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Prognostic value of the expression of CD27 and CD117 in newly diagnosed multiple myeloma patients

Xu Si[1], Jing Zhao[1], Yichuan Song[1], Wenxuan Fu[1] and Rui Zhang[1*]

Abstract

Objective The purpose of this study was to investigate the predictive relevance of CD27 and CD117 expression and the prognostic value in newly diagnosed multiple myeloma (NDMM) patients.

Methods This retrospective cohort study analyzed 160 newly diagnosed multiple myeloma (NDMM) patients at Beijing Chaoyang Hospital (2016–2023), evaluating CD27 (TNF receptor family member regulating plasma cell differentiation) and CD117 (c-KIT proto-oncogene product mediating hematopoietic cell survival) expression patterns via pretreatment flow cytometry. Patients were stratified by CD27/CD117 membrane positivity to assess their combined prognostic significance on disease progression, with survival outcomes tracked through standardized clinical surveillance protocols.

Results The CD27 negative cohort demonstrated severe disease burden, evidenced by elevated β2-MG, increased bone marrow plasma cell infiltration, reduced hemoglobin levels, percentage of high ISS III. Kaplan-Meier analysis demonstrated that CD27 positive cohort showing significantly prolonged median PFS versus CD27 negative counterparts (78 vs. 33 months, $P=0.0078$). While CD117 alone lacked prognostic significance, combined CD27(+) CD117(+) status was associated with superior PFS ($P=0.0041$ vs. subgroups), earlier ISS\MASS staging ($P=0.005$, $P=0.021$), deeper therapeutic remission rates(Protease inhibitor-based therapy, $P=0.009$), and lower frequency of high-risk cytogenetic abnormalities compared to all other combinations, and particularly outperforming CD27(−) CD117(−) patients. Among CD27-expressing patients, CD117 positive patients had better survival performance ($P=0.0424$). Multivariate Cox regression confirmed CD27 positivity as an independent protective factor (HR 0.50, $P=0.009$) and thrombocytopenia (PLT $< 150\times10^9$/L) as a risk predictor (HR 2.28, $P=0.002$), both maintaining significance after adjusting for conventional parameters.

Conclusion CD27 positive patients have a better prognosis, and the combination of CD27 and CD117 allows refined prognostic risk stratification of MM patients. The expression of CD27 and CD117 is associated with improved prognosis.

Keywords Multiple myeloma, Immunophenotype, CD27, CD117, Prognosis

*Correspondence:
Rui Zhang
zr189169@163.com
[1]Department of Clinical Laboratory, Beijing Chao-yang Hospital, Capital Medical University, No. 8, Gongtinan Road, Chao-yang District, Beijing 100020, P.R. China

Introduction

Multiple myeloma (MM), a malignancy of plasma cells (PCs) which represents approximately 10% of all hematologic malignancies [1, 2], exhibits biological complexity and clinical heterogeneity manifesting as hypercalcemia, osteolytic lesions, anaemia, renal impairment, and infection susceptibility. Despite therapeutic advances extending median survival, only 10–15% achieve long-term disease control [3], with most patients experiencing relapsing-remitting progression characterized by diminishing remission intervals and cumulative treatment resistance [4–6]. This incurability underscores the critical need for precise prognostic stratification to guide therapeutic decision-making.

The utilization of multiparameter flow cytometry immunophenotyping has become progressively more prevalent for the diagnostic and prognostic assessment of hematologic malignancies [7–9]. However, its application in MM remains contentious, particularly regarding discordant prognostic interpretations of immunophenotypic markers like CD117 [10–13]. Current limitations stem from isolated analyses of single markers rather than integrated evaluation of complementary biomarkers, which makes immunophenotyping inaccurate for the prognostic evaluation of MM. Motivated by the persistent prognostic ambiguity associated with CD117 expression in multiple myeloma (MM), we conducted a synergistic analysis incorporating CD27, a consistently validated prognostic marker across multiple cohorts, to compensate for CD117's interpretative limitations. This dual-marker paradigm aims to establish a refined immunophenotypic stratification framework that enhances prognostic precision while resolving existing discrepancies in single-marker evaluations.

CD27, a tumor necrosis factor receptor superfamily member, mediates plasma cell differentiation through CD70 ligand binding, with its expression progressively declining from monoclonal gammopathy of undetermined significance (MGUS) to active myeloma - complete loss correlating with malignant transformation [14, 15]. In contrast, CD117 (c-Kit), a tyrosine kinase receptor undetectable in normal plasma cells, becomes expressed in 30% of MM cases, driving proliferative signaling through PI3K/AKT pathways [10, 16]. While CD27 depletion reflects terminal differentiation arrest, CD117 acquisition suggests clonal evolution towards autonomous growth. Robillard N et al. [17] first proposed the prognostic utility of combined CD27/CD117 immunophenotyping at diagnosis, highlighting that patients co-negative for both markers may require enhanced clinical surveillance due to accelerated disease progression. Building on this foundational work, our study systematically evaluated the synergistic prognostic value of CD27 and CD117 in conjunction, bridging a critical gap in the refinement of accurate prognostic risk stratification for MM by combined immunoantigen typing.

To systematically investigate the prognostic interplay of CD27 and CD117 in multiple myeloma (MM), we performed a retrospective cohort study profiling these biomarkers' expression via flow cytometry (FCM) in 160 patients, integrating flow cytometric profiles with fluorescence in situ hybridization (FISH)-detected cytogenetic abnormalities, clinical characteristics, and laboratory parameters.

