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LETTER

Prognostic value of peripheral eosinophil counts in patients with newly diagnosed multiple myeloma

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Precise risk stratification is crucial for selecting the optimal risk-adapted treatment for newly diagnosed multiple myeloma (NDMM) patients. Various prognostic factors and staging systems have been developed to predict NDMM patient outcomes. The Durie-Salmon (D-S) staging system reflects tumor burden and clinical progression staging with prognostic value. However, the discrepancy in outcomes between D-S stage II and III patients is not significant and the efficacy in prognostic prediction in the era of new drugs is somewhat unsatisfactory[1]. Furthermore, some assessment methods used in the International Staging System (ISS), revised-ISS (R-ISS), R2-ISS, and other staging systems, including fluorescence *in situ* hybridization (FISH) and positron emission tomography-computed tomography (PET-CT), still have deficiencies, such as inadequate availability of equipment, high costs, and time-consuming procedures. Developing inexpensive, ready-to-use detection indicators and easily interpretable risk stratification systems remain meaningful. In contrast, current prognostic models for NDMM do not incorporate host immune status or bone marrow microenvironment. We hypothesized that peripheral blood cell populations may influence NDMM patient outcomes. A retrospective study was conducted involving 326 NDMM patients treated in our center from November 2013 to June 2023. The impact of routine blood parameters, biochemical indicators, extramedullary disease, as well as major known risk factors on NDMM patients outcomes were analyzed.

Baseline NDMM patient characteristics

This study was a retrospective analysis and was approved by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University School of Medicine (Approval no. 2024-2281-01). A total of 326 NDMM patients were enrolled in this study with a median age of 66 years (range, 36–88 years), of which 186 patients were male and 140 were female. The baseline clinical and laboratory characteristics of NDMM patients are summarized in **Table S1**. Descriptions of data acquisition and statistical analysis are available in **Supplementary Material**.

Recent evidence from animal models has revealed comprehensive antitumor mechanisms involving eosinophils[2,3]. Whether the eosinophil count is associated with the outcomes of MM was investigated in the current study. Therefore, the clinical characteristics and treatment responses between NDMM patients with low and high peripheral eosinophil counts were compared. The optimal peripheral eosinophil count cut-off value in NDMM patients was based on X-tile software. The best peripheral eosinophil count cut-off value was 0.03×10^9/L (**Figure S1A, S1B**). At the time of diagnosis 92 (28.2%) patients were in the low eosinophil count group and 234 (71.8%) patients were in the high eosinophil count group. NDMM patients with low peripheral eosinophil counts at *de novo* were associated with unfavorable clinical characteristics. Moreover, patients with low peripheral eosinophil

