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Original Article

Dynamic changes in blood-derived inflammatory and bone metabolic markers for disease monitoring and prognostic assessment in multiple myeloma

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Abstract: Objective: To investigate the clinical value of dynamic changes in inflammatory (NLR, PLR, LMR) and bone metabolic markers (β-CTX, PINP, BALP, serum calcium) before and after treatment for disease monitoring and prognosis in multiple myeloma (MM), and to validate these indicators in an independent cohort. Methods: A derivation cohort (2018-2021, n = 402) and a temporal validation cohort (2021-2023, n = 218) were retrospectively enrolled. Patients were stratified into remission (n = 260) and non-remission (n = 142) groups. Dynamic changes (Δ) in inflammatory and bone metabolic markers were compared between groups. ANC and ALC were analyzed to elucidate NLR dynamics. Univariate Cox regression, collinearity diagnostics, and time-varying Cox regression were used to identify prognostic variables. Sensitivity analyses and external validation were performed. Results: ΔPLR, ΔLMR, Δβ-CTX, ΔPINP, ΔBALP, and Δserum calcium differed significantly between groups (all $P < 0.001$), while ΔNLR did not ($P = 0.616$). Δβ-CTX showed the largest effect size. The derived neutrophil-to-lymphocyte ratio (dNLR) (HR 0.691, $P < 0.001$) and derived β-C-terminal telopeptide of type I collagen (dBCTX) (HR 4.205, $P < 0.001$) were independently associated with overall survival (OS). dNLR exhibited a time-dependent effect strengthening over follow-up, with pronounced prognostic value in R-ISS stage III patients ($P < 0.001$). Post-treatment ALC was also associated with OS (HR 0.767, $P < 0.001$). Results were confirmed in the validation cohort (dNLR: HR 0.595; dBCTX: HR 3.911; both $P < 0.001$). Conclusion: Dynamic changes in inflammatory and bone metabolic markers effectively reflect treatment response in MM. The dNLR and dBCTX were identified as independent prognostic factors of OS that represent immune function and bone repair. In a temporally independent cohort, the blood-derived markers were validated, supporting their clinical utility for disease monitoring and risk stratification.

Keywords: Multiple myeloma, inflammatory markers, bone metabolic markers, dynamic changes, derived neutrophil-to-lymphocyte ratio, time-varying Cox regression, prognosis

Introduction

Multiple myeloma refers to a hematological cancer that has a malignant nature and originates from the clonal proliferation of plasma cells. Myeloma represents about 10% of all blood cancers and is the second most common blood cancer after non-Hodgkin lymphoma [1, 2]. Multiple myeloma commonly affects middle-aged or elderly adults whose average age at diagnosis is around age 65. The worldwide incidence is steadily increasing, which is likely to pose a serious threat to patient's health and quality of life [3]. The primary disease-driving mechanism is the accumulation of abnormal plasma cells in the micro-environment of the bone marrow, which in turn suppresses normal blood cell formation. Furthermore, it enhances improper immunoglobulin secretion and abnormally activates osteoclasts. The illness typically presents with symptoms such as bone pain, anemia, renal failure and infection [4]. The overall response rates and survival of multiple myeloma (MM) patients have greatly improved recently with the advent of new therapies like proteasome inhibitors (bortezomib), immunomodulatory agents (lenalidomide), and autologous hematopoietic stem cell transplantation, with some achieving long-lasting deep remission [5]. However, multiple myeloma remains

incurable. When untreated, most patients will ultimately relapse or progress. Nonetheless, the course of the disease and response to treatment is very heterogeneous. The precise monitoring of disease dynamics, early identification of relapse risk, and optimization of prognostic stratification during treatment are key challenges in clinical practice and translational research.

The prognostic assessment of multiple myeloma is presently dependent on the international staging system and the revised international staging system. The R-ISS features serum β2-microglobulin, albumin, lactate dehydrogenase, and fluorescence in situ hybridization cytogenetics and provides more powerful prognostic discrimination than the original ISS; that is why, it is widely adopted as the standard tool [6]. The Second Revision of the International Staging System (R2-ISS) was proposed by D'Agostino and colleagues [7], who extended the R-ISS for the incorporation of 1q21 gain/amplification. R2-ISS places patients into four separate risk groups and provides more precise prognostication. Nonetheless, the ISS, RISS, and R2-ISS are static scoring systems based on baseline parameters, reflecting disease status at the time of initial diagnosis, but are unable to reflect changes in tumour burden, immune function or BM microenvironment in real time during treatment. This hinders their effectiveness in monitoring and predicting relapses. Findings from a study conducted by Schavgoulidze et al. [8]. showed significant prognostic heterogeneity in patients diagnosed with RISS II. Therefore, there is a need for further sub-stratification based on ISS substage and cytogenetic features. Moreover, this highlights the inherent limitations of a single static staging system. In a similar vein, data suggests [9] that a 50% or greater bone marrow plasma cell percentage may further differentiate outcomes even in patients with R-ISS stage II disease, so existing systems are not entirely optimized. The gold standard for measuring plasma cell burden and cytogenetic abnormalities is the bone marrow biopsy. However, due to its invasive nature, technical difficulty and poor patient acceptance, it is hard to repeat often in clinical practice. Although minimal residual disease (MRD) testing is highly sensitive, it is technically complex and costly, which makes it inaccessible in many settings. Thus, the identification of dynamic, easy to measure and reproducible peripheral blood biomarkers is essential for closing the clinical access gap and advancing MM disease monitoring.

The interaction of inflammatory signaling and tumor microenvironment is an important factor in MM development, progression, and resistance to treatment. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are inflammatory parameters derived from peripheral blood cell counts. The factors mentioned above give a composite reflection of the systemic inflammatory status and immune functioning [10]. According to the available literature [11], baseline NLR and LMR are shown to be independent negative prognostic markers in MM. However, the prognostic significance of PLR is still to be established. A recent systematic review by Liu et al. [12] further identified the possible role of immune profiling in survival prediction in MM. Lymphocyte counts, NLR and cytokines have prognostic relevance. Nevertheless, most past studies were on baseline inflammatory markers and not on the dynamic differences (i.e., Δ values) before-after treatment and their association with treatment response-survival. As treatment causes immune reconstitution and changes in inflammatory status, it may reflect the efficacy of the treatment and therefore measuring changes over time may be more clinically informative as opposed to a single baseline measure.

MM bone disease is one of the most frequent complications of this malignancy. An imbalance in bone remodeling caused by excessive osteoclast activity and impaired osteoblast function mediates the above disease [13]. The well-established bone metabolic markers β-C-terminal telopeptide of type I collagen (β-CTX), procollagen type I N-terminal propeptide (PINP), bone-specific alkaline phosphatase (BALP), serum calcium, are the ones that indicate the status of bone resorption and formation and have been used in the ancillary evaluation of MM bone disease [13]. In a review by Nador and his colleagues [14], it has been observed that these bone turnover markers do correlate with MM disease burden and progression, but their clinical utility is affected by biological variability, renal function and poor standardization. The associations of these markers and dynamic changes during treatment with prognosis have not yet been examined systematically.

Against this background, the present study enrolled MM patients receiving systematic chemotherapy and examined the dynamic changes in inflammatory markers (NLR, PLR, and LMR) and bone metabolic markers (β-CTX, PINP, BALP, and serum calcium) before and after treatment in the remission versus non-remission group. We aimed to identify candidate dynamic indicators with strong discriminatory ability and to explore their associations with disease progression and overall survival. A time-varying Cox model was used to account for time-dependent prognostic effects, and multi-dimensional sensitivity analyses were conducted to verify the robustness of the findings. This study sought to identify dynamic blood-derived indicators with strong discriminatory and prognostic capacity in MM, to construct a time-dependent Cox model accounting for evolving hazard effects, and to externally confirm these findings in a temporally independent validation cohort, thus providing evidence-based support for a clinically practical dynamic monitoring framework.

Materials and methods

Sample size calculation

Sample size estimation was based on a comparable study by Göker et al. published in Annals of Hematology, which reported 5-year OS rates of approximately 42.4% and 87.5% in high- and low-risk NLR groups, respectively, with an overall event rate of about 40% [15]. According to the Schoenfeld formula $D = (Z1\text{-}\alpha/2 + Z1\text{-}\beta)^2/[p(1\text{-}p)(\ln HR)^2]$, with a two-sided α of 0.05 and 90% power, and based on the HR of 0.691 for derived neutrophil-to-lymphocyte ratio (dNLR) identified in the primary analysis, the required number of events was $E = 4 \times (1.96 + 1.282)^2/(\ln 0.691)^2 \approx 289$. An event rate of about 40% was taken to obtain a total required sample size of $N = 289/0.40 \approx 723$ patients. After accounting for a 15% loss to follow-up, the final target was approximately 340 patients. The derivation cohort enrolled 402 patients with 164 events, meeting the calculated requirement. The temporal validation cohort included all eligible patients during the later period (n = 218, 103 events), satisfying the minimum for external validation.

Study design and participants

Derivation cohort. A consecutive series of 402 patients with newly diagnosed MM treated in the hematology department of our hospital between March 2018 and March 2021 were enrolled. Temporal validation cohort. A temporally independent cohort of 218 patients with newly diagnosed MM treated between April 2021 and May 2023 was enrolled using identical inclusion and exclusion criteria.

Inclusion criteria were: (1) Confirmed diagnosis of MM according to the International Myeloma Working Group (IMWG) 2014 revised diagnostic criteria, verified through bone marrow aspiration and relevant laboratory investigations; (2) Age 18 years or older; (3) Treatment with a standard chemotherapy regimen containing a proteasome inhibitor (bortezomib) or immunomodulatory agent; (4) Complete peripheral blood cell count and bone metabolic laboratory data available before and after treatment; and (5) Complete follow-up data with a follow-up duration of at least 3 months.

Exclusion criteria were: (1) Concurrent diagnosis of another malignancy or severe immune system disease; (2) Active infection, autoimmune disease, or other systemic conditions that could affect inflammatory markers; (3) Prior exposure to any anti-myeloma regimen (i.e., non-treatment-naive patients); (4) Missing clinical data or follow-up information; and (5) Inability to undergo response assessment after treatment.

The Medical Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University reviewed and approved this study. As per applicable regulations, informed consent in written form was waived due to data being anonymized and reliance on a retrospective design. All procedures were performed in accordance with the guidelines of the Declaration of Helsinki.

Clinical data collection

Clinical data were extracted retrospectively from the hospital's electronic medical records. They were assessed for: (1) Demographic details like age and sex, (2) Staging information at baseline (ISS and R-ISS), (3) Initial treatment (bortezomib-based vs other), (4) Bone destruction status on imaging (X-ray, CT, MR), (5) Laboratory parameters at baseline (Hb, Cr, β2-MG, Alb, %BM PCs), and (6) Follow-up (start date [date of diagnosis], date of last follow-up, time to progression, date of death). OS was defined as the interval from diagnosis to death

from any cause or last follow-up. The follow-up cutoff date was May 2024.

Laboratory measurements

All laboratory tests were performed in the clinical laboratory and nuclear medicine department of our hospital using standardized operating procedures. Peripheral blood cell counts, including absolute neutrophil, lymphocyte, monocyte, and platelet counts, were measured on a Sysmex XN-9000 automated hematology analyzer (Sysmex Corporation, Japan). Absolute neutrophil (ANC) and lymphocyte (ALC) were extracted from complete blood count data for further analysis of the cellular components underlying NLR dynamics. Serum biochemistry markers including creatinine, albumin, and serum calcium were measured on a Beckman Coulter AU5800 automated biochemical analyzer (Beckman Coulter, USA). Hemoglobin and β2-microglobulin were also measured on the above platforms; β2-microglobulin was quantified by immunoturbidimetry. Bone metabolic markers β-CTX, PINP, and BALP were all measured by electrochemiluminescence immunoassay on a Roche Cobas e801 analyzer (Roche, Switzerland). Fasting venous blood samples for all the above markers were collected once within one week before the start of chemotherapy (baseline) and once within four weeks after the end of the last evaluated cycle of chemotherapy (post-treatment). Bone marrow plasma cell percentage was determined by morphological differential counting of bone marrow aspirate smears with a minimum of 200 nucleated cells counted.

Calculation of inflammatory markers and assessment of dynamic changes

Three inflammatory indicators were calculated from peripheral blood cell counts. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The PLR was calculated as the platelet count divided by the absolute lymphocyte count. The LMR was calculated as the absolute lymphocyte count divided by the absolute monocyte count. The dynamic change magnitude (Δ value) for each indicator was defined as the post-treatment value minus the pre-treatment baseline value (Δ = post-treatment value - pre-treatment value). For survival analyses, the derived NLR (dNLR) was used as the primary prognostic indicator. The dNLR is a standardized transformation of the change in NLR from before to after treatment (specific calculation method outlined in Results section). The Δ value definition was similarly applied for calculating the dynamic change magnitudes for other bone metabolic markers (β-CTX, PINP, BALP, serum calcium) too.

Response assessment criteria

Assessment of response to treatment was conducted based on the IMWG uniform response criteria, including stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR). Patients who reached PR or better were classified as being in remission (n = 260), while those who did not reach PR (SD and PD) were classified as non-remission patients (n = 142). Assessment of response was performed after 4 to 6 cycles of the standard induction chemotherapy. It was determined independently by at least two senior hematologists as per laboratory details.