Materials and methods

Study designed and patients enrolled

Consecutive patients with NDMM were retrospectively identified through electronic medical records at Chaoyang Hospital between September 2016 and December 2023. Exclusion criteria comprised a concurrent diagnosis of plasma cell leukemia or incomplete baseline clinical data. After screening, 160 NDMM patients meeting the International Myeloma Working Group (IMWG) diagnostic criteria [18] were enrolled, comprising 82 males and 78 females. Progression-free survival (PFS), defined as the time from treatment initiation to first disease progression or death, was assessed with a median duration of 33 months. All patients received induction, consolidation, and/or maintenance therapies, with treatment response evaluated per IMWG uniform response criteria. Follow-up data were retrospectively collected until April 2024. The study was approved by the Beijing Chaoyang Hospital's ethical committee(2022-ke-48).

Research variables

Baseline characteristics were systematically documented, encompassing demographic parameters (gender, age), hematological indices (hemoglobin [HGB], platelet count), biochemical markers (serum calcium, lactate dehydrogenase [LDH], alkaline phosphatase [ALP], creatine kinase [CK], creatinine [CREA], albumin [ALB], total protein [TP], globulin [GLB], albumin/globulin [A/G] ratio, uric acid [URIC], carbamide [UREA], β2-microglobulin), M-protein type, and bone marrow plasma cell infiltration percentage.

Among all prognostic factors described in MM, we recorded the International Staging System (ISS), the DurieSalmon (DS), Mayo Additive Staging System (MASS) and the variety of cytogenetic abnormalities (CAs) from each patients. CD138-enriched bone marrow samples were isolated using immunomagnetic bead separation for standardized FISH analysis at diagnosis. We interrogated six clinically relevant cytogenetic abnormalities: del(17p), t(4;14), t(11;14), t(14;16), del(13q), and 1q21 amplification/gain, applying standardized thresholds (≥20% nuclei for deletions/amplifications, ≥10% for translocation [19]). Chromosome 1q21 alterations

were classified as amplification (≥ 4 copies) or gain (2–3 copies). The MASS staging system, recently validated for MM prognosis, integrated five high-risk parameters: t(4;14)/t(14;16), 1q21 amplification/gain, del(17p), ISS III, and elevated LDH, stratifying patients into stages I (0 points), II (1 point), or III (≥ 2 points) based on cumulative risk factors [20, 21].

Flow cytometry immunophenotyping

Bone marrow aspirates from NDMM patients were collected in EDTA-anticoagulated tubes. Aliquots containing $> 1 \times 10^6$ nucleated cells were transferred to pre-labeled flow cytometry tubes pre-loaded with standardized titers of surface membrane antibodies. After 30 min of dark incubation at room temperature, samples underwent sequential pre-processing steps including erythrocyte lysis and permeabilization. Following fluorescence calibration and spectral compensation adjustments on a BD FACS Canto II flow cytometer (BD Biosciences, USA), data acquisition was performed with a minimum threshold of 100,000 nucleated cells per tube or until sample depletion. According to the recommendation of EuroFlow [22], the following fluorescent antibody combinations were used to test bone marrow samples from each patient: Fluorescently labeled mouse anti-human monoclonal antibodies CD38, CD138, CD19, CD56, CD117, CD27, CD28, CD269 (BD, USA), cKappa FITC and cLambda PE (Lianke). Cellular markers were analyzed using FACS Diva software (BD Biosciences, USA), with an antigen positivity of ≥ 20% was considered positive, consistent with institutional diagnostic protocols and published criteria [10, 23].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 26.0 (Armonk, NY) and GraphPad Prism 8 (San Diego, CA). Descriptive statistics were used to describe the clinical characteristics of the patients. Continuous variables with normal/non-normal distributions were analyzed by Student's t-test/Mann-Whitney U test, respectively. Categorical variables were compared using χ^2 or Fisher's exact tests as appropriate. Progression-free survival (PFS) was evaluated by Kaplan-Meier curves with log-rank testing. Cox proportional hazards models generated univariate and multivariate hazard ratios (HRs) with 95% confidence intervals (CIs). All tests used two-sided $P < 0.05$ significance thresholds.

Result

Patient baseline clinical characteristics

Data was gathered from a total of 160 cases. Table 1 summarizes the fundamental clinical characteristics of the cohort consisting of 160 multiple myeloma (MM) patients. There were 82 male (51.25%) and 78 (48.75%) female patients, with a male to female ratio of 1.05. The median age was 60 years (33–86 years), there were no significant differences in genders and ages between the two groups. For CD27 group, the CD27 negative patients were significantly associated with lower levels of Hb ($P = 0.010$), higher levels of β2-MG ($P = 0.006$) and more severe bone marrow plasma cell infiltration ($P < 0.0001$). However, the platelet, blood calcium, LDH, ALP, CK, CREA, albumin, total protein, globulin, A/G, URIC, UREA and the type of myeloma did not differ significantly. And for CD117 groups, statistically significant differences were observed in LDH and ALP levels ($P = 0.029$ and $P = 0.016$), but not in other indicators. Then, we also evaluated the ISS stage, DS stage and different treatment strategies between the two groups. Statistical analysis revealed significant differences in chemotherapy regimen utilization between the CD27 and CD117 subgroups ($P = 0.001$). Specifically, monoclonal antibody-based combination therapies were administered to a significantly higher proportion of patients in both CD27 negativity and CD117 negativity cohorts ($P = 0.001$), whereas no statistically discernible variations were observed among other treatment regimens. Furthermore, a significantly higher proportion of patients in the CD27 negativity cohort were classified as ISS stage III compared to the CD27 positivity group ($P = 0.005$), indicating a potential association between CD27 negativity and advanced disease burden.