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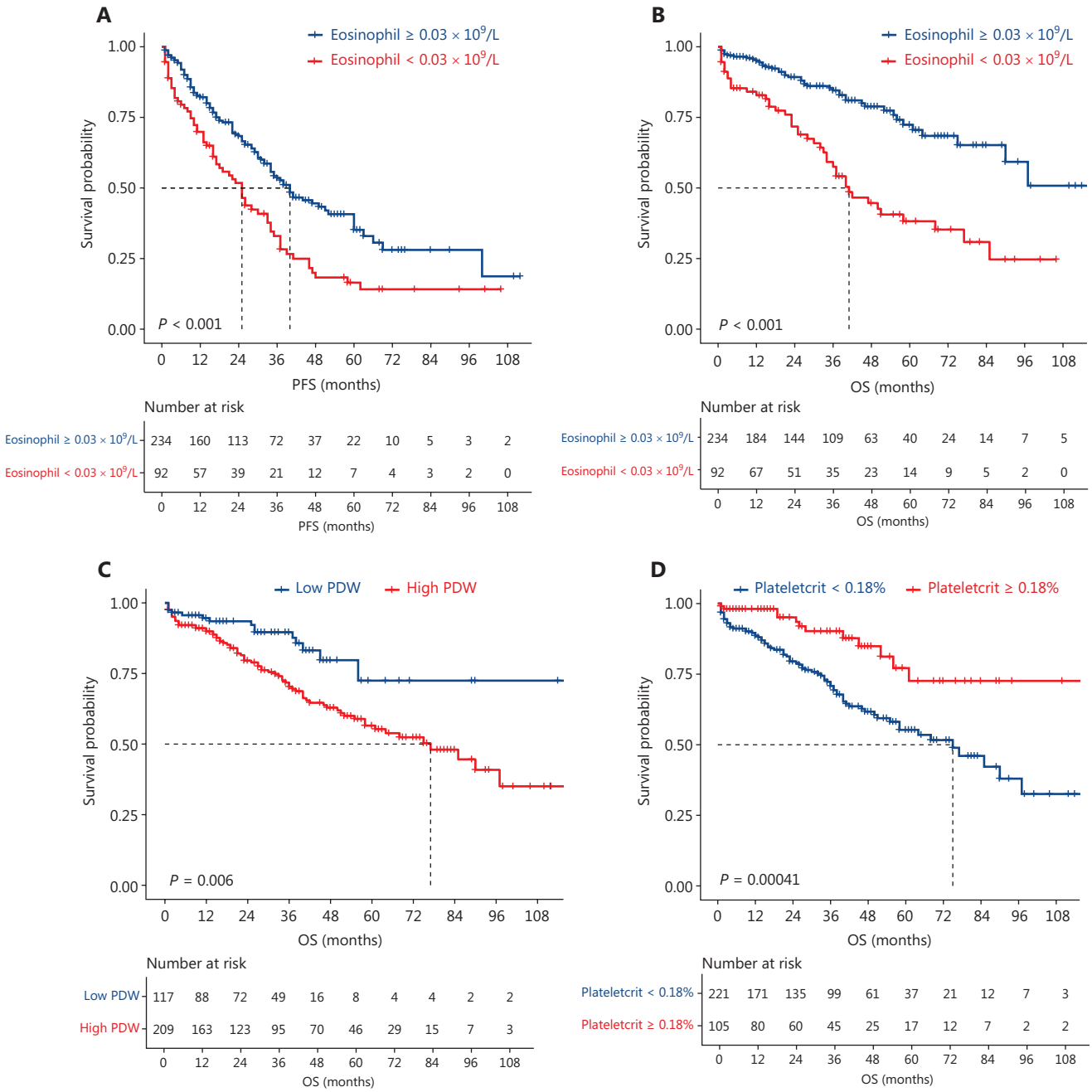


Figure 1 (Continued)

counts were more likely than patients with high peripheral eosinophil counts to have anemia (70.7% *vs.* 55.6%; $P = 0.012$), thrombocytopenia (60.9% *vs.* 40.6%; $P < 0.001$), lower mean corpuscular volume (MCV) (58.7% *vs.* 45.3%; $P = 0.029$), a lower peripheral lymphocyte count (63% *vs.* 44%; $P = 0.002$), elevated platelet distribution width (PDW) (81.5% *vs.* 57.3%; $P < 0.001$), and elevated serum lactate dehydrogenase (LDH) (23.9% *vs.* 12.4%; $P = 0.01$) and C-reactive protein (CRP) level (45.7% *vs.* 30.8%; $P = 0.011$). More importantly, NDMM patients with low peripheral eosinophil counts were less likely to achieve partial remission (PR) or better responses after 4 courses of induction therapy compared to patients with high peripheral eosinophil counts at *de novo* (71.7% *vs.* 84.2%; $P = 0.01$; **Table S2**).