Statistical analysis

Statistical analyses were carried out using R software (version 4.3.2/4.3.3) and SPSS version 26.0. A significance level of $P < 0.05$ was used in the two-tailed test throughout. The procedures are as follows: (1) Descriptive statistics and group comparisons: Normally distributed continuous variables are represented by mean ± standard deviation and compared by independent samples t-test; categorical variables are shown by frequencies (percentages) and compared by chi-square or Fisher's exact test. (2) Within-group comparisons before and after treatment: Paired t-test was applied. (3) Evaluation of the magnitude of dynamic changes (Δ values): Comparisons between groups were made by independent samples t-test and Cohen's d was calculated to assess the discriminative ability. (4) Relationship between dynamic patterns and disease progression: Chi-square or trend chi-square tests were used to evaluate this relationship. (5) Correlation analyses: Pearson or Spearman coefficients were calculated and presented in a correlation matrix. (6) Univariate Cox proportional hazards regression: Variables related to overall survival (OS) were chosen and the results are expressed as hazard ratios (HRs) with 95% confidence intervals

(CIs). Moreover, post-treatment ALC was also evaluated by univariate Cox regression as an indicator of immune recovery. (7) Collinearity diagnostics: Variance inflation factor (VIF), generalized VIF (GVIF) and the corrected measure GVIF^(1/(2×Df)) were calculated for variables with an overall P < 0.1 in univariate analysis. (8) Testing for proportional hazards (PH) assumption: This was performed by Schoenfeld residuals and the scaled Schoenfeld residual plots were generated to show the varying hazard effects with time. (9) In the multiple regression model, candidate variables were selected based on univariate Cox regression (the criterion is P < 0.1) and then collinearity diagnostics. After passing these steps, these variables were entered into the time-varying Cox regression, including the time interaction terms (× log[time + 1]) for those not satisfying the proportional hazards assumption. Time-varying Cox regression: For variables which do not satisfy the PH assumption, time interaction terms (× log[time + 1]) were added and time-varying HR curves were drawn to illustrate the changes of prognostic effects over the follow-up time. (10) Kaplan-Meier survival analysis: Patients were stratified according to the optimal dNLR cut-off; survival curves were compared using the log-rank test. (11) Sensitivity analyses: Robustness was checked by four methods: landmark analysis (excluding patients who died within 6 months of enrollment), trimmed analysis (excluding dNLR values beyond ± 3 standard deviations from the mean), trend analysis (assessing dose-response relationship) and multivariate adjusted analysis (including age, hemoglobin, creatinine, serum albumin, β2-microglobulin, bone marrow plasma cell percentage and R-ISS stage). (12) External validation: All primary analyses including univariate Cox regression, collinearity diagnostics, PH assumption testing, time-varying Cox modeling and Kaplan-Meier analysis were independently repeated in the temporal validation cohort without recalculating the cut-off points or model coefficients. (13) Assessment of model performance and clinical utility: Time-dependent receiver operating characteristic (ROC) curves were constructed using a landmark binary outcome at 36 months, the area under the curve (AUC) and 95% confidence interval (CI) were estimated by the pROC package and DeLong method. Calibration was evaluated by comparing the predicted 36-month event probabilities with the observed (Kaplan-Meier) probabilities in quintiles of predicted risk, supplemented by Hosmer-Lemeshow goodness-of-fit test and Brier score. Decision curve analysis (DCA) was performed to evaluate the net benefit of the model-based treatment strategy at various threshold probabilities. All evaluations were carried out separately in the derivation and validation cohorts.

Results

Comparison of baseline clinical characteristics between remission and non-remission groups

Statistically significant differences were found between the remission and non-remission groups in ISS staging (P < 0.001) and R-ISS staging (P = 0.003), with the non-remission group having a higher proportion of advanced-stage patients. Significant differences were also noted for hemoglobin (P < 0.001), creatinine (P < 0.001), β2-microglobulin (P < 0.001), serum albumin (P < 0.001), and bone marrow plasma cell percentage (P < 0.001). The frequency of bone destruction was higher in the non-remission group (P = 0.001). Follow-up duration (P < 0.001) and progression/death status (P < 0.001) also differed significantly between groups. In contrast, age (P = 0.094), sex (P = 0.479), and treatment regimen (P = 0.432) did not differ significantly between groups (all P > 0.05) (**Table 1**).

Changes in inflammatory markers before and after treatment

Within the remission group, NLR decreased significantly after treatment (P < 0.001), as did NLR in the non-remission group (P < 0.001). However, pre-treatment and post-treatment NLR did not differ significantly between groups (both P > 0.05). PLR decreased significantly after treatment in the remission group (P < 0.001) but showed no significant change in the non-remission group (P = 0.354). Pre-treatment PLR did not differ between groups (P = 0.919), while post-treatment PLR differed significantly (P < 0.001). LMR increased significantly after treatment in the remission group (P < 0.001) but declined significantly in the non-remission group (P < 0.001). Pre-treatment LMR did not differ between groups (P = 0.530), whereas post-treatment LMR differed significantly (P < 0.001) (**Figure 1**).

Table 1. Comparison of baseline clinical characteristics between the remission and non-remission groups

Characteristic	Remission group (n = 260)	Non-remission group (n = 142)	Statistic	*P* value
Age (years)	62.3 ± 9.0	64.1 ± 10.7	-1.682	0.094
Sex			0.500	0.479
Male	148 (56.92%)	86 (60.56%)		
Female	112 (43.08%)	56 (39.44%)		
ISS staging			15.927	< 0.001
Stage I	72 (27.69%)	18 (12.68%)		
Stage II	118 (45.38%)	64 (45.07%)		
Stage III	70 (26.92%)	60 (42.25%)		
R-ISS staging			11.362	0.003
Stage I	27 (10.38%)	6 (4.23%)		
Stage II	169 (65.00%)	81 (57.04%)		
Stage III	64 (24.62%)	55 (38.73%)		
Treatment regimen			0.617	0.432
Bortezomib-based	182 (70.00%)	94 (66.20%)		
Other regimens	78 (30.00%)	48 (33.80%)		
Hemoglobin (g/L)	102.3 ± 18.8	94.9 ± 16.8	4.007	< 0.001
Creatinine (μmol/L)	101.5 ± 34.2	120.7 ± 44.1	-4.511	< 0.001
β2-microglobulin (mg/L)	4.6 ± 1.4	5.6 ± 2.2	-4.820	< 0.001
Serum albumin (g/L)	36.0 ± 5.1	32.5 ± 5.2	6.456	< 0.001
Bone marrow plasma cell percentage (%)	35.6 ± 15.3	45.5 ± 17.4	-5.705	< 0.001
Bone destruction			10.764	0.001
Present	168 (64.62%)	114 (80.28%)		
Absent	92 (35.38%)	28 (19.72%)		
Follow-up duration (months)	44.2 ± 15.6	31.7 ± 19.8	6.525	< 0.001
Progression/death	78 (30.00%)	86 (60.56%)	35.520	< 0.001

Note: ISS, International Staging System; R-ISS, Revised International Staging System; β2-MG, Beta-2 microglobulin. Continuous variables are presented as mean ± standard deviation; categorical variables as n (%).

Changes in bone metabolic markers before and after treatment

Within the remission group, β-CTX levels decreased significantly after treatment ($P < 0.001$), whereas they increased significantly in the non-remission group ($P < 0.001$). Pre-treatment β-CTX did not differ between groups ($P = 0.641$), while post-treatment levels differed significantly ($P < 0.001$). PINP declined significantly after treatment in the remission group ($P < 0.001$) but showed no significant change in the non-remission group ($P = 0.408$). Pre-treatment PINP did not differ between groups ($P = 0.842$), whereas post-treatment PINP differed significantly ($P < 0.001$). BALP decreased significantly after treatment in both groups, though the reduction was more pronounced in the remission group (remission: $P < 0.001$; non-remission: $P = 0.044$). Pre-treatment BALP differed significantly between groups ($P < 0.001$), and the difference remained significant post-treatment ($P < 0.001$). Serum calcium decreased significantly after treatment in the remission group ($P < 0.001$) but rose significantly in the non-remission group ($P = 0.002$). Pre-treatment and post-treatment serum calcium both differed significantly between groups (both $P < 0.001$) (**Figure 2**).

Comparison of dynamic change magnitudes for inflammatory and bone metabolic markers

Further comparison of pre-to-post-treatment change magnitudes revealed that ΔPLR ($P < 0.001$), ΔLMR ($P < 0.001$), Δβ-CTX ($P < 0.001$), ΔPINP ($P < 0.001$), ΔBALP ($P < 0.001$), and ΔSerum calcium ($P < 0.001$) all differed significantly between the remission and non-remission groups. The remission group showed more

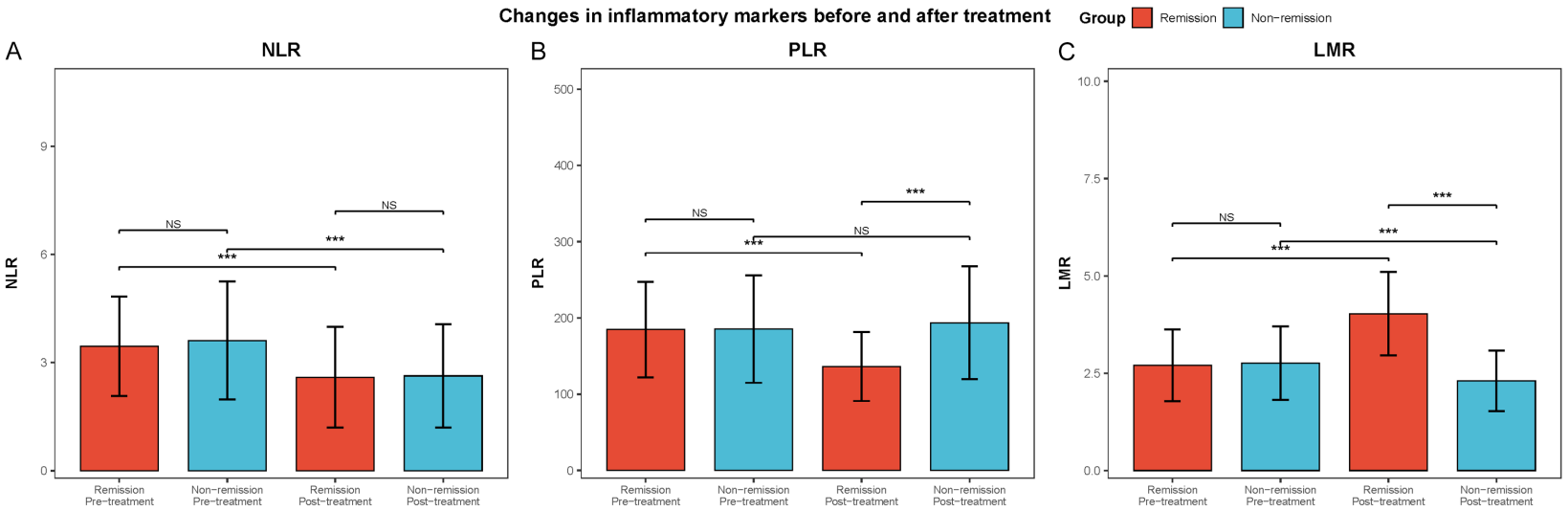


Figure 1. Comparison of changes in inflammatory markers before and after treatment between the remission and non-remission groups. A. Changes in NLR before and after treatment in the remission and non-remission groups. B. Changes in PLR before and after treatment in the remission and non-remission groups. C. Changes in LMR before and after treatment in the remission and non-remission groups. Note: NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; NS, Not significant; ***P < 0.001.

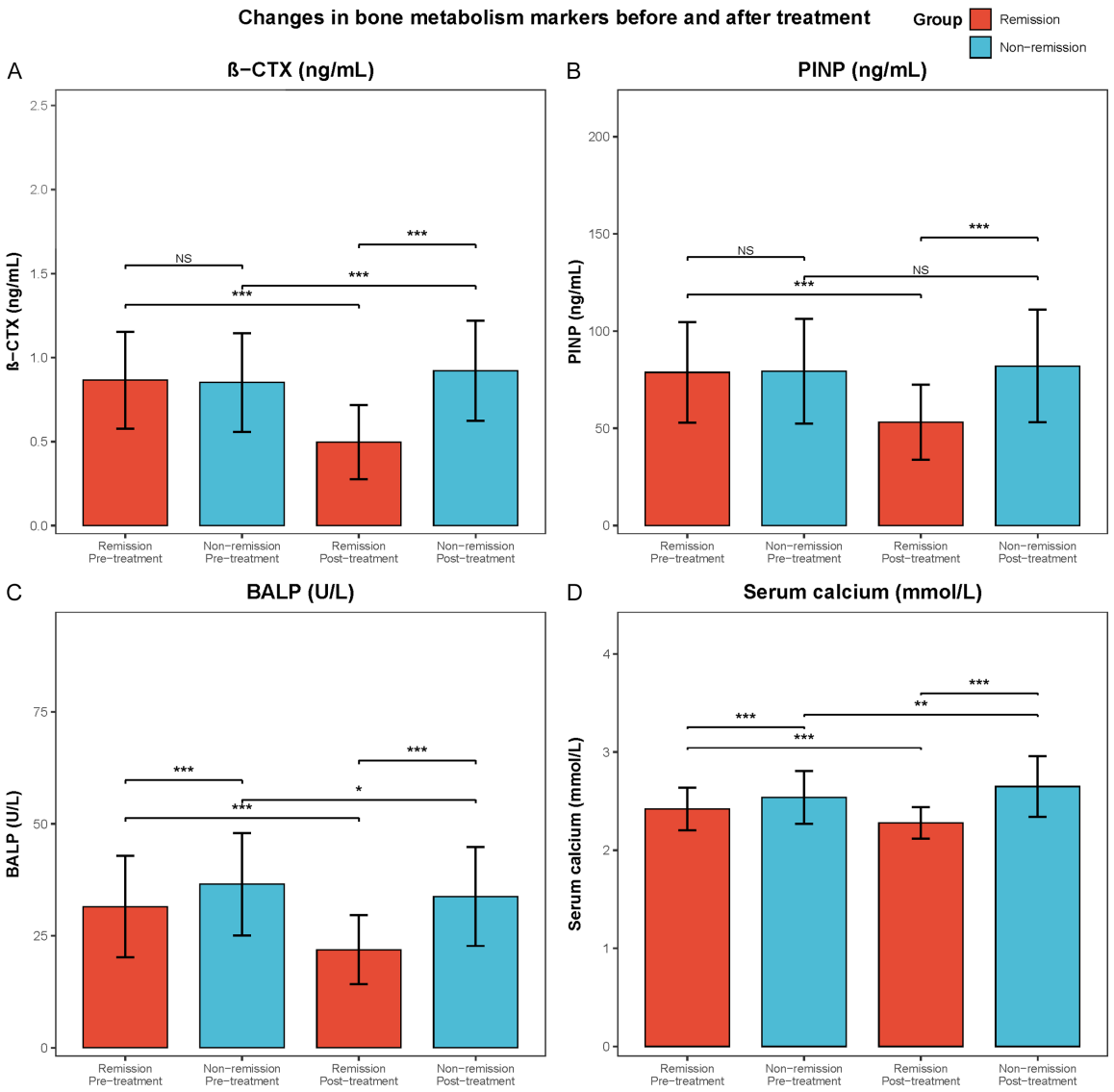


Figure 2. Comparison of changes in bone metabolic markers before and after treatment between the remission and non-remission groups. A. Changes in β-CTX before and after treatment in the remission and non-remission groups. B. Changes in PINP before and after treatment in the remission and non-remission groups. C. Changes in BALP before and after treatment in the remission and non-remission groups. D. Changes in serum calcium before and after treatment in the remission and non-remission groups. Note: β-CTX, Beta C-terminal telopeptide of type I collagen; PINP, Procollagen type I N-terminal propeptide; BALP, Bone-specific alkaline phosphatase; Ca, Serum calcium; NS, Not significant; *P < 0.05; **P < 0.01; ***P < 0.001.

marked decreases in PLR, β-CTX, PINP, BALP, and serum calcium, along with a more pronounced increase in LMR. By contrast, ΔNLR did not differ significantly between groups (P = 0.616) (**Figure 3**).