Prognostic evaluation and risk stratification factors

To guide treatment decision-making, multiple validated risk stratification systems have been developed to differentiate risk levels in newly diagnosed multiple myeloma (MM) patients. These systems incorporate key indicators including disease stage, depth of treatment response and cytogenetic abnormalities, which are central to MM prognosis. Patients were stratified into four subgroups based on CD27 and CD117 expression: CD27(+) CD117(+) ($n = 29$), CD27(+)CD117(-) ($n = 42$), CD27(-) CD117(+) ($n = 41$), and CD27(-)CD117(-) ($n = 48$). By analyzing differences between these subgroups across established prognostic parameters, we evaluated the clinical relevance of combined CD27/CD117 status within this multidimensional risk assessment framework.

The distribution patterns of CD27/CD117 expression subgroups across prognostic staging systems revealed significant associations. Significant differences in both the International Staging System (Fig. 1A, $P = 0.005$) and Mayo Additive Staging System (Fig. 1C, $P = 0.012$). In the International Staging System (ISS), CD27(+)CD117(+) patients were predominantly stratified in ISS stage I (48%) compared to stage III (20.7%), while CD27(-) CD117(-) subgroups conversely peaked in ISS stage III (60% vs. 22.9% in stage I). Similar stratification was

Table 1 Association of CD27 and CD117 antigen expression patterns with baseline clinical and biological characteristics in MM patients

Characteristic	CD27- (*n* = 89)	CD27+ (*n* = 71)	*P* value	CD117- (*n* = 90)	CD117+ (*n* = 70)	*P* value
Sex, n(%)			0.845			0.780
Male	45(50.60)	37(52.10)		47(52.20)	35(50.00)	
Female	44(49.40)	34(47.90)		43(47.80)	35(50.00)	
Age(yrs), mean ± s.d.	59.13 ± 10.56	60.07 ± 8.57	0.546	58.62 ± 9.84	60.74 ± 9.46	0.171
Immunoglobulin isotype, n(%)			0.367			0.712
Immunoglobulin G (IgG)	37(41.57)	33(46.48)		41(45.56)	29(41.43)	
Light chain type	29(32.58)	16(22.54)		23(25.56)	22(31.43)	
Others[a]	23(25.85)	22(30.98)		26(28.88)	19(27.14)	
ISS stage, n(%)			0.005**			0.086
I + II	38(42.70)	46(64.79)		43(47.78)	43(61.43)	
III	51(57.30)	25(35.21)		47(52.22)	27(38.57)	
DS stage, n(%)			0.182			0.071
I + II	16(17.98)	19(26.76)		15(16.67)	20(28.57)	
III	73(82.02)	52(73.24)		75(83.33)	50(71.43)	
First-line treatment, n(%)			0.001**			0.001**
Proteasome inhibitor (PI)-based programmes[b]	63(70.79)	64(90.14)		61(67.78)	66(94.28)	
Immunomodulator (IMiD)-based programmes[c]	3(3.37)	4(5.63)		5(5.56)	2(2.86)	
Monoclonal Antibody Combination Programmes[d]	23(25.84)	3(4.23)		24(26.66)	2(2.86)	
Autologous stem cell transplantation (ASCT), n(%)	32(35.96)	22(30.99)	0.509	33(36.67)	21(30.00)	0.376
BMPC(%), M(P25, P75)	34.5(19.00, 54.50)	21(10.00, 34.00)	<0.0001***	27.00(13.88, 48.38)	28.00(12.88, 46.88)	0.551
β2-MG(mg/L), M(P25, P75)	5.27(3.31, 9.98)	3.48(2.69, 6.29)	0.006**	4.34(3.04, 10.35)	3.63(2.95, 6.43)	0.092
Hb(g/L), mean ± s.d.	90.21 ± 26.47	101.38 ± 27.06	0.010*	92.72 ± 29.28	98.32 ± 24.17	0.198
PLT($\times 10^9$/L), M(P25, P75)	179.00(127.00, 238.50)	186.00(124.00, 247.00)	0.712	179.00(120.50, 243.75)	183.50(138.50, 242.25)	0.807
Calcium(mmol/L), M(P25, P75)	2.27(2.14, 2.37)	2.23(2.16, 2.36)	0.735	2.27(2.16, 2.36)	2.24(2.12, 2.39)	0.711
LDH (U/L), M(P25, P75)	168.00(146.50, 194.50)	172.00(136.00, 210.00)	0.826	176.00(151.75, 214.00)	161.50(135.00, 190.25)	0.029*
ALP (U/L), M(P25, P75)	65.00(51.00, 91.00)	74.00(57.00, 91.00)	0.404	74.00(55.00, 106.25)	63.00(51.00, 81.50)	0.016*
CK(U/L), M(P25, P75)	48.00(31.50, 77.00)	53.00(38.00, 70.00)	0.531	45.50(32.75, 68.00)	57.25(37.75, 88.25)	0.081
CREA(umol/L), M(P25, P75)	70.10(60.00, 115.00)	68.00(53.10, 125.30)	0.290	74.60(58.80, 129.43)	66.30(55.62, 91.00)	0.073
ALB(g/L), M(P25, P75)	37.10(32.95, 41.90)	37.60(32.70, 42.30)	0.884	37.60(32.70, 42.10)	37.35(33.00, 41.68)	0.914
TP(g/L), M(P25, P75)	72.20(63.60, 102.40)	73.60(62.30, 100.80)	0.491	71.80(63.08, 106.35)	74.00(63.27, 100.93)	0.990
GLB(g/L), M(P25, P75)	33.80(22.35, 70.80)	31.90(21.10, 63.20)	0.292	30.85(21.60, 78.13)	33.80(21.95, 68.25)	0.736
A/G, M(P25, P75)	1.10(0.40, 1.90)	1.20(0.50, 1.80)	0.598	1.30(0.40, 1.83)	1.05(0.50, 1.90)	0.893
URIC(umol/L), M(P25, P75)	395.00(307.00, 511.70)	373.00(308.00, 424.00)	0.200	395.00(317.00, 484.25)	369.50(306.50, 426.00)	0.288
UREA(mmol/L), M(P25, P75)	5.60(4.60, 8.52)	5.89(4.80, 8.49)	0.638	5.98(4.38, 9.66)	5.57(4.68, 7.46)	0.400