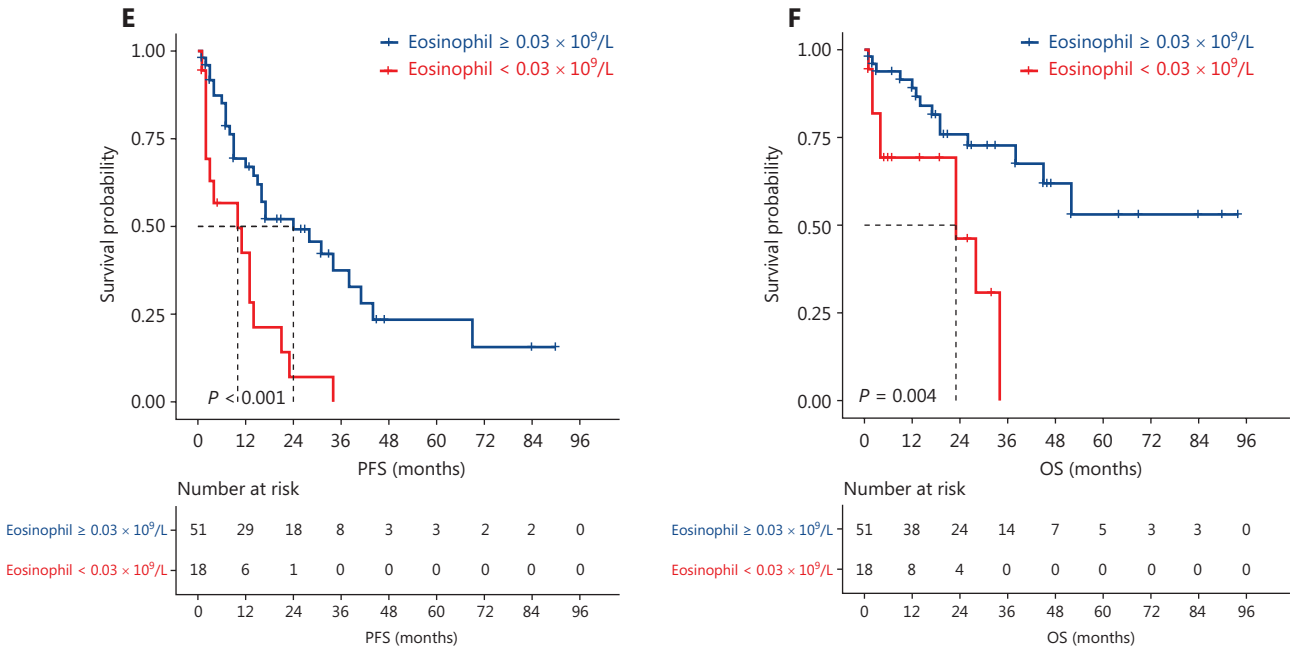


Figure 1 Association of clinical characteristics and the outcomes of newly diagnosed multiple myeloma (NDMM) patients. (A, B) Progression-free survival (PFS) and overall survival (OS) of patients according to the peripheral blood absolute eosinophil count (n = 326); (C) OS of patients based on the peripheral platelet distribution width (PDW) (n = 326); (D). OS of patients based on the peripheral plateletcrit level (n = 326); (E, F) PFS and OS of patients according to the levels of peripheral eosinophil counts in NDMM patients with EMM at *de novo* (n = 69).

Prognostic factors of NDMM patients

The majority of NDMM patients received induction chemotherapy based on proteasome inhibitors (PIs) and/or immunomodulatory drugs (IMiDs). More detailed descriptions of treatment options and definitions of response to treatment are available in the **Supplementary Material**. The median follow-up duration was 39 months (95% CI = 35.2–42.8 months). The median progression-free survival (PFS) duration was 34 months (95% CI = 29.4–38.5 months) and the estimated 3- and 5-year PFS rates were 47% and 18%, respectively. The median overall survival (OS) duration was 90 months (95% CI = 71.2–109.8 months) and the estimated 3- and 5-year OS rates were 51% and 45%, respectively.

Patients with low peripheral eosinophil counts (< 0.03 × 10^9/L) had worse PFS and OS (both, P < 0.001) compared to patients with high peripheral eosinophil counts at *de novo*. The median PFS for patients in the low and high peripheral eosinophil count groups was 25 (95% CI = 18.6–31.4 months) and 40 months (95% CI = 30.8–49.2 months), respectively (**Figure 1A**). The median OS for patients in the low and high peripheral eosinophil count groups was 41 months (95% CI =30.6–51.4 months) and not reached (NR), respectively (**Figure 1B**). Patients with a high PDW (> 16.2%) (**Figure 1C**) and low plateletcrit (< 0.18%; **Figure 1D**) were associated with worse OS. Patients with a high percentage of BMPCs (> 20%; **Figure S2A, S2B**), extramedullary multiple myeloma (EMM) at *de novo* (**Figure S2C, S2D**), or treatment efficacy < PR after 4 courses of induction therapy (**Figure S3A, S3B**) significantly affected the PFS and OS among NDMM patients. Patients with an elevated LDH level (> 250 μ/L) (**Figure S3C**) had a worse OS. Patients with ISS stage III (**Figure S3D**) had a worse PFS.

