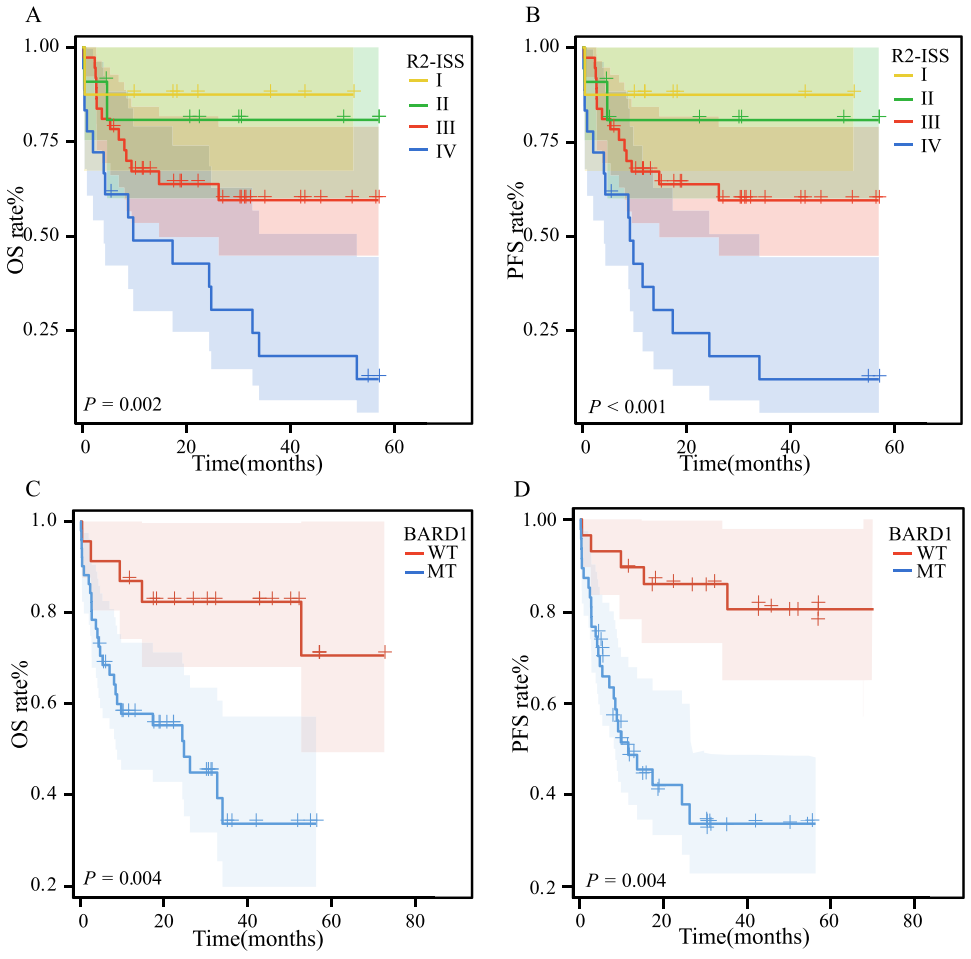

Figure 3 Survival curves for different groups based on R2-ISS and BARD1 mutation status. (**A**) OS for R2-ISS categories, (**B**) PFS for R2-ISS categories, (**C**) OS for BARD1 mutation status. (**D**) PFS for BARD1 mutation status.
Abbreviations: WT, wild-type; MT, mutant.

Table 2 Multivariate Analysis of NDMM

Clinical Data	OS		PFS	
	HR;95% CI	P value	HR;95% CI	P value
R2-ISS				
I	0.165 (0.021–1.272)	0.084	0.161 (0.021–1.245)	0.007
II	0.235 (0.052–1.059)	0.059	0.284 (0.07 −1.050)	0.059
III	0.441 (0.212–0.920)	0.029	0.161 (0.021–1.245)	0.080
IV	Reference	Reference	Reference	Reference
BARD1	2.823 (1.039–7.674)	0.042	2.874 (1.058–7.804)	0.038