Others[a]: The number of patients with Immunoglobulin A (IgA), Immunoglobulin D (IgD), and non-secretory subtypes

Proteasome inhibitor (PI)-based programmes[b]: VRD (bortezomib + lenalidomide + dexamethasone), PCD/BCD (bortezomib + cyclophosphamide + dexamethasone)

Immunomodulator (IMiD)-based programmes[c]: Rd (lenalidomide + dexamethasone), PD (pomalidomide + dexamethasone)

Monoclonal Antibody Combination Programmes[d]: Dara-VRD (daratumumab + VRD), PDD (pomalidomide + daratumumab + dexamethasone)

Abbreviations: s.d. standard deviation, *Hb* Hemoglobin, *ALB* albumin, *TP* Total Protein, *GLB* globulin, *A/G* albumin/globulin, *Urea* Carbamide, *URIC* uric acid

P-value was calculated using the Mann–Whitney test, the t-test and the chi-squared test

*$P<0.05$, **$P<0.01$ and ***$P<0.001$ indicating significant difference among groups

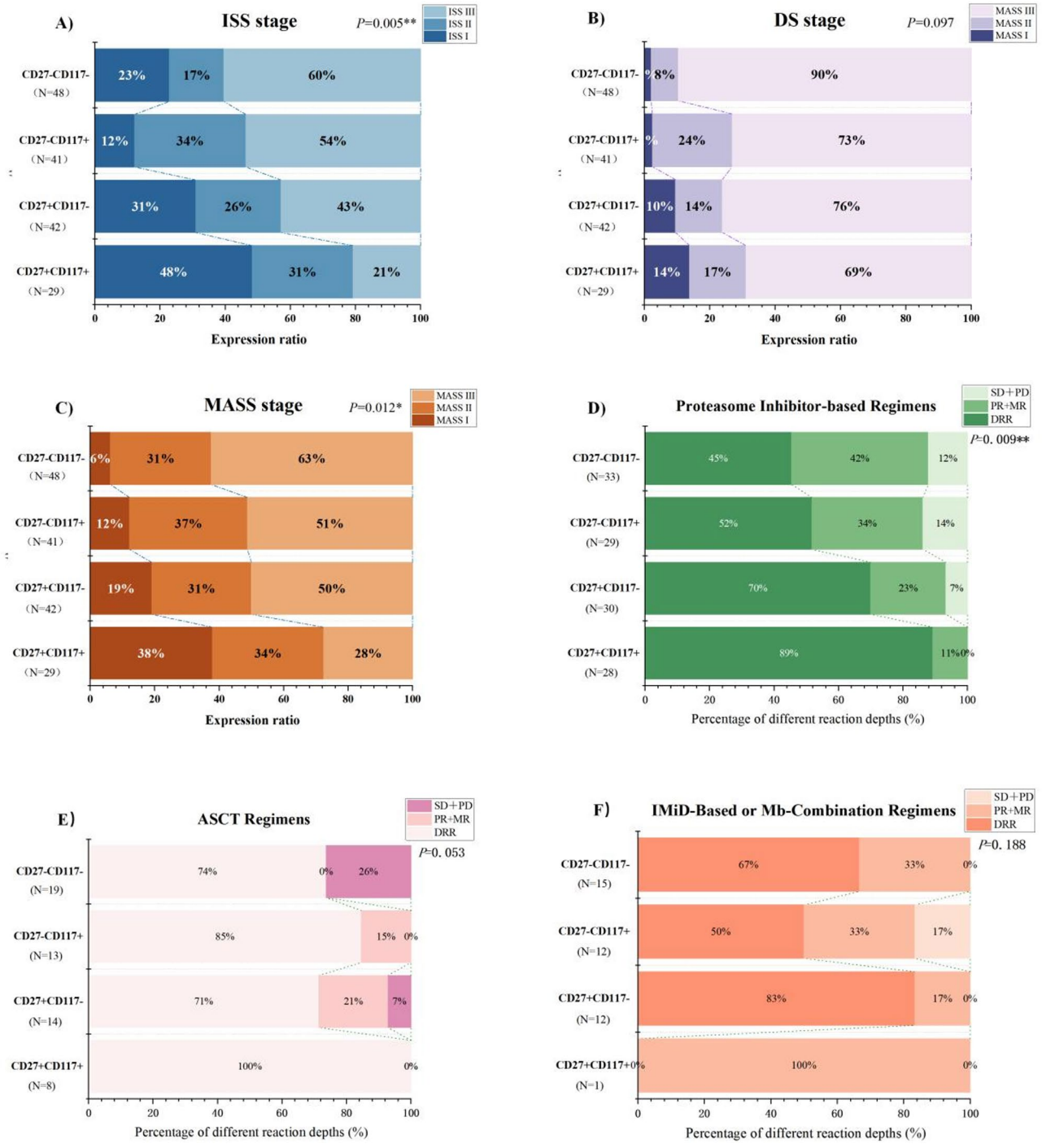

Fig. 1 Heterogeneity of CD27/CD117 expression subgroups across prognostic stratification systems and treatment response in multiple myeloma. **A** ISS stage, **B** DS stage, **C** Mayo MASS stage, **D** PI-based regimens Short-term treatment response (post-4-cycle chemotherapy); **E** IMiD-based or Mb-combination regimens Short-term treatment response (post-4-cycle chemotherapy); **F** ASCT regimens Short-term treatment response (post-transplant). *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ indicating significant difference among groups

observed in the Mayo Additive Staging System (MASS), with CD27(+)CD117(+) representation decreasing from 37.9% (stage I) to 27.6% (stage III), contrasted by CD27(-)CD117(-) subgroups increasing from 6.3 to 62.6% across corresponding stages. Notably, Durie-Salmon staging showed no intergroup stratification ($P = 0.097$, Fig. 1B).

Patients were stratified into three treatment groups: PI-based regimens, immunomodulatory agent-based

Table 2 Cytogenetic abnormalities classified by CD27 and CD117 expression

	CD27-CD117-	CD27-CD117+	CD27+CD117-	CD27+CD117+	*P* value
	N = 48	*N* = 41	*N* = 42	*N* = 29	
1q21 gain\amplification	33 (37.90%)	19 (21.80%)	26 (29.90%)	9 (10.30%)	0.006**
Del (17/17p)	7 (38.90%)	5 (27.80%)	6 (21.30%)	0 (0.00%)	0.218
t (4;14)	10 (35.70%)	4 (14.30%)	12 (42.90%)	2 (7.10%)	0.047*
t (14;16)	21 (43.80%)	11 (22.90%)	13 (27.10%)	3 (6.30%)	0.019*
Del (13)	4 (21.10%)	0 (0.00%)	11 (57.90%)	4 (21.10%)	0.002**
t (11;14)	21 (28.80%)	23 (31.50%)	17 (23.30%)	12 (16.40%)	0.474
Negative	2 (22.20%)	1 (11.10%)	1 (11.10%)	5 (55.60%)	0.315

P-value was calculated using the chi-squared test

*$P<0.05$, **$P<0.01$ indicating significant difference among groups