Multivariate analysis confirmed the predictive significance of the 4 factors for PFS and OS among NDMM patients, including the absolute number of eosinophils in the peripheral blood < 0.03 × 10^9/L [PFS: hazard ratios (HR) = 1.719, 95% confidence intervals (CI) = 1.234–2.393, P = 0.001; OS: HR = 2.207, 95% CI = 1.418–3.434, P < 0.001], the percentage of BMPCs > 20% (PFS: HR = 1.495, 95% CI = 1.078–2.073, P = 0.016; OS: HR = 1.791, 95% CI = 1.125–2.852, P = 0.014), with EMM at *de novo* (PFS: HR = 2.537, 95% CI = 1.74–3.699, P < 0.001; OS: HR = 2.931, 95% CI = 1.748–4.916, P < 0.001), and treatment efficacy < PR after 4 courses of induction therapy (PFS: HR = 2.153, 95% CI = 1.486–3.121, P < 0.001; OS: HR =

Table 1 Univariable and multivariable analyses for NDMM patient outcomes (n = 326)

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PFS				
Age > 65 years	1.11 (0.818–1.505)	0.503		
ISS stage III *vs.* stage I and stage II	1.584 (1.168–2.148)	0.003*	1.577 (1.138–2.186)	0.006
R-ISS stage III *vs.* stage I and stage II	1.683 (1.191–2.376)	0.003*		
Hgb < 100 g/L	1.425 (1.037–1.959)	0.029*		
MCV < 94 fL	1.386 (1.022–1.879)	0.036*		
RDW > 14%	1.261 (0.918–1.731)	0.153		
Plt < 150 × 10^9/L	1.315 (0.971–1.78)	0.077		
PDW > 16.2%	1.303 (0.928–1.83)	0.126		
Plateletcrit < 0.18%	1.419 (0.997–2.018)	0.052		
Lymphocytes < 1.4 × 10^9/L	1.505 (1.110–2.041)	0.008*		
Eosinophils < 0.03 × 10^9/L	1.81 (1.325–2.472)	< 0.001*	1.719 (1.234–2.393)	0.001
Ca^{2+} > 2.52 mmol/L	1.254 (0.867–1.815)	0.23		
Cr > 177 μmol/L	1.529 (1.060–2.204)	0.023*		
LDH > 250 μ/L	1.668 (1.128–2.466)	0.01*		
CRP > 6 g/L	1.083 (0.788–1.487)	0.624		
BMPCs > 20%	1.689 (1.225–2.328)	0.001*	1.495 (1.078–2.073)	0.016
EMM (Yes)	2.202 (1.555–3.118)	< 0.001*	2.537 (1.740–3.699)	< 0.001
Treatment efficacy (< PR) after 4 courses	2.812 (1.971–4.012)	< 0.001*	2.153 (1.486–3.121)	< 0.001
OS				
Age > 65 years	1.152 (0.755–1.757)	0.511		
ISS stage III *vs.* stage I and stage II	1.527 (1.003–2.325)	0.048*		
R-ISS stage III *vs.* stage I and stage II	1.474 (0.914–2.377)	0.111		
Hgb < 100 g/L	1.181 (0.767–1.819)	0.45		
Plt < 150 × 10^9/L	1.563 (1.026–2.382)	0.038*		
MCV < 94 fL	1.491 (0.975–2.278)	0.065		
Lymphocytes < 1.4 × 10^9/L	1.458 (0.957–2.222)	0.079		
Eosinophils < 0.03 × 10^9/L	2.934 (1.931–4.458)	< 0.001*	2.207 (1.418–3.434)	< 0.001
RDW > 14%	1.477 (0.939–2.324)	0.091		
PDW > 16.2%	2.253 (1.287–3.943)	0.004*	1.863 (1.043–3.329)	0.036
Plateletcrit < 0.18%	2.925 (1.591–5.377)	< 0.001*	2.113 (1.120–3.985)	0.021
Ca^{2+} > 2.52 mmol/L	1.04 (0.613–1.767)	0.884		
Cr > 177 μmol/L	1.686 (1.040–2.735)	0.034*		
LDH > 250 μ/L	2.16 (1.319–3.536)	0.002*	1.877 (1.117–3.156)	0.018
CRP > 6 g/L	1.342 (0.875–2.057)	0.178		

Table 1 Continued

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
BMPCs > 20%	1.93 (1.228–3.035)	0.004*	1.791 (1.125–2.852)	0.014
EMM (Yes)	2.112 (1.304–3.420)	0.002*	2.931 (1.748–4.916)	< 0.001
Treatment efficacy (< PR) after 4 courses	3.296 (2.064–5.264)	< 0.001*	2.481 (1.525–4.037)	< 0.001

NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; ISS, International Staging System; R-ISS, revised-ISS; Hgb, hemoglobin; MCV, mean corpuscular volume; RDW, red blood cell distribution width; Plt, platelets; PDW, platelet distribution width; Ca^{2+}, calcium; Cr, creatinine; LDH, lactate dehydrogenase; CRP, C-reaction protein; BMPCs, bone marrow plasma cells; EMM, extramedullary multiple myeloma; PR, partial remission; OS, overall survival.