a mutation frequency of 100%.[14] Additionally, this study revealed correlations between mutations in BCL6, BIRC3, HLA-DQA1, and VCAN and adverse prognosis in multiple myeloma, suggesting their potential utility as prognostic markers for identifying high-risk patients requiring tailored treatment regimens. Other studies have also identified common mutated genes in multiple myeloma patients, including KRAS, NRAS, TP53, BRAF, IRF4, and MYC.[15,16] Hu et al analyzed 40 NDMM patients and identified ATM, CUL4B, IRF4, KRAS, and NRAS as the most frequently mutated genes in their cohort.[17] Notably, IRF4 mutations were associated with prolonged PFS and OS. However, ATM and CUL4B mutations did not significantly impact PFS or OS in this study. Contradictory findings in the literature highlight the complexity of genotype-phenotype relationships in multiple myeloma. For instance, another report found that ATM mutations were associated with poorer survival, with 2-year OS reduced to 50% in ATM-mutated patients compared to 80.3% in non-mutated patients.[18] These discrepancies underscore the need for comprehensive, multi-faceted research approaches to fully elucidate the intricate connections between genetic mutations and clinical outcomes in multiple myeloma.

In our research, we detected mutations similar to those reported in other studies. However, we observed a distinct spectrum of high-frequency mutations. The top ten mutated genes in our study were KMT2C, BARD1, NCOR1, POLQ, BRCA2, KMT2D, MAGI1, ARID2, ATRX, and GNAQ. The differences in commonly mutated genes between our study and others may be attributed to ethnic and regional variations, as well as differences in sample size. Our study uniquely identified the BARD1 mutation as an independent risk factor affecting the prognosis of multiple myeloma patients. We successfully constructed a nomogram using both BARD1 mutation status and R-ISS score to predict 1-, 3-, and 5-year OS and PFS rates. This nomogram revealed that patients with a BARD1 mutation experienced significantly shorter 3-year OS (33.7% vs. 82.4%, P = 0.004) and PFS (38.9% vs. 75.5%, P = 0.004) compared to the wild-type group. Our BARD1 mutation and R2-ISS prognostic model demonstrated predictive performance comparable to established GEP-based signatures (eg, SKY92, CGS, immune-related gene pairs) in stratifying multiple myeloma patients by survival outcomes,[7,19,20] with time-dependent AUC values reaching 0.961 for 5-year OS and 0.956 for 5-year PFS. However, our model offers distinct advantages by integrating BARD1 mutation into the R2-ISS staging system, enhancing this established clinical framework without requiring specialized gene expression platforms. This approach delivers excellent long-term predictive accuracy with broad clinical accessibility, while potentially complementing GEP-based classifiers by capturing orthogonal biological information related to DNA damage repair dysfunction. Overall, these findings suggest that the BARD1 mutation may play a crucial role in the onset and progression of multiple myeloma. Further comprehensive investigation is warranted to fully elucidate the association between BARD1 mutation and NDMM.

The BRCA1-associated RING domain protein (BARD1) forms a critical heterodimer with breast cancer susceptibility protein 1 (BRCA1), playing a pivotal role in DNA damage repair. This interaction occurs through their N-terminal RING domains, resulting in a complex with E3 ubiquitin ligase activity. This enzymatic function is essential for tagging specific proteins with ubiquitin, thereby signaling them for various cellular processes. Of particular importance is the E3 ubiquitin ligase activity of the BARD1-BRCA1 complex in the DNA damage response pathway. It is instrumental in repairing double-strand breaks via homologous recombination, a process crucial for maintaining genomic integrity and preventing carcinogenesis.[9] Recent research by Qi Hu et al has provided valuable insights into the complex biological functions of the BRCA1-BARD1 heterodimer, elucidating its regulatory role in DNA repair mechanisms.[21] These findings underscore