Selection of candidate dynamic indicators and their relationship to disease progression

After screening the candidate dynamic indicators, all except ΔNLR showed statistically significant between-group differences: ΔPLR (P < 0.001), ΔLMR (P < 0.001), Δβ-CTX (P < 0.001), ΔPINP (P < 0.001), ΔBALP (P < 0.001), and ΔSerum calcium (P < 0.001). Based on standardized effect sizes, Δβ-CTX had the strongest discriminatory capacity, followed by ΔLMR, while ΔNLR had the smallest effect size. Analysis of dynamic patterns for selected indicators showed that NLR patterns were significantly associated with disease progression (overall trend P < 0.001), with patients showing

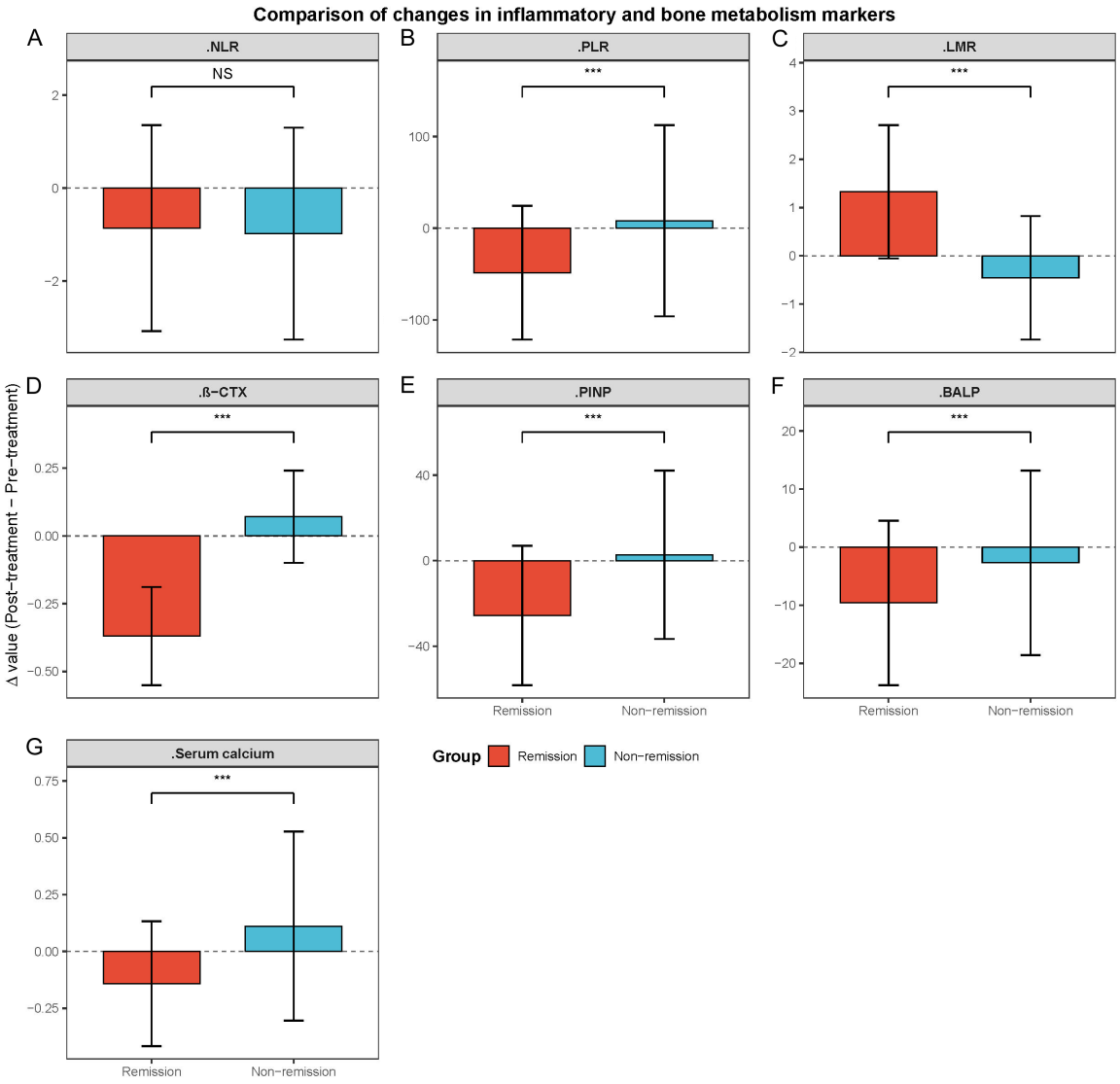


Figure 3. Comparison of the dynamic change magnitudes of inflammatory and bone metabolic markers between the remission and non-remission groups. A. ΔNLR between the remission and non-remission groups. B. ΔPLR between the remission and non-remission groups. C. ΔLMR between the remission and non-remission groups. D. Δβ-CTX between the remission and non-remission groups. E. ΔPINP between the remission and non-remission groups. F. ΔBALP between the remission and non-remission groups. G. ΔSerum calcium between the remission and non-remission groups. Note: ΔNLR, Delta neutrophil-to-lymphocyte ratio; ΔPLR, Delta platelet-to-lymphocyte ratio; ΔLMR, Delta lymphocyte-to-monocyte ratio; Δβ-CTX, Delta beta C-terminal telopeptide of type I collagen; ΔPINP, Delta pro-collagen type I N-terminal propeptide; ΔBALP, Delta bone-specific alkaline phosphatase; ΔCa, Delta serum calcium; NS, Not significant; ***P < 0.001.

NLR decline having a higher progression rate than those with NLR increase. LMR dynamic patterns were similarly associated with disease progression (P = 0.018), with progression risk generally declining as LMR shifted from a falling to a rising trajectory. The study showed that the patterns of β-CTX were also significantly associated with disease progression (P < 0.001); those whose β-CTX were declining had a lowered risk of progression whereas those with stable or rising β-CTX had an increased risk. The findings from our study highlight that dynamic indicators exhibiting profound changes, particularlyβ-CTX and LMR, will be of great value for disease progression monitoring (**Figure 4**).

Correlation between dynamic indicators and baseline clinical characteristics

Correlation analysis showed that ΔNLR was negatively correlated with ΔLMR (r = -0.492, P

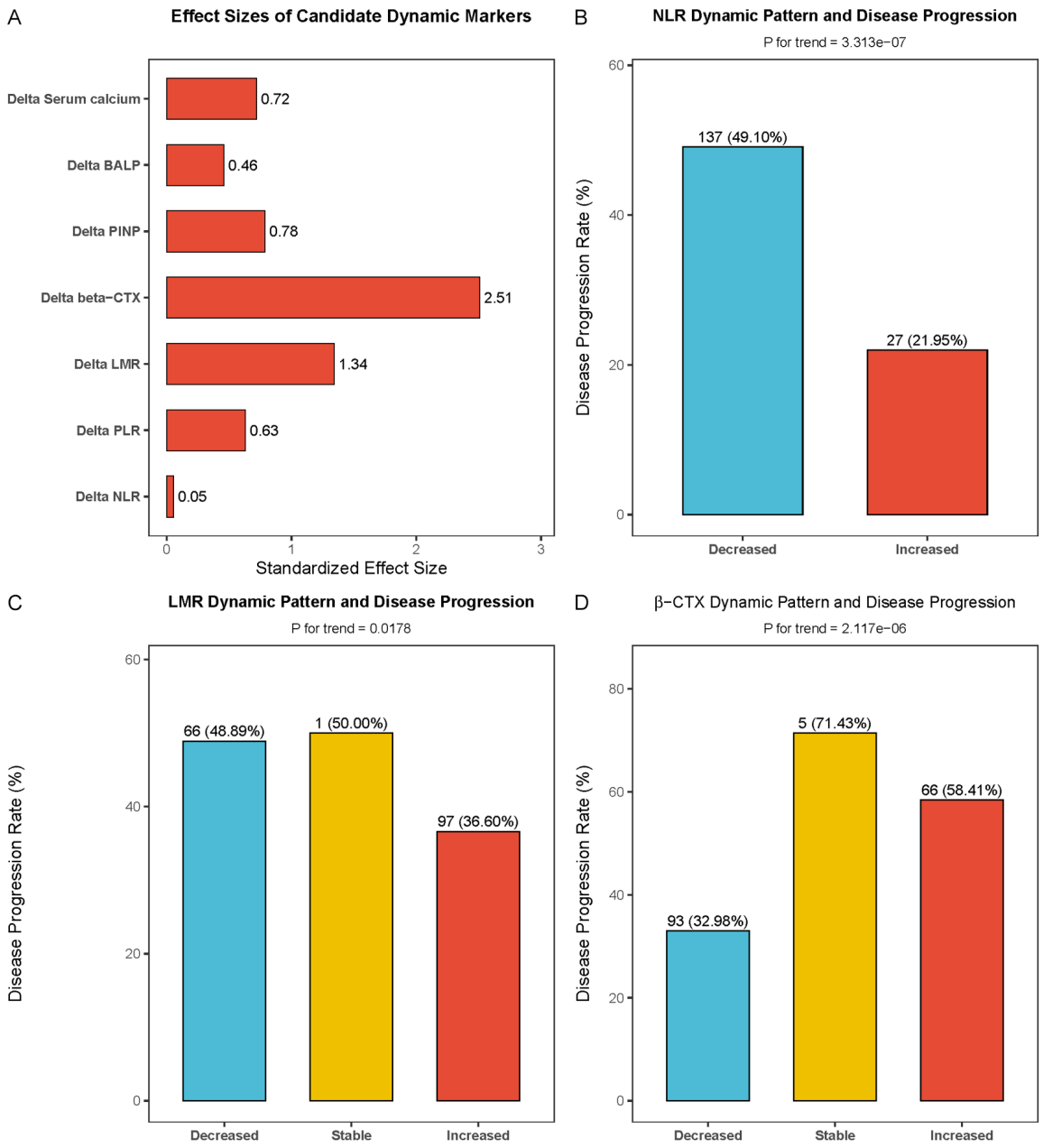


Figure 4. Selection of candidate dynamic indicators and their relationship with disease progression. A. Comparison of standardized effect sizes for candidate dynamic indicators. B. Relationship between NLR dynamic patterns and disease progression. C. Relationship between LMR dynamic patterns and disease progression. D. Relationship between β-CTX dynamic patterns and disease progression. Note: ΔNLR, Delta neutrophil-to-lymphocyte ratio; ΔPLR, Delta platelet-to-lymphocyte ratio; ΔLMR, Delta lymphocyte-to-monocyte ratio; Δβ-CTX, Delta beta C-terminal telopeptide of type I collagen; ΔPINP, Delta procollagen type I N-terminal propeptide; ΔBALP, Delta bone-specific alkaline phosphatase; ΔCa, Delta serum calcium; NS, Not significant.

< 0.001) and positively correlated with Δβ-CTX ($r = 0.230$, $P < 0.001$). ΔNLR was also positively correlated with hemoglobin ($r = 0.261$, $P < 0.001$), creatinine ($r = 0.117$, $P = 0.019$), and serum albumin ($r = 0.168$, $P < 0.001$), while it correlated negatively with β2-microglobulin ($r = -0.139$, $P = 0.005$), bone marrow plasma cell percentage ($r = -0.233$, $P < 0.001$), and R-ISS staging ($r = -0.204$, $P < 0.001$). ΔLMR correlated negatively with Δβ-CTX ($r = -0.308$, $P < 0.001$) and with hemoglobin ($r = -0.105$, $P = 0.035$). Δβ-CTX correlated positively with creati-

nine (r = 0.138, P = 0.006) and negatively with serum albumin (r = -0.129, P = 0.010). Hemoglobin correlated negatively with β2-microglobulin (r = -0.101, P = 0.044) and positively with serum albumin (r = 0.156, P = 0.002); it was inversely associated with bone marrow plasma cell percentage (r = -0.201, P < 0.001), ISS staging (r = -0.169, P < 0.001), and R-ISS staging (r = -0.195, P < 0.001). β2-microglobulin correlated positively with ISS staging (r = 0.417, P < 0.001) and R-ISS staging (r = 0.856, P < 0.001). Serum albumin correlated negatively with bone marrow plasma cell percentage (r = -0.278, P < 0.001) and R-ISS staging (r = -0.134, P = 0.007). Bone marrow plasma cell percentage correlated positively with R-ISS staging (r = 0.135, P = 0.007), and ISS correlated positively with R-ISS staging (r = 0.502, P < 0.001). Treatment regimen correlated negatively with bone destruction (r = -0.101, P = 0.043). No other correlations reached statistical significance (all P > 0.05) (**Figure 5**).