or Mb-combination regimens, and ASCT. Treatment responses after four cycles were categorized as deep remission (DRR: sCR/CR/VGPR), intermediate (PR/MR), or ineffective (SD/PD). Across CD27/CD117-defined subgroups, the CD27(+)CD117(+) cohort demonstrated superior DRR rates in PI-based regimens (89% vs. 45–70% in other subgroups, $P = 0.009$, Fig. 1D), whereas CD27(-)CD117(+) patients showed predominant ineffective responses (14% vs. 0–12%). This differential response pattern was not significant in ASCT transplant patients and patients treated with immunomodulators and monoclonal antibodies as the basis of treatment (Fig. 1E-F, $P = 0.053$ and 0.188).

We assessed the distribution of high-risk cytogenetic abnormalities across four CD27/CD117 expression subgroups, as per the 2016 International Myeloma Working Group (IMWG) criteria [24]. CD27/CD117 expression subgroups exhibited distinct cytogenetic abnormality profiles (Table 2). The CD27(-)CD117(-) group exhibited the highest prevalence of abnormalities and the CD27(+)CD117(+) subgroup demonstrated the lowest aberration burden, particularly 1q21 gain/amplification (37.9% in double negativity group vs. 10.3% in double positivity group, $P = 0.006$) and t(14;16) (43.8% vs. 6.3%, $P = 0.019$). Among CD27-expressing cases, CD117 negativity cells showed significantly higher rates than CD117 positivity cells for del(13q) (57.9% vs. 21.1%, $P = 0.002$) and t(4;14) (42.9% vs. 21.9%, $P = 0.047$). These findings align with the hierarchical risk stratification, where co-loss of CD27/CD117 correlates with genomic instability and IMWG-defined high-risk features.

Survival analysis

To visually evaluate the prognostic value of antigen combinations in multiple myeloma progression, Kaplan-Meier analysis revealed significant stratification of PFS across subgroups. (Fig. 2A-E). CD27(+) patients exhibited superior outcomes versus CD27(−) counterparts (median PFS: 78 vs. 33 months, $P = 0.0078$, Fig. 2A), while CD117 status alone showed no independent prognostic value (57 vs. 36 months, $P = 0.1723$, Fig. 2B). Notably, the combined expression patterns demonstrated enhanced prognostic discrimination (Fig. 2C, $P = 0.0261$), with the CD27(+)CD117(+) subgroup achieving superior outcomes, significantly outperforming CD27(+)CD117(-) (47 months, $P = 0.0424$), CD27(-)CD117(+) (39 months, $P = 0.0083$), and CD27(-)CD117(-) groups (31 months, $P = 0.0027$). Pairwise comparisons confirmed significant differences between CD27(+)CD117(+) and all other subgroups (Fig. 2D, $P = 0.0041$), though no significant divergence was observed between CD27(-)CD117(-) and non-CD27(-)CD117(-) groups (Fig. 2F, $P = 0.0702$). The prognostic interaction between CD27 and CD117 expression revealed distinct survival patterns: the CD27(+)CD117(+) subgroup demonstrated superior progression-free survival (PFS) compared to CD27(+)CD117(-) counterparts ($P = 0.0424$, Fig. 2E). Conversely, CD117 expression failed to confer survival benefits in CD27(-) patients ($P = 0.7871$, Fig. 2G).