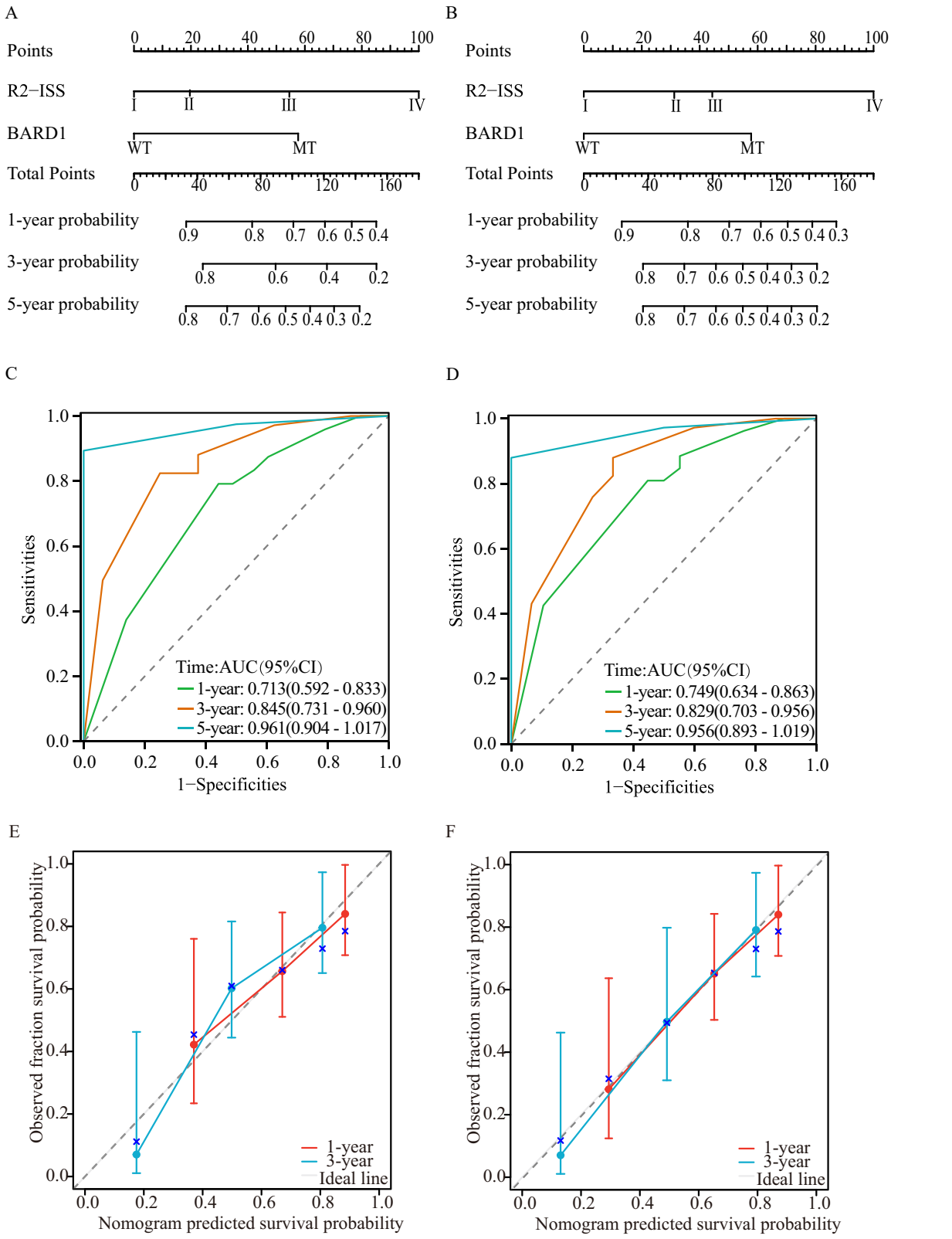

Figure 4 Construction and validation of the nomogram based on BARD1 mutation and R2-ISS stage. The nomograms developed for OS (**A**) and PFS (**B**) differentiate between wild-type (WT) and mutant (MT) categories, serving as predictive visual tools. Within each nomogram, variables are represented by line segments of varying lengths, illustrating their relative impact on the predicted outcome. Points assigned to each variable are projected vertically onto the score axis, corresponding to specific variable scores. The summation of scores from all variables yields a comprehensive total score for each patient. By aligning this total score with the corresponding vertical axis, one can readily interpret the model-predicted survival rates at 1-, 3-, and 5-year intervals. Time-dependent ROC curves for OS (**C**) and PFS (**D**) are presented for 1-, 3-, and 5-year intervals. Calibration plots utilized for model verification at the 1- and 3-year time points are displayed for OS (**E**) and PFS (**F**), demonstrating the concordance between predicted and observed outcomes.

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the importance of this protein complex in safeguarding genomic stability and preventing tumor formation, opening new avenues for potential therapeutic interventions in cancer research.