Univariate cox regression and collinearity diagnostics

Univariate Cox regression showed that R-ISS stage III compared to stage I was significantly associated with a higher mortality risk (P < 0.001), whereas stage II versus stage I did not reach significance (P = 0.215). Among dynamic indicators, both the derived neutrophil-to-lymphocyte ratio (dNLR) (P < 0.001) and derived β-C-terminal telopeptide of type I collagen (dBCTX) (P < 0.001) were significantly associated with overall survival (OS), indicating prognostic relevance for both. Albumin (P < 0.001), hemoglobin (P = 0.001), and bone marrow plasma cell percentage (P = 0.014) also showed significant associations with OS. In contrast, dLMR (P = 0.143), sex (P = 0.241), creatinine (P = 0.404), bone destruction (P = 0.791), treatment regimen (P = 0.846), and age (P = 0.956) did not reach statistical significance (all P > 0.05, **Figure 6A**). Collinearity diagnostics for variables with an overall P < 0.1 in univariate analysis found that VIF or corrected GVIF values for dNLR, albumin, bone marrow plasma cell percentage, hemoglobin, dBCTX, and R-ISS staging were all low, indicating no substantial multicollinearity. These variables were therefore eligible for inclusion in subsequent multivariable analyses (**Figure 6B**).

Proportional hazards assumption testing for candidate multivariable cox regression model

Proportional hazards testing for candidate variables in the multivariable model showed that dBCTX satisfied the proportional hazards assumption (P = 0.679). In contrast, dNLR (P < 0.001), bone marrow plasma cell percentage (P < 0.001), albumin (P < 0.001), hemoglobin (P < 0.001), and R-ISS staging (P < 0.001) all violated this assumption. The global test also indicated that the overall model did not satisfy proportional hazards (P < 0.001). Scaled Schoenfeld residual plots confirmed that regression coefficients for dNLR, bone marrow plasma cell percentage, albumin, hemoglobin, and R-ISS staging showed clear trends over time, while dBCTX was relatively stable. These results indicated that the candidate multivariable Cox model exhibited time-dependent effects, restricting the applicability of a conventional proportional hazards model. Subsequent analyses therefore incorporated time interaction terms or stratified modeling approaches (**Figure 7A-G**).

Time-varying cox regression analysis

After accounting for time-dependent effects, the time-varying Cox regression showed that the baseline effect of dNLR was significantly associated with OS (P < 0.001), and its interaction with time was also statistically significant (P < 0.001), indicating that the influence of dNLR on mortality risk changed as follow-up progressed. dBCTX, entered as a proportional hazards term, remained significantly associated with OS (P < 0.001). The baseline effect of albumin was associated with OS (P = 0.026), with a significant time interaction (P = 0.018), indicating that the prognostic impact of albumin was not constant over time. Similarly, the baseline effect of hemoglobin was significantly associated with OS (P < 0.001), and its time interaction was significant (P < 0.001), indicating a non-constant hazard effect (**Figure 8A**). The baseline effect and time interaction for bone marrow plasma cell percentage were both non-significant (P = 0.574 and P = 0.249, respectively). Time-varying hazard curves showed that the hazard effect corresponding to dNLR grew stronger with increasing follow-up time; hazard effects for albumin and hemoglobin also showed dynamic patterns, whereas the

Dynamic blood markers in multiple myeloma

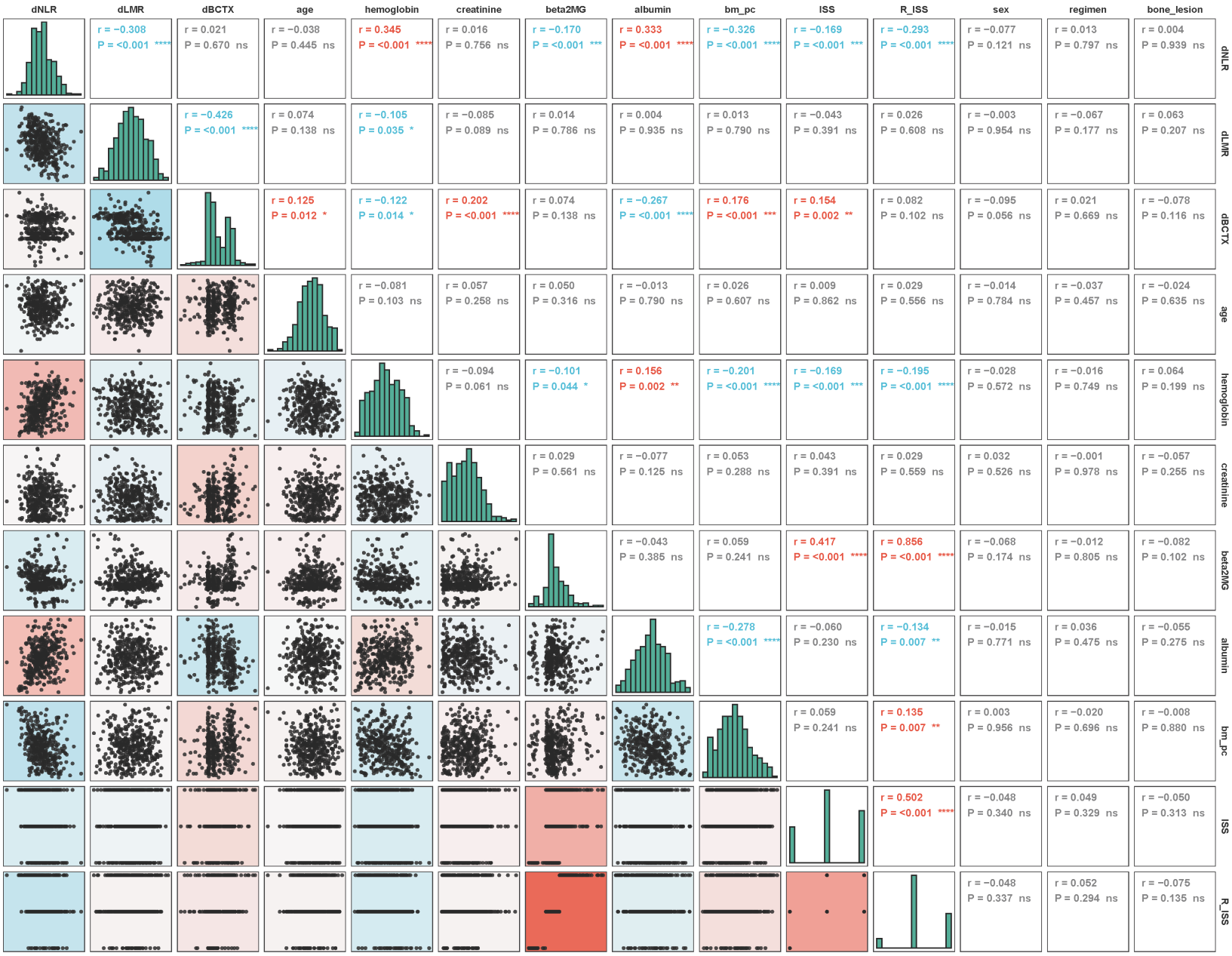


Figure 5. Correlation matrix of dynamic indicators and baseline clinical characteristics. A. Distribution histograms for each variable. B. Pairwise scatter plots for each variable. C. Pairwise correlation coefficients and corresponding *P* values. Note: ΔNLR, Delta neutrophil-to-lymphocyte ratio; ΔLMR, Delta lymphocyte-to-monocyte ratio; Δβ-CTX, Delta beta C-terminal telopeptide of type I collagen; Hb, Hemoglobin; β2-MG, Beta-2 microglobulin; R-ISS, Revised International Staging System; ISS, International Staging System; ns, Not significant; *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

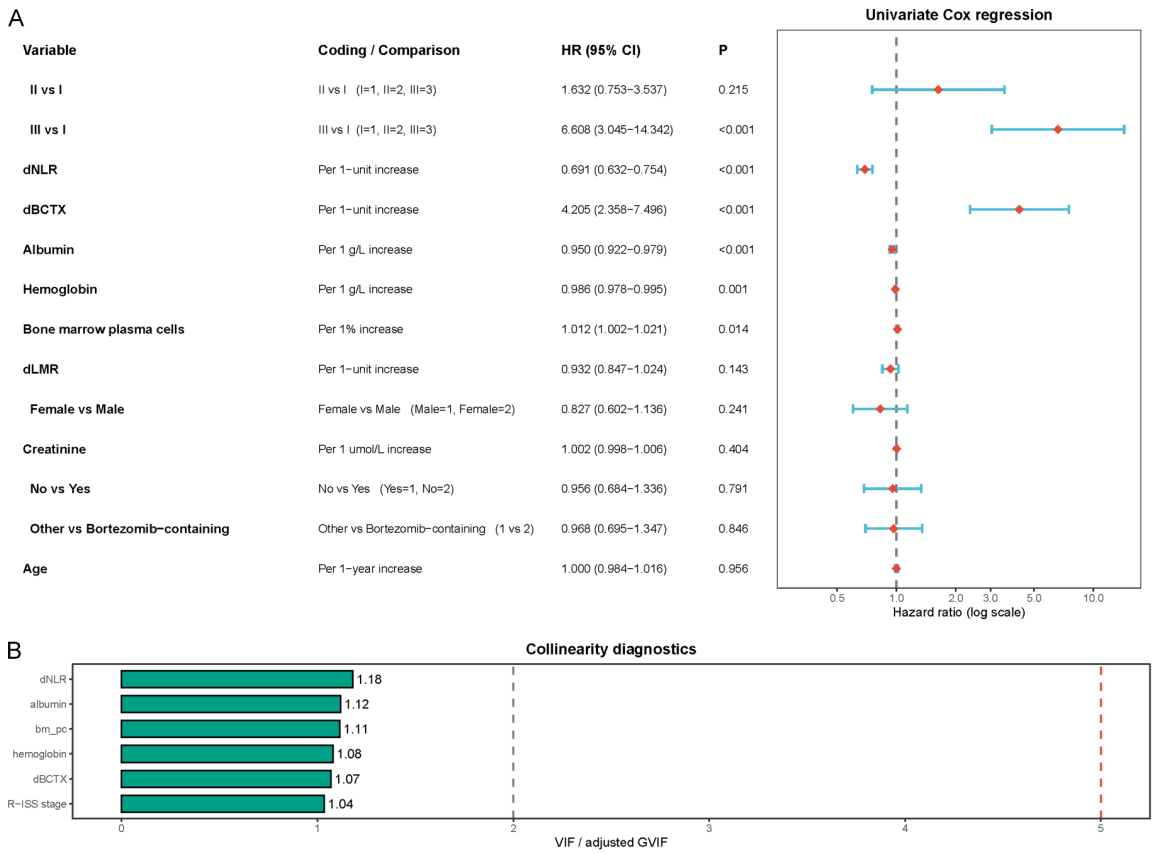


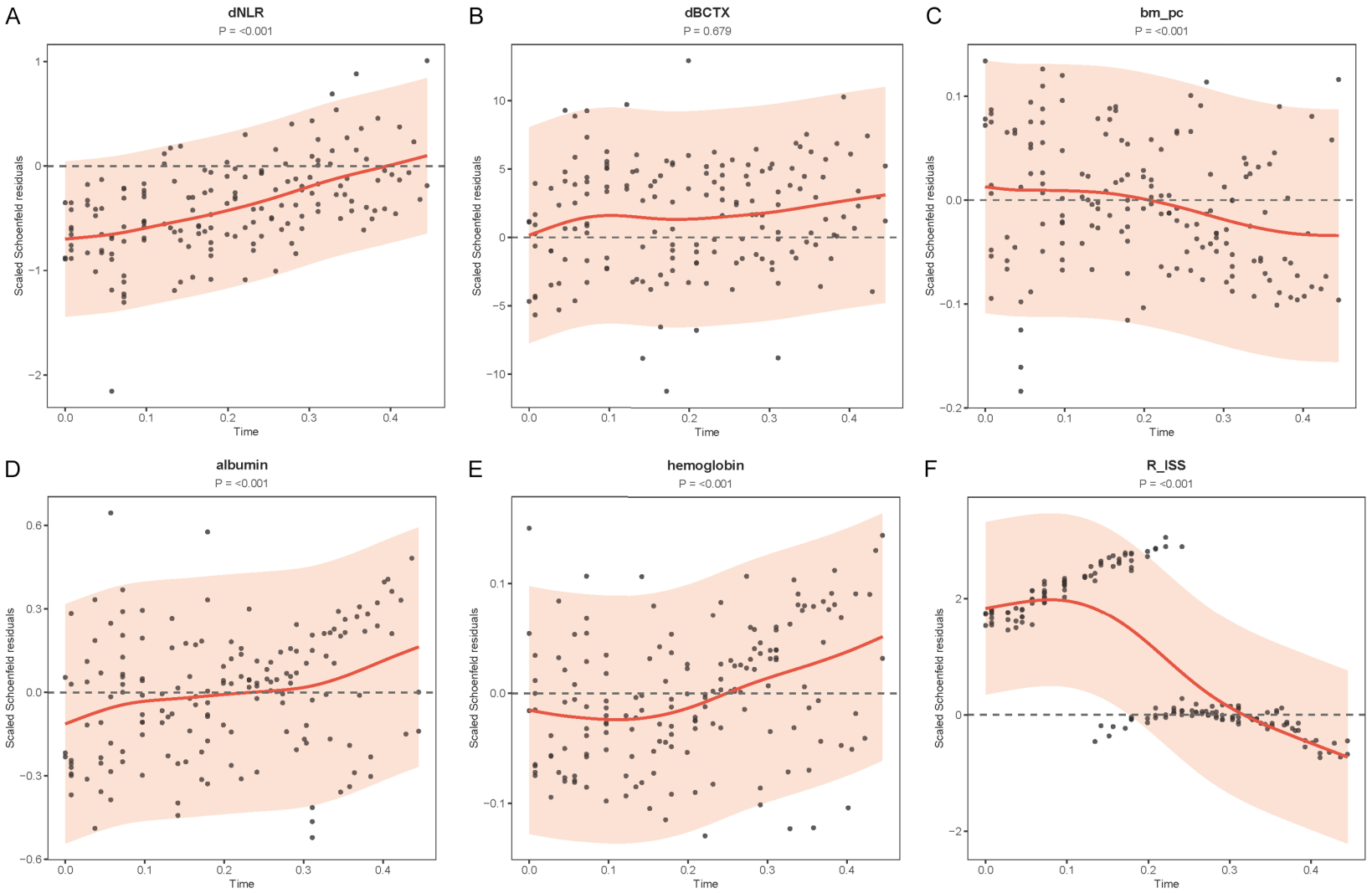
Figure 6. Univariate Cox regression analysis and collinearity diagnostics. A. Forest plot of univariate Cox regression for each candidate variable. B. Collinearity diagnostic results for variables with an overall P < 0.1. Note: HR, Hazard ratio; CI, Confidence interval; dNLR, Derived neutrophil-to-lymphocyte ratio; dLMR, Delta lymphocyte-to-monocyte ratio; dBCTX, Delta beta C-terminal telopeptide of type I collagen; R-ISS, Revised International Staging System; VIF, Variance inflation factor; GVIF, Generalized variance inflation factor.