2.481, 95% CI = 1.525–4.037, $P < 0.001$; **Table 1**). Furthermore, an ISS stage III (HR = 1.577, 95% CI = 1.138–2.186, $P = 0.006$) had adverse effects on PFS. A baseline PDW > 16.2% (HR = 1.863, 95% CI = 1.043–3.329, $P = 0.036$), plateletcrit < 0.18% (HR = 2.113, 95% CI = 1.12–3.985, $P = 0.021$), and LDH > 250 μ/L (HR = 1.877, 95% CI = 1.117–3.156, $P = 0.018$) were independent prognostic predictors of OS at the time of diagnosis (**Table 1**).

Impact of cytogenetic abnormalities on NDMM patient prognosis

Cytogenetic data were available for 180 patients, among which 117 (65%) had 1q gain/amplification, 127 (70.5%) had del(13q), 25 (13.9%) had del(17p), and 79 (43.9%) had IgH translocations. Survival analysis revealed that patients with del(17p) had a significantly inferior PFS ($P = 0.005$; **Figure S4A**), while patients with a 1q gain/amplification showed a trend of worse OS ($P = 0.05$; **Figure S4B**).

Multivariate analyses of the impact of cytogenetic abnormalities on NDMM patient outcomes showed that del(17p) was an independent adverse prognostic factor for PFS in NDMM patients (HR = 2.335, 95% CI = 1.323–4.12, $P = 0.003$), while 1q gain/amplification was an independent adverse prognostic factor for OS in NDMM patients (HR = 2.323, 95% CI =1.077–5.009, $P = 0.032$; **Table S3**). More importantly, even taking into account of the impact of cytogenetic abnormalities on NDMM patient outcomes, lower peripheral eosinophil counts at *de novo* remain an independent prognostic factor for worse PFS (HR = 2.627, 95% CI = 1.612–4.281, $P < 0.001$) and OS (HR = 3.258, 95% CI = 1.667–6.367, $P < 0.001$) for NDMM patients ($P < 0.001$; **Table S3**).

Prognostic impact of the peripheral eosinophil count in patients with EMM

A total of 69 patients were shown to have EMM at *de novo*, of which 39 had extramedullary bone-related lesions and 30 had extramedullary extraosseous lesions. The peripheral eosinophil count also significantly affected the prognosis of patients with EMM. Patients with EMM who had a low peripheral eosinophil count (< 0.03×10^9/L) had worse PFS ($P = 0.001$) and OS ($P = 0.004$) compared to patients with EMM who had a high peripheral eosinophil count at *de novo*. The median PFS among patients with EMM and low and high peripheral eosinophil counts was 10 (95% CI = 1.0–22.3) and 24 months (95% CI = 8.7–39.3), respectively ($P = 0.001$; **Figure 1E**). The median OS of patients with EMM who had low and high peripheral eosinophil counts was 23 months (95% CI = 4.2–41.8) and not reached (NR), respectively ($P = 0.004$; **Figure 1F**). Furthermore, NDMM patients with EMM at *de novo* who had a baseline Hgb < 100 g/L or plateletcrit < 0.18% had inferior OS (**Figure S5A, S5B**). ISS stage III patients with EMM at *de novo* had worse PFS compared to ISS stage I or II patients with EMM (**Figure S5C**).

Multivariate analysis confirmed that a lower peripheral eosinophil count (HR = 3.116, 95% CI = 1.567–6.195, $P = 0.001$), ISS stage III (HR = 2.603, 95% CI = 1.307–5.186, $P = 0.007$), and LDH > 250 μ/L (HR = 4.429, 95% CI = 2.067–9.493, $P < 0.001$) were independent risk factors for PFS in patients with EMM. An Hgb < 100 g/L (HR = 6.88, 95% CI = 2.391–19.791, $P < 0.001$), plateletcrit < 0.18% (HR = 4.302, 95% CI = 1.397–13.25, $P = 0.011$), and treatment efficacy < PR after 4 courses of induction therapy (HR = 3.456, 95% CI =

1.261–9.474, $P = 0.016$) were independent prognostic predictors of OS in patients with EMM (**Table S4**).