The interaction between the BRCA1-BARD1 complex and histone H2A is a two-step process. Recognition: The complex identifies and binds to monoubiquitin attached to the N-terminus of histone H2A. Ubiquitylation: Following recognition, the BRCA1-BARD1 complex promotes ubiquitylation at the C-terminus of H2A, significantly impacting chromatin structure and function. By inhibiting polyubiquitin chain extension, the BRCA1-BARD1 complex prevents proteasomal degradation of histones, thereby maintaining chromatin integrity. This is crucial for accurate repair of DNA double-strand breaks. This precise regulatory mechanism is a key aspect of BARD1's tumor-suppressing activity, highlighting its importance in cancer prevention through effective DNA damage response and repair. This regulatory crosstalk, where BRCA1-BARD1 recognition of N-terminal monoubiquitin on H2A cooperatively promotes C-terminal ubiquitylation and blocks polyubiquitin chain formation, is one of the mechanisms underlying BARD1's antitumor properties. BARD1 plays a critical role in tumor suppression. Mutations in BARD1 have been strongly associated with increased risks for familial breast and ovarian cancers, as well as various sporadic tumors.[22,23]

The presence of BARD1 mutations, resulting in isoforms lacking the RING and/or ankyrin repeat domains, can significantly alter the functionality of the BRCA1/BARD1 heterodimer. This alteration particularly affects the ubiquitin ligase activity of the complex, which is crucial for orchestrating various regulatory pathways, including DNA damage response, cell cycle control, chromatin architecture, and hormonal signaling. Deficiency in this functional activity due to mutations disrupts these critical cellular pathways, leaving cells vulnerable to accumulating DNA damage, chromatin disorganization, and unchecked proliferation-all hallmarks of cancer development.[8] Targeting BARD1 isoforms presents an intriguing therapeutic strategy, especially considering the significant role of BRCA1-BARD1 in DNA repair and tumor suppression. Lepore et al observed changes in BARD1 expression levels using vorinostat on various cancer cell lines, including AML, MCF-7 breast cancer, and Kelly neuroblastoma cells.[24] Vorinostat treatment increased levels of miR-19a and miR-19b, which subsequently enhanced cancer cell apoptotic activity through targeted expression at the BARD1 3'UTR. In the past two decades, histone deacetylases have emerged as significant targets for therapeutic intervention in multiple myeloma.[25] However, investigations into the correlation between HDAC functional mechanisms and the BARD1 gene remain limited. Our retrospective analyses have revealed that multiple myeloma patients harboring BARD1 gene mutations exhibit poorer OS and PFS. Consequently, there is an urgent need for more comprehensive research to understand the pathogenic role of the BARD1 gene in multiple myeloma patients and to investigate potential relationships between BARD1 expression and the efficacy of HDAC inhibitors. Supported by our findings and existing literature, both domestic and international, targeted suppression of the BARD1 gene shows promise as a novel treatment strategy for NDMM.

Conclusion

In conclusion, our research has unveiled the potential of employing the BARD1 gene mutation status along with the R2-ISS score to develop a nomogram that can successfully forecast 1-, 3-, and 5-year OS and PFS for patients with newly diagnosed MM. The results offer precise and functional predictions, thus meeting the immediate needs in the field of genomic research. However, several limitations of this study should be acknowledged. The high costs associated with next-generation sequencing may impede its widespread usage and, consequently, its practicality. Furthermore, the relatively small number of patients harboring BARD1 mutations limits the statistical power for deeper subgroup analyses, and our findings require validation in larger, independent cohorts. The retrospective nature of the dataset affects the strength and generalizability of the findings. In addition, due to the limited use of anti-CD38-based quadruplet regimens in our cohort, the impact of these therapies on the prognostic value of the identified genetic alterations could not be assessed, highlighting the need for validation in patients treated with modern immunotherapy. Finally, the current scope of our research has not explored the underlying pathogenesis of the BARD1 gene in MM. Future prospective, multicenter study with expanded sample size should be conducted to further validate the prognostic value of BARD1 mutations, decipher the pathological processes involving BARD1, perform more in-depth subgroup analyses, and investigate novel therapeutic targets that emerge from these insights.

Abbreviations

NDMM, Newly diagnosed multiple myeloma; CAR-T, Chimeric Antigen Receptor T-Cell Therapy; DS, Durie-Salmon; R2-ISS, Second Revision of the International Staging System; BARD1, BRCA1-Associated RING Domain 1; OS, Overall Survival; PFS, Progression-Free Survival; time-ROC, time-dependent receiver operating characteristic; KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, Gene ontology; AUC, Area under curve.

Data Sharing Statement

Data supporting the discovery of this study are available from the corresponding authors, Yun Lin, on reasonable request.

Ethics Approval and Consent to Participate

This single-center retrospective study received approval from the institutional review board of Fujian provincial hospital and complied with the Declaration of Helsinki, with an exemption from informed consent requirements.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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