effect for bone marrow plasma cell percentage was relatively flat. Collectively, these findings indicate that dNLR, albumin, and hemoglobin exhibit marked time-dependent prognostic effects in MM, while dBCTX maintains a consistently significant and stable prognostic signal throughout the model (**Figure 8B**).

Prognostic value of dNLR dynamic stratification, R-ISS subgroup analysis, and time-varying effects

After stratifying patients by the optimal dNLR cutoff, the differences in OS across risk groups were statistically significant (log-rank P < 0.001). Overall, patients with rising dNLR had the best OS, followed by those with stable dNLR, while those with declining dNLR had the poorest outcomes - demonstrating that dNLR dynamics can effectively stratify survival risk in MM patients. Further comparisons confirmed that low- and intermediate-risk groups had consistently better outcomes than the high-risk group, with a clear gradient in 3-year OS rates (**Figure 9A**).

Stratified Cox regression showed that dNLR was significantly associated with OS in R-ISS stage III patients (P < 0.001) but not in R-ISS stage I-II patients (P = 0.561). Findings from interaction tests were indicative of significant heterogeneity in the prognostic value of dNLR across R-ISS subgroups (P < 0.001). This finding suggests that the prognostic value of dNLR is dependent on disease stage (**Figure 9B**). Examination of the time-varying effect analysis revealed that the hazard effect of dNLR on mortality strengthened over follow-up time. During early follow-up, the hazard ratio associated with dNLR was about 1, and as time progressed it became greater than 1. This suggests that the prognostic impact of dNLR is significantly time-depen-


A
dNLR
P = <0.001
B
dBCTX
P = 0.679
C
bm_pc
P = <0.001
D
albumin
P = <0.001
E
hemoglobin
P = <0.001
F
R_ISS
P = <0.001
Scaled Schoenfeld residuals
Time

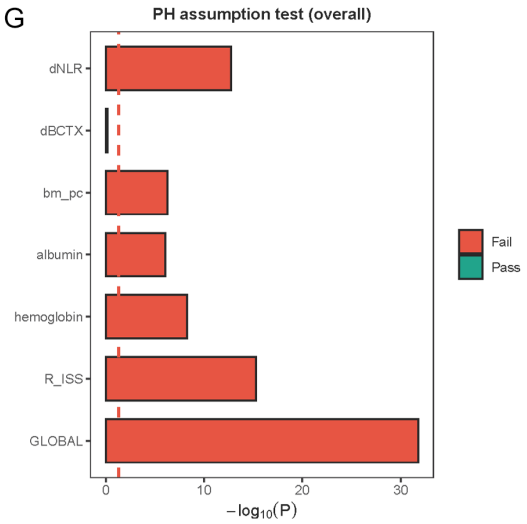
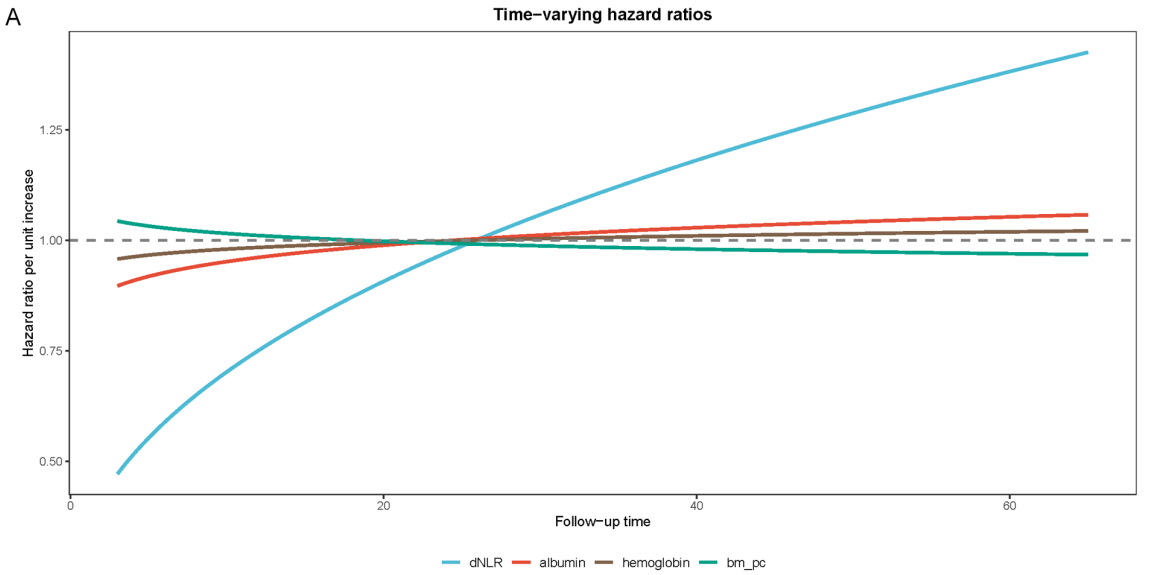


Figure 7. Proportional hazards assumption testing for the candidate multivariable Cox regression model. A. Scaled Schoenfeld residual plot for dNLR. B. Scaled Schoenfeld residual plot for dBCTX. C. Scaled Schoenfeld residual plot for bone marrow plasma cell percentage. D. Scaled Schoenfeld residual plot for albumin. E. Scaled Schoenfeld residual plot for hemoglobin. F. Scaled Schoenfeld residual plot for R-ISS staging. G. Proportional hazards assumption test results for individual variables and the overall model. Note: PH, Proportional hazards; SSR, Scaled Schoenfeld residuals; dNLR, Derived neutrophil-to-lymphocyte ratio; dBCTX, Delta beta C-terminal telopeptide of type I collagen; bm_pc, Bone marrow plasma cells; Alb, Albumin; Hb, Hemoglobin; R-ISS, Revised International Staging System.



B

Variable	Interpretation	Coef (95% CI)	P
dNLR	Baseline effect	−1.300 (−1.697 to −0.902)	<0.001
dBCTX	PH term	1.441 (0.754 to 2.127)	<0.001
Bone marrow plasma cells	Baseline effect	0.080 (0.038 to 0.122)	<0.001
Albumin	Baseline effect	−0.191 (−0.337 to −0.044)	0.011
Hemoglobin	Baseline effect	−0.075 (−0.119 to −0.031)	<0.001
dNLR × log(time+1)	Time interaction	0.395 (0.269 to 0.521)	<0.001
bm_pc × log(time+1)	Time interaction	−0.027 (−0.041 to −0.013)	<0.001
albumin × log(time+1)	Time interaction	0.059 (0.013 to 0.105)	0.012
hemoglobin × log(time+1)	Time interaction	0.023 (0.009 to 0.037)	0.001

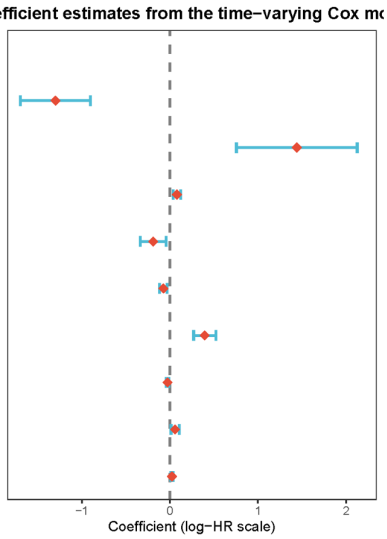


Figure 8. Results of time-varying Cox regression analysis. A. Time-varying hazard ratio curves for dNLR, albumin, hemoglobin, and bone marrow plasma cell percentage. B. Coefficient estimates and 95% CIs for each variable in the time-varying Cox model. Note: TVCM, Time-varying Cox model; HR, Hazard ratio; CI, Confidence interval; dNLR, Derived neutrophil-to-lymphocyte ratio; dBCTX, Delta beta C-terminal telopeptide of type I collagen; bm_pc, Bone marrow plasma cells; Alb, Albumin; Hb, Hemoglobin.

dent. In later follow-up, dNLR had more risk stratifying ability (**Figure 9C**).

Sensitivity analysis of the association between dNLR and overall survival

The relationship between dNLR and OS was consistently observed across analyses. The dNLR proved to be a significant predictor of overall survival (OS) in the primary analysis ($P < 0.001$). In landmark analysis, this association remained significant after excluding patients who died within 6 months ($P < 0.001$). Removing dNLR values outside ± 3 standard deviations in the trimmed analysis resulted in similarly robust results ($P < 0.001$). When we divided the patients into tertiles of dNLR for trend analysis, the survival risk differences between tertile levels were still significant ($P < 0.001$). The independent association between dNLR and OS remained significant after further adjustments for covariates including age, hemoglobin, creatinine, serum albumin, β2-microglobulin, bone marrow plasma cell percentage, and R-ISS staging ($P < 0.001$), indicating that this indicator was reliable and stable (**Table 2**).

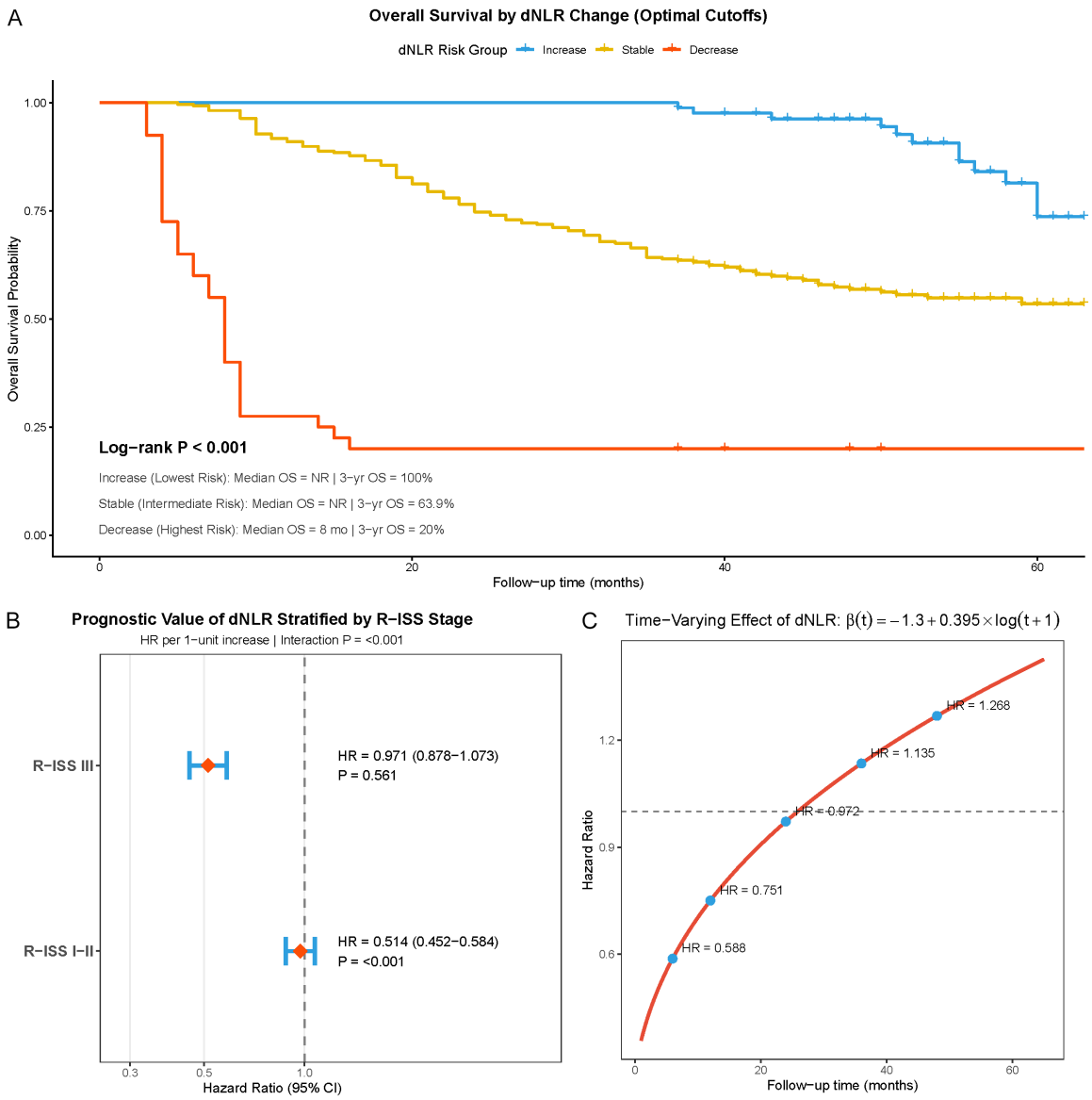


Figure 9. Prognostic value of dNLR dynamic stratification, R-ISS subgroup analysis, and time-varying effect analysis. A. Kaplan-Meier overall survival curves for different dNLR dynamic risk groups. B. Forest plot of the prognostic value of dNLR across different R-ISS subgroups. C. Time-varying hazard ratio curve for dNLR over follow-up time. Note: dNLR, Derived neutrophil-to-lymphocyte ratio; OS, Overall survival; R-ISS, Revised International Staging System; HR, Hazard ratio; CI, Confidence interval; NR, Not reached.