Finally, univariate and multivariate Cox regression analyses identified CD27 and platelet count (PLT) as independent prognostic factors for multiple myeloma progression (Table 3). CD27 positivity emerged as an independent protective factor, with consistent hazard ratios in both univariate (HR 0.51, 95% CI 0.31–0.85, $P = 0.009$) and multivariate analyses (HR 0.50, 95% CI 0.29–0.84, $P = 0.009$). Thrombocytopenia ($PLT < 150 \times 10^9/L$) independently predicted poorer outcomes, demonstrating elevated risks in both models (multivariate HR 2.28, 95% CI 1.36–3.82, $P = 0.002$). While β2-microglobulin, Hb and DS stage reached significance in univariate analysis ($P = 0.049$, 0.018 and 0.025), it did not retain prognostic value after adjustment. Other clinical parameters including ISS/MASS staging, therapeutic regimens, and biochemical markers showed no statistically significant associations in multivariate models. These results confirm CD27 expression and platelet

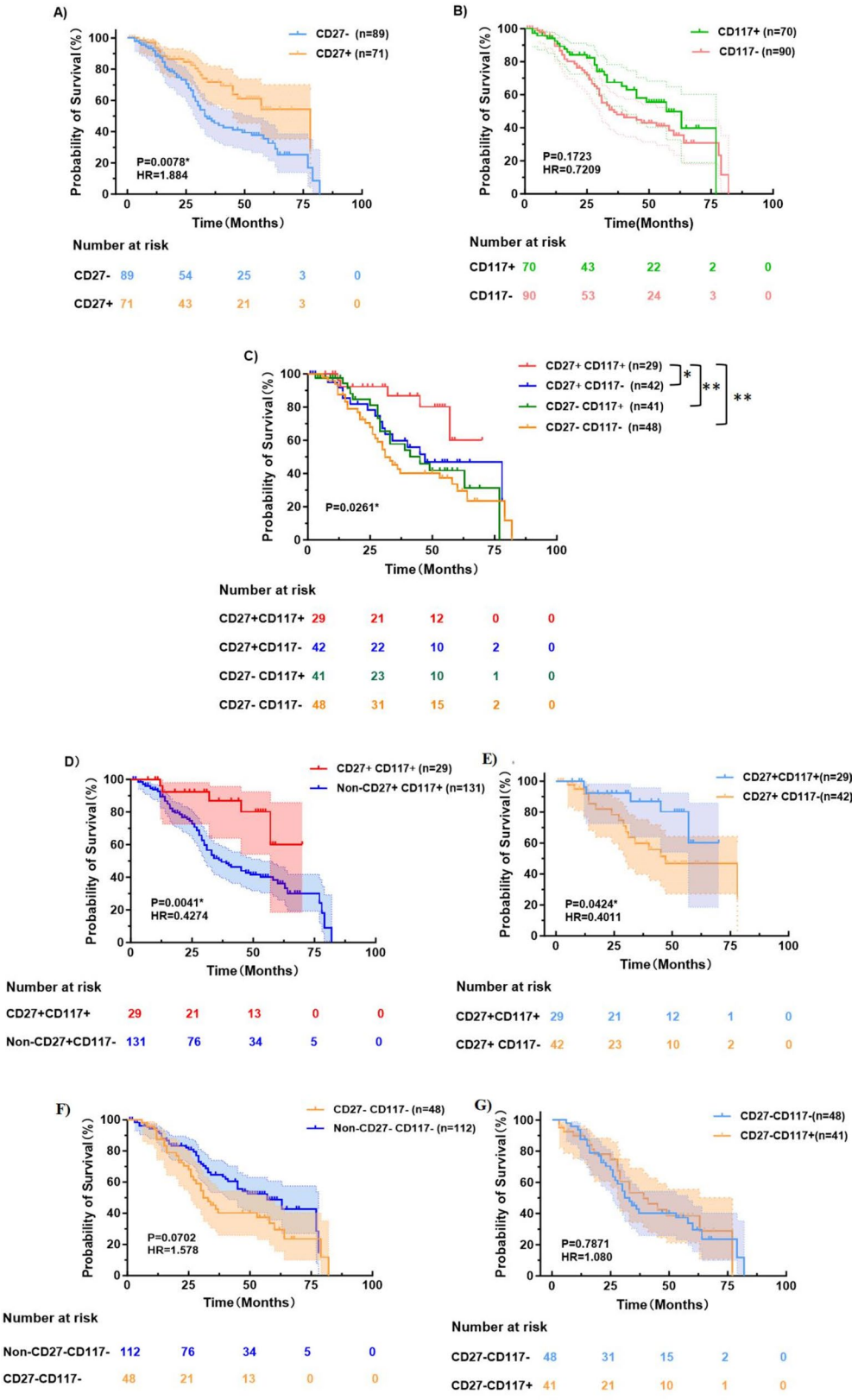

Fig. 2 Kaplan–Meier curves for PFS based on CD27 and CD117 expression. PFS between the CD27 positivity and CD27 negativity patients (**A**); the CD117-positive and CD117-negative patients (**B**); the CD27(+)CD117(+), CD27(+)CD117(-), CD27(-)CD117(+) and CD27(-)CD117(-) patients (**C**); the CD27(+)CD117(+)and non-CD27(+)CD117(+)patients (**D**); the CD27(-)CD117(-) and non-CD27(-)CD117(-) patients (**E**); the CD27(+)CD117(+)and CD27(+)CD117(-) patients (**F**); the CD27(-)CD117(-) and CD27(-)CD117(+) patients (**G**)

Table 3 Impact of baseline characteristics on PFS in univariate and multivariate analysis

Variables	Univariate Analysis		Multivariate Analysis	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value
CD27- vs. CD27+	0.510 (0.307–0.848)	0.009**	0.496 (0.294–0.838)	0.009**
CD117- vs. CD117+	0.717 (0.443–1.162)	0.177		
ISS stage III vs. I + II	1.253 (0.792–1.981)	0.335		
DS stage III vs. I + II	2.230 (1.106–4.493)	0.025*	1.781 (0.841–3.769)	0.132
MASS stage III vs. I + II	0.996 (0.609–1.533)	0.884		
Age ≥ 65 vs. <65	0.799 (0.474–1.349)	0.402		
Sex (male vs. female)	0.744 (0.467–1.187)	0.215		
Prior ASCT	0.925 (0.572–1.496)	0.750		
PI-based programmes	0.674 (0.409–1.109)	0.120		
IMiD-based programmes	1.111 (0.267–4.620)	0.885		
Mb Combination Programmes	1.503 (0.901–2.507)	0.119		
PLT ≥ 150 vs. <150 × 10^9/L	2.354 (1.474–3.759)	<0.0001***	2.278 (1.358–3.820)	0.002**