This is the first report of a relationship between the peripheral eosinophil count and the prognosis of NDMM patients. Specifically, a lower number of peripheral eosinophils was shown to be an independent prognostic predictor of PFS and OS in NDMM patients, indicating that the peripheral eosinophil count may be a valuable predictive biomarker for NDMM patients. Eosinophils, recognized as innate immune cells, have multiple functions. Published studies have shown that eosinophils infiltrate the tumor microenvironment in various types of cancers, including Hodgkin's lymphoma, lung cancer, breast cancer, and colorectal cancer[4]. Eosinophils can synthesize and secrete several cytokines, including interleukin (IL)-4, IL-5, IL-10, IL-12, IL-13, tumor necrosis factor-α (TNF-α), and transforming growth factor-β (TGF-β), which can induce increased expression of adhesion molecules on cancer cell surfaces, resulting in inhibition of cancer cell metastasis[5]. Furthermore, eosinophils secrete an eosinophilic cationic protein, eosinophil derived neurotoxin, and other soluble mediators including cytokines and chemokines, CCL11,CCL5, CCL24, CCL26, CCL7, and CCL13, to inhibit tumor cell growth or directly induce cytotoxic effects on tumor cells[6]. Eosinophils also exert indirect anti-tumor effects through multiple pathways, such as induction of T cell activation *via* antigen presentation[5], which regulates the infiltration and activation of tumor-specific $CD8^+$ T cells into tumor tissues by secretion of well-known T cell attractants [C-X-C motif chemokine ligand (CXCL) 9 and CXCL10][3], as well as inhibiting tumor-mediated angiogenesis[7]. Furthermore, *in vitro* experiments were performed to assess the effects of eosinophils on the proliferation and survival of MM cells when co-cultured. Eosinophils exhibited inhibition of MM cell proliferation at an eosinophil-to-tumor (E:T) ratio of 20:1 after 48- and 72-h co-culturing (**Figure S6A**).

It has also been reported that eosinophils have anti-tumor effects in colorectal, gastric, liver, lung, and renal cancers, and melanoma, in which patients with an increased number of eosinophils in the peripheral blood tend to have a better response to treatment and superior survival[8]. Jia et al.[2] performed a retrospective analysis to determine whether peripheral blood cells have an impact on the outcomes of patients with B-lineage non-Hodgkin lymphoma who received anti-CD19 chimeric antigen receptor T (CAR-T) cell immunotherapy. Jia et al.[2] showed that B-cell non-Hodgkin lymphomas (B-NHL) patients with a higher baseline eosinophil count had higher objective response rates than patients with a low eosinophil count. A higher baseline eosinophil count was also significantly associated with a durable PFS[2]. A preclinical lymphoma model showed that depletion of eosinophils using anti-Siglec-F or anti-CCR3 impaired intratumoral CAR-T cell recruitment and reduced CAR-T cell anti-tumor efficacy[2]. Taken together, the results herein add evidence to the established roles of eosinophils in anti-tumor effects, suggesting the predictive value of the number of eosinophils in blood for NDMM patients, although the underlying mechanisms warrant elucidation.

In conclusion, the number of eosinophils in blood at the time of diagnosis was shown to be an independent prognostic factor for NDMM patients. Indeed, the eosinophil count is a promptly available, easily interpretable, and inexpensive prognostic indicator suitable for routine clinical use. By combining the established prognostic factors, the absolute number of eosinophils in a complete blood cell count can serve as a good addition to current MM prognostic systems, especially in some areas where FISH cannot be routinely carried out. The current study had some limitations, including a retrospective analysis, a limited number of patients, and a lack of cytogenetic data in some patients. Therefore, further research with a larger number of cases and prospective research is warranted to validate these findings. It is also worth noting that immune cells have pivotal roles in the tumor microenvironment. Future clinical studies are also warranted to perform the analysis incorporating non-tumor cells, including eosinophils with immune cells to ensure comprehensive insights of the MM microenvironment, as well as cellular composition changes within the bone marrow.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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Contributed data or analysis tools: Xu Chen, Xiaoyan Yue, Hao Jiang, Qianqian Yang, Jinwen Huang, Wenjue Pan, Xiujie Zhao, Xiufeng Yin, Panpan Wang, Liangning Hu, Xiaoli Guo, Fangfei Shao, Haowen Xiao

Performed the analysis: Xu Chen, Xiaoyan Yue

Wrote the paper: Xu Chen, Xiaoyan Yue, Haowen Xiao.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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