Temporal external validation of dNLR and dBCTX

The temporal validation cohort comprised 218 patients (median follow-up 53.0 months) with 103 deaths. Baseline characteristics were comparable to the derivation cohort (Table S1). Univariate Cox regression confirmed that dNLR (HR 0.595, 95% CI 0.528-0.670, P < 0.001), dBCTX (HR 3.911, 95% CI 1.938-7.891, P < 0.001), R-ISS stage (III vs. I: HR 8.58, P = 0.003), albumin (HR 0.935, P < 0.001), hemoglobin (HR 0.987, P = 0.016), and bone marrow plasma cell percentage (HR 1.022, P < 0.001) were significantly associated with OS (Figure S1A-F). dLMR, age, sex, creatinine, treatment regimen, and bone lesions were not significant. Collinearity diagnostics showed low variance inflation factors for all candidates (all GVIF^(1/(2×Df)) < 2; Figure S1G).

Proportional hazards testing (Figure S2A) revealed that dBCTX satisfied the assumption (P = 0.322), whereas dNLR, albumin, hemoglobin,

Table 2. Sensitivity analysis of the association between dNLR and overall survival

Analysis	N	HR	95% CI (lower)	95% CI (upper)	*P* value
Primary analysis (all patients)	402	0.691	0.632	0.754	< 0.001
Landmark analysis (excluding deaths ≤ 6 months)	384	0.751	0.686	0.822	< 0.001
Trimmed analysis (excluding dNLR ± 3 SD)	400	0.693	0.633	0.759	< 0.001
Tertile trend analysis (per 1 tertile increase)	402	0.520	0.427	0.632	< 0.001
Multivariable-adjusted analysis*	402	0.693	0.630	0.763	< 0.001

Note: dNLR, Derived neutrophil-to-lymphocyte ratio; HR, Hazard ratio; CI, Confidence interval; SD, Standard deviation; R-ISS, Revised International Staging System. *Multivariable-adjusted model includes age, hemoglobin, creatinine, serum albumin, β2-microglobulin, bone marrow plasma cell percentage, and R-ISS staging.

and R-ISS stage violated it (all P < 0.05; global P < 0.001). In the time-varying Cox model (Figure S2B), dNLR had a significant baseline effect (coef -1.646, P < 0.001) and a significant time interaction (coef +0.395, P < 0.001), indicating strengthening protection over follow-up. dBCTX was a stable PH term (coef +1.134, P = 0.003). In Kaplan-Meier analysis, where the study participants were divided using the same dNLR stratification, there was confirmation of the positive discrimination of survival (log-rank P < 0.001). Sensitivity analyses (landmark, trimmed, multivariable-adjusted) all provided support for robustness (all P < 001).

Model discrimination, calibration, and clinical utility

Time-dependent ROC analysis at 36 months identified the dNLR, dBCTX, albumin, haemoglobin, bone marrow plasma cell percentage and R-ISS stage Cox model as having good prognostic accuracy. The AUC in the derivation cohort was found to be 0.831 (Figure 3A). In the temporal validation cohort, we observed a similar AUC of 0.856 (95% CI 0.805-0.907; Figure S3D), and the difference between the two AUCs was not significant (DeLong test, P = 0.464), confirming good discrimination.

Calibration plots, comparing predicted 36-month event probabilities with Kaplan-Meier observed probabilities stratified by quintiles of predicted risk, are shown in Figure S3B and S3E. In both cohorts, the predicted and observed probabilities generally tracked along the diagonal, although the Hosmer-Lemeshow goodness-of-fit test yielded a significant *P*-value (< 0.001) in both cohorts, a result that likely reflects the large sample size and the use of quintile grouping rather than clinically important miscalibration. The Brier scores were 0.174 and 0.163 for the derivation and validation cohorts, respectively, indicating acceptable overall prediction accuracy.

Decision curve analysis demonstrated that the integrated model provided a higher net benefit than the "treat all" or "treat none" strategies across a wide range of threshold probabilities in both the derivation cohort (Figure S3C) and the validation cohort (Figure S3F). For example, at threshold probabilities of 10%, 20%, and 30%, the model's net benefit in the derivation cohort exceeded that of treating all by +0.009, +0.039, and +0.108, respectively; the corresponding improvements in the validation cohort were +0.008, +0.033, and +0.089. The model showed net benefit superiority over the "treat all" strategy across the entire range of thresholds from 1% to 80% in both cohorts, supporting the clinical utility of the risk-based model for guiding 3-year survival-related decisions in patients with MM.

Absolute neutrophil and lymphocyte counts underlying NLR dynamics

To further elucidate the drivers of NLR dynamics, we analyzed the ANC and ALC that constitute NLR (Figure S4). In the remission group, ANC decreased from 5.05 ± 2.62 × 10^9/L at baseline to 2.28 ± 1.09 × 10^9/L after treatment, while ALC decreased mildly from 2.53 ± 1.05 × 10^9/L to 2.24 ± 0.95 × 10^9/L, remaining within the normal range. In the non-remission group, pre-treatment ANC (2.02 ± 0.94 × 10^9/L) was already significantly lower than in the remission group (P < 0.001) and declined further to 0.85 ± 0.37 × 10^9/L after treatment, indicating profound chemotherapy-induced myelosuppression. Similarly, ALC in the non-remission group dropped from 2.08 ± 0.81 × 10^9/L to 0.72 ± 0.32 × 10^9/L, reflecting severe immune depletion. The differences between the patterns suggest that while the decline of

NLR seems to be similar in the two groups, it is on account of different biological reasons - resolution of inflammation with preservation of marrow reserve in remission group, and aggravated myelosuppression and immune exhaustion in the non-remission group. According to the univariate analysis of Cox regression, ALC after treatment was found to be significantly associated with OS (HR 0.767, 95% CI 0.656-0.897, P < 0.001).

Discussion

This study systematically evaluated the value of dynamic changes in inflammatory and bone metabolic markers for disease monitoring and prognosis in MM. Dynamic metrics ΔPLR, ΔLMR, and Δβ-CTX successfully differentiated responders from non-responders in treatment. Δβ-CTX had the highest standardized effect size showing that it was the most sensitive dynamic marker for efficacy. At the prognostic level, both dNLR and dBCTX independently predicted OS in patients with multiple myeloma. The prognostic effect of the dNLR evidently has time dependence and it was most pronounced in high-risk R-ISS stage III patients. Our findings support the development of a prognostic evaluation framework for MM based on dynamic peripheral blood indicators.

Clinical significance of baseline differences between remission and non-remission groups

In the current research, non-remission patients exhibited a significantly greater ISS and R-ISS stage, percentage of plasma cells in bone marrow, creatinine, and β2-microglobulin, as well as lower levels of hemoglobin and serum albumin, and a higher incidence of bone destruction. These findings are consistent with earlier reports and demonstrate that patients who do not respond have a greater overall burden of disease, deeper marrow affection, and a greater degree of system damage at diagnosis. Importantly, comparability in age, sex, and treatment regimen distribution between the groups afforded a reasonably balanced comparability regarding demographic and intervention variables. This may reduce the risk of confounding in subsequent analyses of dynamic indicators. The same pattern of baseline differences indicates that the patients with advanced-staging and high-tumor burden are likely to exhibit more severe immune microenvironment dysregulation and bone metabolic disturbance. Through a single-cell sequencing study, it has been confirmed that the proportion of CD8+ T cells and NKT cells in bone marrow microenvironment decreases with advancement of R-ISS staging, and the degree of immune suppression increases, providing a pathobiological basis for the differential dynamic changes occurring in various groups.

Efficacy monitoring value of dynamic changes in inflammatory markers

PLR and LMR have different kinds of variations in the remission and non-remission groups, while ΔNLR does not show a significant difference between the groups. This indicates that various inflammatory markers have different abilities to reflect the therapeutic effect. For PLR, there is a significant decrease in the remission group after treatment, but not in the non-remission group, resulting in a notable difference in ΔPLR between the groups. The reduction of PLR may suggest an improvement in platelet activation and the restoration of lymphocyte-mediated immunity after effective treatment. However, we should take into account that Qin et al. [17] and Zhang et al. [18] mentioned that a higher baseline PLR is related to a better prognosis for Multiple Myeloma patients, which is contrary to our finding that the decrease of PLR after treatment is associated with remission. One possible reason is that the increased baseline PLR reflects a stronger initial immune response to the tumor (because platelets participate in immune surveillance), while the reduction of PLR after treatment indicates the normalization of inflammation following the reduction of tumor burden. These two findings represent different stages of the disease and therefore have different clinical significances - clearly demonstrating that dynamic monitoring provides more prognostic information than a single baseline measurement. Concerning LMR, the remission group shows a significant increase after treatment, whereas the non-remission group experiences a further decrease, indicating that LMR is a reliable indicator for judging the treatment response. An increase in LMR suggests the recovery of absolute lymphocyte count and the alleviation of monocyte-mediated immune suppression, acting as a key marker of immune reconstitution. Suzuki et al. [19] found that a higher LMR is associated with

MRD-negative status and longer progression-free survival, supporting LMR as an immune monitoring index from the aspect of immune clearance. Additional evidence also suggests [20] that patients with an LMR of 4 or more who receive anti-CD38 antibody-based regimens have better survival, confirming that LMR can reflect the interaction between the host's immune condition and treatment. Moreover, NLR decreases obviously after treatment in both groups without a significant difference in ΔNLR. By analyzing the absolute cell counts of NLR (Additional Figure S4), it is observed that the NLR decrease in the two groups is due to different mechanisms. In the remission group, the ANC (absolute neutrophil count) decreases from a high baseline (5.05 ± 2.62 × 10^9/L) to the normal range (2.28 ± 1.09 × 10^9/L) with a stable lymphocyte count, similar to the reduction of inflammation caused by treatment. In the non-remission group, the ANC is already significantly lower at the baseline (2.02 ± 0.94 × 10^9/L) and drops to a very low level (0.85 ± 0.37 × 10^9/L) after treatment, accompanied by a sharp decline in ALC (absolute lymphocyte count) (from 2.08 ± 0.81 to 0.72 ± 0.32 × 10^9/L). Hence, the NLR decrease in this group reflects chemotherapy-induced myelosuppression and immune depletion rather than a beneficial reduction in inflammation, explaining the contrasting prognostic effects in the two groups. In summary, these results show that the dynamic changes of PLR and LMR are more informative than NLR in evaluating the treatment response of MM. This supplements the previous studies on the prognostic factors of baseline NLR [11, 21] and further confirms that dynamic indicators provide more clinical useful information than single baseline measurements.

Efficacy monitoring value of dynamic changes in bone metabolic markers

Dynamic changes in bone metabolic markers not only reflect treatment efficacy, but also provide objective evidence for evaluating therapeutic response from the perspective of bone remodeling imbalance. Among all possible dynamic indicators, Δβ-CTX has the largest standardized effect size, thus confirming β-CTX as the most sensitive marker for monitoring the treatment effect of MM. A longitudinal study by Auzina et al. [22] also found that β-CTX decreased significantly in treatment responders after 6 months, while it increased in non-responders, which is consistent with our study. Domestic research indicates that β-CTX decreases obviously after treatment in patients who respond, whereas the changes are less noticeable in those who do not respond [23]. β-CTX is a specific degradation product of type I collagen that directly reflects the activity of osteoclasts and the rate of bone resorption. In MM, neoplastic cells continuously activate osteoclasts via the secretion of RANKL and other cytokines, resulting in a significant elevation of β-CTX. With effective treatment, the tumour load reduces, the secretion of RANKL decreases, the activity of osteoclasts is suppressed and consequently, the level of β-CTX falls. However, in non-responder patients, the accelerated proliferation of neoplastic cells leads to increased bone resorption and the level of β-CTX rises, showing opposite changes between the two groups and demonstrating strong discriminative power. The level of PINP decreases significantly after treatment in the remission group, indicating that effective treatment can curb both the bone resorption and bone formation activities, which may be related to the dynamic changes in osteoblast functions within the bone marrow microenvironment. Both groups show a decrease in BALP after treatment, but the remission group shows a greater reduction. The serum calcium level decreases in the remission group while increases in the non-remission group, similar to the trend of β-CTX. Research by Peng et al. [24] combines the corrected serum calcium value higher than 2.75 mmol/L with LMR to construct a simple prognostic model, which confirms the importance of serum calcium in the prognosis of MM. In summary, the dynamic variations of bone metabolic markers can reflect not only the therapeutic effect of MM on bone disease, but also provide objective evidence for evaluating efficacy from the perspective of bone remodeling imbalance - an important supplementary aspect compared to inflammatory indicators.