Hb ≥ 100 vs. <100 g/L	1.760 (1.101–2.811)	0.018*	1.236 (0.733–2.085)	0.426
Albumin ≥ 35 vs. <35 g/L	1.061 (0.651–1.729)	0.812		
LDH ≥ 222 vs. <222U/L	1.172 (0.643–2.137)	0.604		
Creatinine (Cre) ≥ 111 vs. <111umol/L	1.516 (0.923–2.492)	0.100		
ALP ≥ 135 vs. <135U/L	1.008 (0.435–2.338)	0.985		
CK ≥ 180 vs. <180U/L	0.488 (0.150–1.589)	0.233		
Ca ≥ 2.5 vs. <2.5mmol/L	1.179 (0.475–2.928)	0.723		
URIC ≥ 400 vs. <400umol/L	1.001 (0.627–1.596)	0.998		
UREA ≥ 7 vs. <7mmol/L	0.971 (0.593–1.590)	0.907		
β2-MG < 5.5 vs. ≥5.5 mg/L	1.602 (1.002–2.563)	0.049*	0.840 (0.485–1.454)	0.534

Abbreviations: HR HazardRatio, *CI* confidence interval; *$P<0.05$, **$P<0.01$ and ***$P<0.001$ indicating significant difference among groups

levels as robust predictors of disease progression independent of conventional staging systems.

Discussion

Given MM remains an incurable condition with a fatal tendency towards relapse, a multitude of studies focused on the prognostic significance of immunophenotyping as assessed by multiparameter flow cytometry. In this research, we have conducted a retrospective analysis on the potential prognostic significance of CD27 and CD117. Our results show that the expression of CD27 expression provides independent valuable insights into prognosis, but CD117 does not independently predict prognosis. Furthermore, we found that the combination of CD27 and CD117 classified patients into finer risk categories: poor risk CD27(+)CD117(+) patients, intermediate CD27(+)CD117(−) patients and CD27(−)CD117(+) myeloma patients, and high risk CD27(−)CD117(−) patients.

Normal plasma cells exhibit a distinct immunophenotypic profile characterized by CD38, CD138, CD27, CD19, and CD81 expression, while lacking CD56 and CD117, a pattern well-documented in prior studies [17, 25]. CD117 emerges in approximately 30% of malignant plasma cells, consistent with our cohort analysis showing 43.75% positivity (70/160 cases), marginally exceeding historical reports [10, 26]. CD27 positivity (44.38%, 71/160) aligned with contemporary literature [27, 28] but diverged from earlier reports [17, 29], likely reflecting methodological variances in flow cytometric analysis across populations. Strikingly, the CD27+/CD117 + subgroup represented only 18.13% of cases, suggesting possible mutual exclusivity in biological pathways driving immune evasion (CD27 loss) versus proliferative autonomy (CD117 gain).