Prognostic value of dNLR and its time-dependent effect

Univariate Cox regression confirmed that dNLR was significantly associated with OS in MM

patients, but the proportional hazards test revealed that its hazard effect changed substantially over time, violating the standard assumption. A time-varying Cox model was therefore constructed; both the baseline effect of dNLR and its time interaction term were statistically significant. Time-varying HR curves further showed that the prognostic effect of dNLR grew progressively stronger with longer follow-up. The progressively strengthening prognostic effect of dNLR over time is consistent with a hypothesis that immune reconstitution may play an increasing role in long-term survival as the direct effects of chemotherapy diminish. Supporting this, post-treatment ALC - a clinically available proxy of immune recovery - was significantly associated with OS in our data (HR 0.767, P < 0.001). However, dNLR was not significantly correlated with post-treatment ALC (r = -0.025, P = 0.62), suggesting that dNLR does not simply reflect absolute lymphocyte recovery at a single post-treatment timepoint. Rather, as a composite index of the directional change in the neutrophil-lymphocyte balance, dNLR may capture a distinct dimension of immune dynamics beyond absolute lymphocyte counts. Therefore, the interpretation linking the time-dependent effect of dNLR to immune surveillance capacity should be regarded as hypothesis-generating rather than conclusive and warrants validation in prospective studies incorporating serial immune profiling. dNLR, as an integrated reflection of dynamic immune function changes, increasingly demonstrates its prognostic warning value in this later phase. According to recent studies by Corsale et al. [25], a perspective from the bone marrow microenvironment provides mechanistic insight. Their findings indicate that patients whose marrow has a higher granulocyte-to-lymphocyte ratio fare better. Moreover, researchers found that granulocytes boost daratumumab's antibody-dependent cellular cytotoxicity. This provides evidence that shifts in immune cell composition enhance the strength of antitumour immune responses. Therefore, clinicians should evaluate the dNLR trajectories throughout long-term follow-up and not only rely on assessment at diagnosis.

R-ISS subgroup heterogeneity in the prognostic value of dNLR

According the R-ISS subgroups, dNLR has prognostic value, but there is significant heterogeneity. There was a strong correlation between dNLR and OS in R-ISS stage III, P < 0.001, but not in R-ISS stage I-II, P = 0.561. This has important clinical implications. Patients with R-ISS stage III show heavy tumor burden with high cytogenetic risk. At diagnosis these patients have a more extreme systemic inflammatory state. They also have a weaker baseline immune function. Furthermore, these patients are more sensitive to the immune dynamics triggered by treatment. Therefore, changes in inflammatory markers are more prognostic in this population. According to the literature, the bone marrow immune microenvironment of patients with R-ISS stage III diseases displays stronger features of the suppressed state characterized by diminished effector T cells and elevated immune checkpoint molecules [16]. Presumably, this is the reason why this subpopulation is especially affected by the changes in immune dynamic indicators. In stage I-II R-ISS patients which have better prognoses, the intrinsic biological properties of the disease are more important than the marginal contribution of dynamic inflammatory markers in determining outcome. As per the results, monitoring of dNLR should be of clinical importance in the follow-up management of high-risk R-ISS stage III MM patients. dNLR may serve as a reference for risk stratification and treatment adjustment that may complement R-ISS.

Stable prognostic value of dBCTX and a dual-dimensional assessment framework

dBCTX was found to satisfy the proportional hazards assumption (P = 0.679) unlike dNLR. Furthermore, when included in the time-varying Cox model, dBCTX maintained a stable and significant independent prognostic value as a proportional hazards term (P < 0.001). Huang et al. [13] found that baseline β-CTC was also an independent prognostic factor for OS in newly diagnosed MM, with AUC of 0.708 for OS. The effect of dBCTX on MM mortality risk appears not to drift over time and is constant throughout the follow-up period; in other words, it has a generalized prognostic ability that is stronger than the time-varying dNLR. The β-CTX dynamic change, which has been the full course of the disease in MM bone disease, is a persistent pathological process of the disease. Secondly, β-CTX dynamic change has no fundamental relation with the prognosis, as you lengthen

the follow-up time. The complementary roles, through the inflammatory-immune axis and the bone-remodeling axis, represent the prognostic mechanisms responsible. Through the integration of dNLR and dBCTX into prognosis evaluation, we can obtain a more comprehensive assessment of MM patients; namely, from both the perspective of immune function dynamics and bone metabolic response. Thus creating a more complete dynamic prognostics monitoring system.

Microenvironmental remodeling and immune editing underlying dynamic changes

From a tumor biology perspective, the observed changes in inflammatory and bone markers suggested in our study indicate an adaptive remodeling process occurring in the multiple myeloma (MM) bone marrow microenvironment during therapeutic treatment. According to the review by Saitoh and Oda [26], the inflammatory and hypoxic conditions in the MM microenvironment can directly influence the DNA damage response pathways, and unrepairable DNA damage will increase the genomic instability, promoting the progression and drug resistance of the disease. This suggests that the continuous decrease and subsequent increase in β-CTX level in the non-remitting group might not only be the result of treatment failure, but could also be due to the biological consequences of persistent inflammatory transformation and accumulation of DNA damage in the microenvironment. At the same time, evidence from McCachren et al. [27] indicates that the transition from asymptomatic multiple plasma cell myeloma to active MM is associated with a long-term co-evolution between immune responses and tumor cells, involving the exhaustion of T-cells and failure in immune editing as key steps in disease development. The increasing predictive power of dNLR with time can be reasonably explained by this perspective: as the follow-up period extends, the struggle between the immune system and residual tumor cells continues, and patients who cannot establish effective immune reconstitution (indicated by decreasing dNLR) gradually lose their ability to perform immune editing, resulting in recurrence and poor outcomes. Furthermore, Liu et al. [28] pointed out in their review that the main challenge in current MM immunotherapy is to improve the immunogenicity of tumor cells and overcome the immune suppression in the microenvironment. The dynamic monitoring methods of dNLR and LMR described in our study may serve as useful tools for assessing the status of immune microenvironment and identifying patients who are likely to benefit from immunotherapy, providing practical reference information for clinical decisions. In conclusion, the clinical significance of these dynamic indicators lies not only in their statistical relationship with prognosis, but also in their capability to indirectly reflect the dynamic balance of immune-tumor interaction in the MM microenvironment, offering a clinical observation window for a better understanding of MM biology. The independent prognostic value of both dNLR and dBCTX were confirmed in a different time-coordinated validation cohort. The effect sizes are approximately the same as those in the derivation cohort (dNLR HR 0.595 vs. 0.691; dBCTX HR 3.911 vs. 4.205), and the time-dependent behavior of dNLR is fully reproduced, providing strong evidence for its clinical usefulness in prognosis evaluation. The stable Prognostic Homogeneity (PH) of dBCTX further confirms its reliability as a bone remodeling marker at different disease stages.

Limitations

There are a few limitations of this study. To begin with, a temporal validation cohort from the same institution corroborated the primary findings, though both cohorts were retrospective and single-center in design. While the use of a temporal split helps reduce era-related confounding, it does not completely eliminate institutional bias. Multicenter prospective validation is still warranted. In addition, high-risk cytogenetic abnormality del(17p), t(4;14) and MRD test data were not collected uniformly, which may have excluded important prognostic information and compromised the prognostic model's adequacy/testing robustness. A significant limitation was that patients who had autologous hematopoietic stem cell transplantation were excluded; Alzahrani et al. [29] showed the prognostic utility of R2-ISS in transplant-eligible populations, and applicability to this population requires separate assessment. As a fourth limitation of this study, each marker was measured only once before and once after treatment. This precluded any continuous dynamic profile across the full course of treatment. Future work

should explore multi-timepoint longitudinal monitoring approaches. To sum up, the hypothesis-generating evidence that time-dependent prognostic effect of the dNLR reflects the immune surveillance capacity is limited by the absence of direct immune phenotyping data. The association of post-treatment ALC with OS was significant, however the lack of association of dNLR with post-treatment ALC indicates that they measure independent immune functions. Serial immune profiling in a future study will help in the validation of the mechanism.

Conclusion

In conclusion, dynamic changes of inflammatory and bone metabolic markers can reflect treatment response effectively in MM. Both dNLR and dBCTX independently predicted OS and their robustness was confirmed in a temporally independent validation cohort. Indicators that require simple and reproducible tests and procedures can be useful adjunct measures to monitor disease and risk.

Disclosure of conflict of interest

None.

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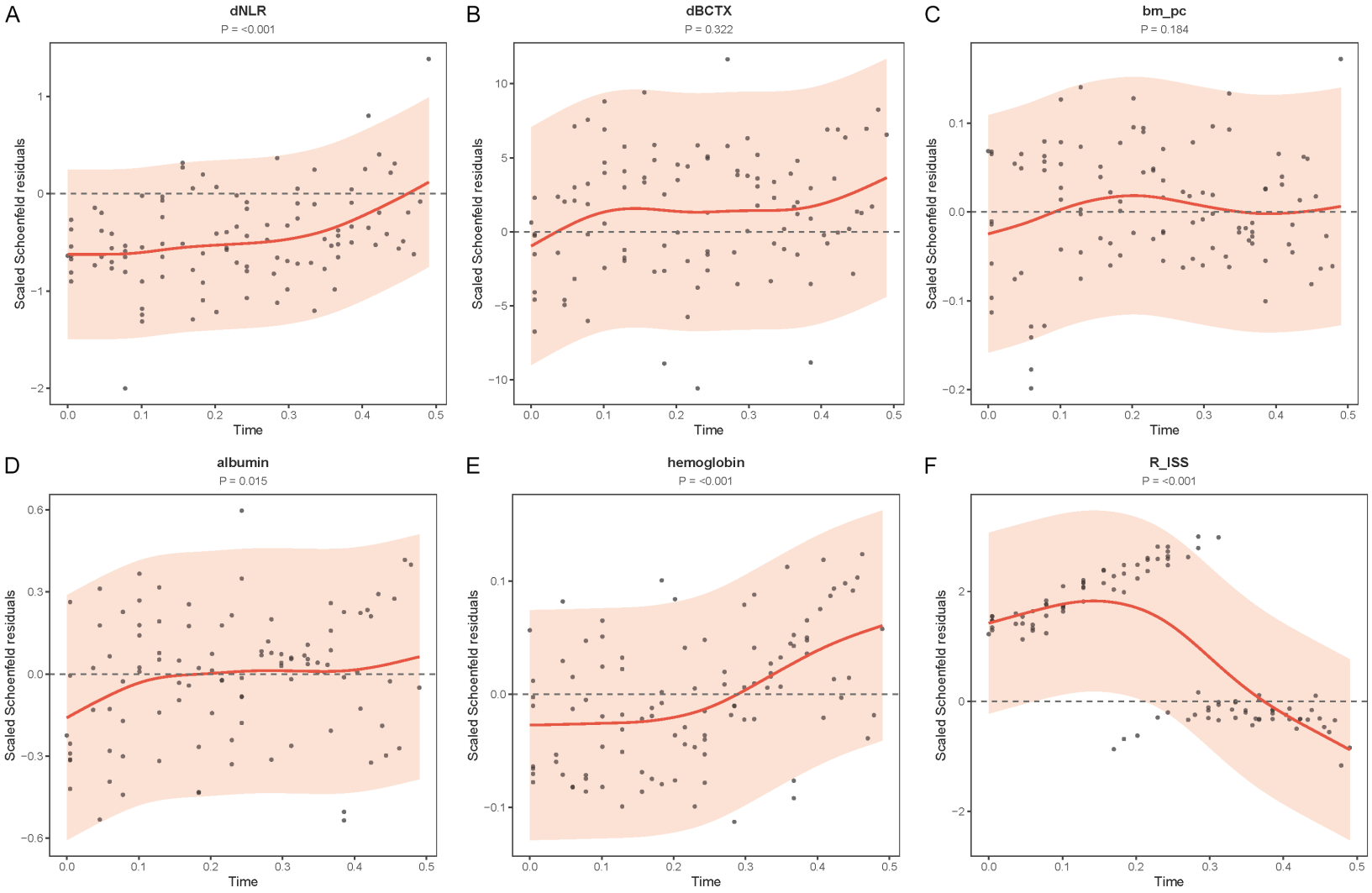
Table S1. Comparison of baseline clinical characteristics between the derivation and validation cohorts

Characteristic	Derivation	Validation	Statistic	*P*_value
Age (years)	62.9 ± 9.6	63.0 ± 9.8	-0.120	0.904
Sex			0.136	0.712
Male	234 (58.21%)	131 (60.09%)		
Female	168 (41.79%)	87 (39.91%)		
ISS staging			2.299	0.317
Stage I	90 (22.39%)	40 (18.35%)		
Stage II	182 (45.27%)	96 (44.04%)		
Stage III	130 (32.34%)	82 (37.61%)		
R-ISS staging			5.170	0.075
Stage I	33 (8.21%)	10 (4.59%)		
Stage II	250 (62.19%)	128 (58.72%)		
Stage III	119 (29.60%)	80 (36.70%)		
Treatment regimen			0.050	0.824
Bortezomib-based	276 (68.66%)	147 (67.43%)		
Other	126 (31.34%)	71 (32.57%)		
Hemoglobin (g/L)	99.7 ± 18.4	97.6 ± 18.7	1.304	0.193
Creatinine (μmol/L)	108.3 ± 39.0	107.9 ± 39.0	0.108	0.914
β2-microglobulin (mg/L)	4.9 ± 1.8	5.1 ± 1.5	-0.947	0.344
Serum albumin (g/L)	34.7 ± 5.4	34.5 ± 5.5	0.492	0.623
Bone marrow plasma cell percentage (%)	39.1 ± 16.7	38.1 ± 16.2	0.719	0.473
Bone destruction			0.001	0.971
Present	282 (70.15%)	154 (70.64%)		
Absent	120 (29.85%)	64 (29.36%)		

Note: ISS, International Staging System; R-ISS, Revised International Staging System; β2-MG, Beta-2 microglobulin. Continuous variables are presented as mean ± standard deviation; categorical variables as n (%).