Our study employed standardized IMWG parameters to assess pretreatment CD27/CD117 expression patterns in relation to baseline clinical characteristics. The CD27(−) cohort demonstrated severe disease burden, evidenced by elevated β2-microglobulin (β2-MG), increased bone marrow plasma cell infiltration, reduced hemoglobin (Hb) levels, percentage of high ISS III, correlating with markedly shortened PFS. These clinical-pathological correlations mechanistically align with CD27's dual regulatory functions, wherein CD27-CD70 interactions mediate apoptosis induction through death domain signaling pathways [14], and CD27 also suppresses malignant plasma cell proliferation via PERK-ATF4 cascade activation [30]. Regarding CD117, the elevated alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels, biomarkers indicative of enhanced osteolytic activity and tumor metabolic burden, observed in CD117 (c-KIT)-negative MM patients. Moreover, our results, as well as from Zheng et al [13], found that CD117

expression is not linked to a substantially longer PFS ($P > 0.05$) and was not an independent prognostic factor for MM. However, Several studies have indicated that the absence of CD117 is associated with an unfavorable prognosis [10, 11, 31]. These observations underscore the necessity for combinatorial biomarker models that integrate proliferative markers (CD117) with CD27 to resolve prognostic ambiguities.

Our integrated analysis of CD27/CD117 co-expression patterns revealed significant prognostic stratification capacity. CD27(-)CD117(-) patients exhibited the highest prevalence of advanced ISS and MASS III stage ($P < 0.05$), both established high-risk parameters [20, 32]. While CD27(+)CD117(+) cases showed the lowest progression-risk profile. This demonstrates that CD27(+)CD117(+) patients show less adverse prognostic factors than CD27(−)CD117(−) patients. Notably, CD27(-)CD117(-) and CD27(-)CD117(+) subgroups demonstrated inferior treatment responses, whereas CD27(+)CD117(+) patients achieved deeper therapeutic remissions. These findings suggest CD27/CD117 co-expression status may serve as a novel predictor of both baseline risk and treatment responsiveness in NDMM.

Furthermore, we observed the relationship between MM antigen expression and cytogenetic abnormalities, which were insufficient in previous research. We found that the unequivocal high-risk genetic index t(4;14) (FGFR3/MMSET dysregulation), t(14;16) (c-MAF overexpression), and 1q21 gain (CKS1B amplification) was statistically different in the CD27 and CD117 subgroups. CD27(+)CD117(+) patients exhibited minimal high-risk abnormalities compared to CD27(-)CD117(-) counterparts- patterns aligning with their superior progression-free survival [33, 34]. CD27 signaling via the TRAF2-SHP-1 axis enhances tumoricidal T-cell responses [35], CD27 potentially restraining FGFR3-driven proliferation via IFN-γ-mediated apoptosis, while CD117-mediated PI3K/AKT activation counteracts CKS1B-driven chromosomal instability. Interestingly, we found the highest prevalence of t(4;14) and the intermediate-risk cytogenetic indicator del(13) in patients with CD27(+) CD117(-) cohort, suggesting that CD117 loss disrupts genomic maintenance pathways even in the presence of CD27-mediated immune surveillance. This cytogenetic model advances the IMWG's precision medicine paradigm by demonstrating how the expression of surface antigens reflects and shapes the genetic architecture of MM. Future studies should explore whether CD27 agonism or CD117-targeted CAR-T can mitigate high-risk cytogenetic evolution.

Our survival analyses revealed critical prognostic synergism between CD27 and CD117 co-expression. Patients with CD27(+)CD117(+) phenotype demonstrated significantly longer progression-free survival (PFS) compared to other subgroups (median PFS: 62 vs. 31–47 months, $P = 0.0041$), whereas CD27(-)CD117(-) cases showed the poorest outcomes. Notably, CD117 expression refined risk stratification within CD27-positive patients ($P = 0.0424$), confirming the clinical value of combinatorial assessment. This synergistic prognostic effect likely stems from complementary biological mechanisms: CD27 maintains immune surveillance through CD70-mediated T cell activation [30, 35], while CD117 preserves genomic stability via PI3K/AKT-dependent DNA damage response. We hypothesize that CD27(+) CD117(+) co-expression may enhance survival signaling (e.g. via PI3K/AKT or NF-κB pathways) or microenvironmental crosstalk, thereby promoting therapeutic sensitivity—particularly to proteasome inhibitors, as evidenced by deeper remission rates ($P = 0.009$). This aligns with emerging evidence that CD117 (c-KIT) expression in myeloma may modulate drug responsiveness rather than intrinsic tumor aggression.

While our study provides comprehensive insights into the prognostic significance of CD27/CD117 co-expression patterns in MM, several limitations warrant consideration. Firstly, this was a single-center retrospective study. Secondly, the limited relapse data prevented an in-depth discussion on the relationship between CD27 and CD117 expression and relapsed multiple myeloma. Thirdly, mechanistic dissection of how CD27 and CD117 affect myeloma prognosis in microenvironmental control should be performed in future studies.

Conclusions

In conclusion, this study establishes CD27 expression as a robust predictor of prolonged progression-free survival (PFS) in multiple myeloma, with CD27/CD117 co-expression emerging as a synergistic prognostic biomarker pair. Although this has not been fully mechanistically investigated, the combined immunophenotyping of CD27 and CD117 could help to refine prognostic risk stratification of myeloma patients, leading to early intervention to reduce the risk of progression and prolong survival. We assert that these findings can assist in establishing a prognosis for MM patients in the clinic, with the potential to improve patient outcomes.

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Authors' contributions

X.Si wrote the original draft and contributed to writing—review and editing, methodology, and data curation. J.Zhao, Y.C.Song and W.X.Fu contributed to methodology and data curation. R.Zhang supervised the project, and contributed to the validation of the results. All authors reviewed the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Beijing Chaoyang Hospital's ethical committee (2022-ke-48).
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Chaoyang Hospital (no. 2022-ke-48), with the need for written informed consent waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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