A
dNLR
P = <0.001
B
dBCTX
P = 0.322
C
bm_pc
P = 0.184
D
albumin
P = 0.015
E
hemoglobin
P = <0.001
F
R_ISS
P = <0.001
Scaled Schoenfeld residuals
Time

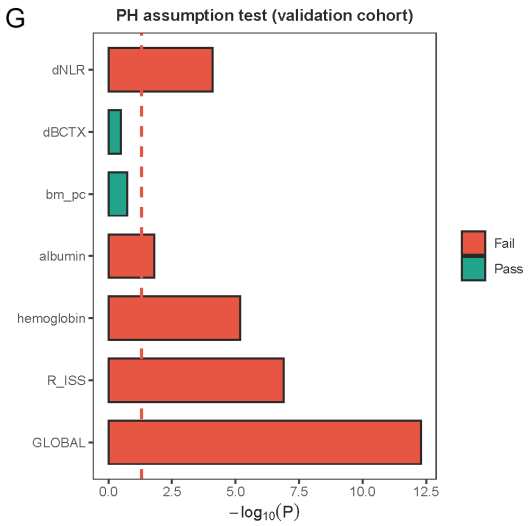
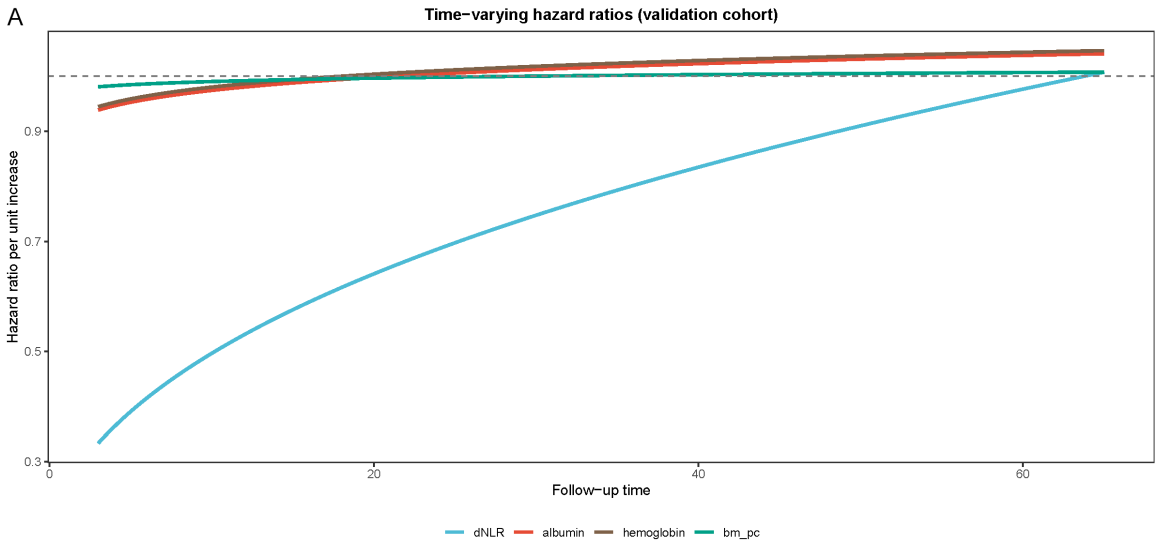
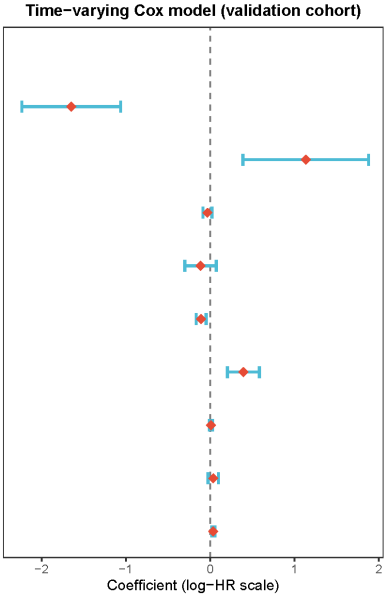


Figure S1. External temporal validation cohort-univariate Cox regression and collinearity diagnostics. A. Forest plot of univariate Cox regression for candidate variables in the validation cohort (n = 218). HRs are shown with 95% CIs. B. Generalized variance inflation factors (GVIF^(1/(2×Df))) for variables with overall P < 0.1; all values < 2 indicate no substantial collinearity. Note: HR, Hazard ratio; CI, Confidence interval; dNLR, Derived neutrophil-to-lymphocyte ratio; dLMR, Derived lymphocyte-to-monocyte ratio; dBCTX, Derived β-C-terminal telopeptide of type I collagen; R-ISS, Revised International Staging System.

A



B



Variable	Interpretation	Coef (95% CI)	P
dNLR	Baseline effect	−1.646 (−2.231 to −1.061)	<0.001
dBCTX	PH term	1.134 (0.389 to 1.880)	0.003
Bone marrow plasma cells	Baseline effect	−0.033 (−0.086 to 0.021)	0.234
Albumin	Baseline effect	−0.114 (−0.301 to 0.072)	0.229
Hemoglobin	Baseline effect	−0.107 (−0.167 to −0.048)	<0.001
dNLR × log(time+1)	Time interaction	0.395 (0.205 to 0.585)	<0.001
bm_pc × log(time+1)	Time interaction	0.010 (−0.009 to 0.028)	0.309
albumin × log(time+1)	Time interaction	0.037 (−0.025 to 0.099)	0.243
hemoglobin × log(time+1)	Time interaction	0.037 (0.017 to 0.056)	<0.001

Figure S2. External temporal validation cohort-proportional hazards testing and time-varying Cox regression. A. Scaled Schoenfeld residual test. Bar chart shows -$\log_{10}$(P) for each variable and global model; red dashed line indicates P = 0.05. Scatter plots with spline fits display residuals against time. B. Time-varying Cox model results. Left panel: coefficient estimates and 95% CIs. Right panel: time-varying HR curves for dNLR, albumin, hemoglobin, and bone marrow plasma cell percentage. The protective effect of dNLR strengthens over follow-up. Note: dNLR, Derived neutrophil-to-lymphocyte ratio; dBCTX, Derived β-C-terminal telopeptide of type I collagen; bm_pc, Bone marrow plasma cell percentage; Alb, Albumin; Hb, Hemoglobin; PH, Proportional hazards; HR, Hazard ratio; CI, Confidence interval.

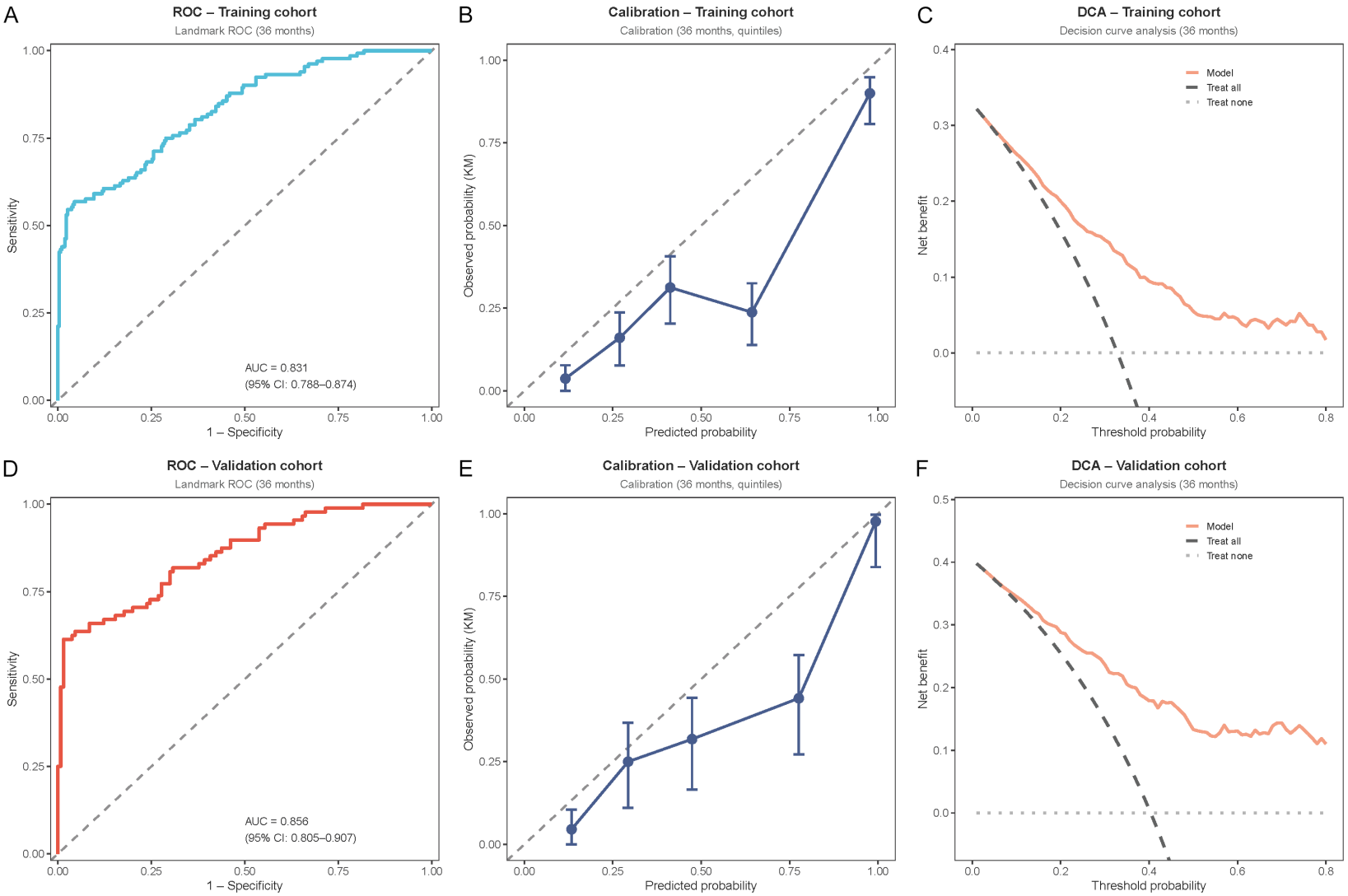


Figure S3. Time-dependent ROC curves, calibration, and decision curve analysis for the integrated Cox model in the derivation (n = 402) and temporal validation (n = 218) cohorts. A-C. Derivation cohort. A. Time-dependent ROC curve at 36 months with AUC (95% CI). B. Calibration plot comparing predicted 36-month event probabilities (quintiles) with Kaplan-Meier observed probabilities. The dashed diagonal represents perfect calibration. C. Decision curve analysis showing the net benefit of the risk-based model versus treat-all or treat-none strategies across threshold probabilities. D-F. Corresponding analyses in the validation cohort. Note: ROC, Receiver operating characteristic; AUC, Area under the curve; CI, Confidence interval; dNLR, Derived neutrophil-to-lymphocyte ratio; dBCTX, Derived β-C-terminal telopeptide of type I collagen.

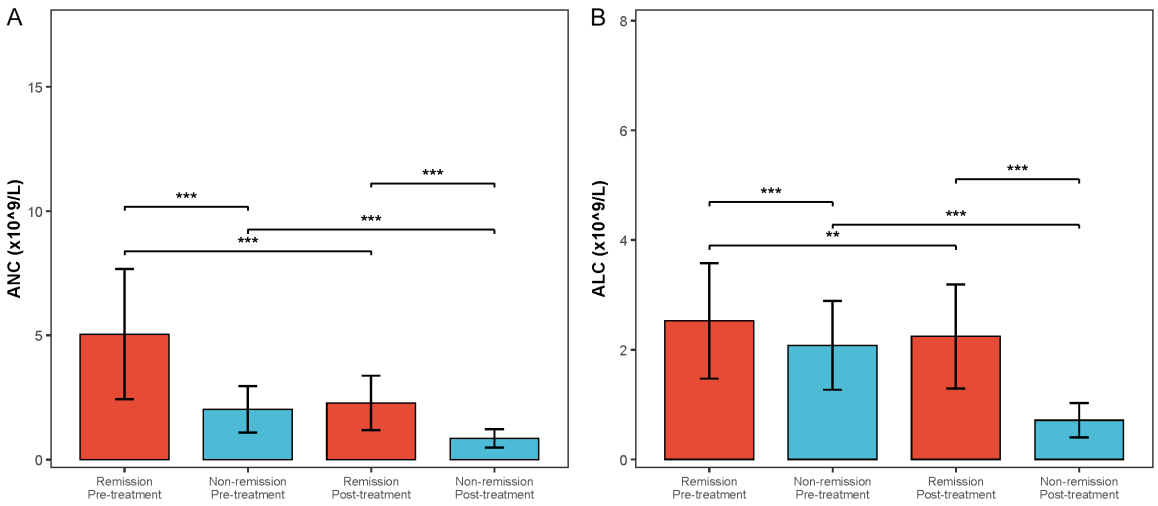


Figure S4. Changes in absolute neutrophil and lymphocyte counts before and after treatment between the remission and non-remission groups. A. Changes in ANC before and after treatment in the remission and non-remission groups. B. Changes in ALC before and after treatment in the remission and non-remission groups. Note: ANC, Absolute neutrophil count; ALC, Absolute lymphocyte count; **P < 0.01; ***P < 0.001.