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– REVIEW –

Prognostic Significance of Neutrophil to Lymphocyte Ratio in Multiple Myeloma Patient

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Abstract: *Multiple myeloma represents a hematologic malignancy characterized by the abnormal proliferation of plasma cells in the bone marrow. Through this proliferation, the malignant plasma cells disrupt normal blood cell production, subsequently causing the clinical hallmarks of this pathology: bone destruction, anemia, renal impairment and a highly increased susceptibility to infections. Despite the therapeutic options available, multiple myeloma remains an incurable disease (1). The rising use of combination therapies, triplets or quadruplets, by using immunomodulatory drugs, monoclonal antibodies and targeted therapies, elicited improved survival rates and a significant improvement of the quality of life of these patients. However, there is a luring need to precisely quantify the life horizons of these patients, therefore the most recent tool for this estimate has been developed, the R-ISS score. The R-ISS score uses various biomarkers such as serum β2-microglobulin, serum albumin, LDH levels and a more refined tool, the cytogenetic abnormalities list, to predict the outcome of each case. The addition of the precise cytogenetic risk groups boosted the sensitivity of the previous ISS score, but also unveiled the existing discrepancies in accessing modern diagnostic tools across treatment centers (2). Moreover, patient-oriented reports pointed out that from a patient perspective the highest perceived cost had been perceived until the neoplasm diagnostic was established, hence the reluctance for specialized investigations (eg. FISH testing and karyotypes etc.) (3).*

Keywords: *multiple myeloma, platelet-to-lymphocyte ratio, neutrophyl-to-lymphocyte ratio, prognostic score*

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Introduction

Considering these economic factors, more and more investigators turned towards scavenging the already available variables. Amongst all hematological malignancies, the complete blood count is one of the standard investigations performed, widely available and well standardized due to the progress in automated cytometers which are ubiquitously available. Therefore, it was a reasonable assumption to investigate this resource and it proved to deliver promising results from the first time it was hypothesized, not only in hematological neoplasms, as it was researched also in other malignancies (4).The aim of this review is to highlight the most promising data and concepts regarding various cytologic

ratios and their prospective correlation with the disease course in multiple myeloma patients.

Blood cell indicies at diagnosis – variations and significance

Hematological parameters play a crucial role in diagnostic evaluation and prognosis stratification of multiple myeloma patients. Amongst these, the red blood cell indices such as mean erythrocyte volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW) often show characteristic variations at diagnosis. These indices not only reflect the degree of bone marrow infiltration and associated anemia but may also serve as indirect markers of disease severity and systemic involvement.

The red blood cell distribution width (RDW), a parameter routinely included in complete blood count (CBC) tests, has been identified as a marker of systemic inflammation. Multiple myeloma (MM) is characterized by an inflammatory bone marrow microenvironment, which may contribute to alterations in RDW (15). Red blood cell distribution width (RDW), traditionally used to differentiate types of anemia, has recently emerged as a prognostic indicator in various cancers. In this study, we conducted a meta-analysis to evaluate the association between RDW and survival outcomes in patients with hematologic malignancies (15, 16).

Almost 70% of myeloma patients present with anemia at the time of diagnosis and it is a hallmark of bone marrow replacement with malignant plasma cells, as well as chronic inflammation, renal impairment and erythropoietin deficiency. Usually, the anemia is normocytic normochronic, but an associated folate deficiency can be seen as macrocytic anemia (17).

The study of Carlisi et al, shows that in the overall cohort of multiple myeloma patients, a mortality rate of 40% was observed, with 36.4% of deceased patients being male and 43.1% female. Compared to survivors, deceased patients showed a significant increase in age, red cell distribution width (RDW), RDW-to-albumin ratio, and RDW-to-hemoglobin ratio. Additionally, this subgroup exhibited notable decreases in hematocrit, total serum protein, calculated whole blood viscosity (as estimated by the de Simone formula), serum albumin, albumin-to-fibrinogen ratio, and hemoglobin concentration (18).

Neutrophils involvement

In terms of prognostic values, a higher count of neutrophils has been consistently reported to predict a shorter overall survival and a reduced progression-free survival (PFS) (5). The current literature attributes three major biological mechanisms that contribute to the disease course, namely: immunosuppressive role, a tumor microenvironment modulation and an upregulation in inflammatory pathways.

In multiple myeloma, neutrophils present a dysfunctional immune response, by having a reduced phagocytic activity and an increased expression of arginase-1 (Arg-1) which has a suppressive effect on T-cell activation (6). Chronic inflammation is another factor of the inflammatory pathways activated by a high number of neutrophils, known to induce resistance to therapy in many neoplastic diseases (5).

Lymphocyte involvement

Although multiple myeloma (MM) is traditionally characterized as a malignancy of clonal plasma cells, growing evidence underscores the pivotal role of the broader immune microenvironment—especially lymphocytes—in driving disease development and progression. T cells, B cells, and natural killer (NK) cells contribute in complex ways, ranging from promoting tumor growth to shaping therapeutic outcomes and facilitating immune evasion (19).

Regulatory T (Treg) cells are crucial for dampening normal immune responses and maintaining immune system balance. Patients with monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) exhibit a notable increase in $CD4^+CD25^+$ T cells compared to healthy donors (25% and 26%, respectively, versus 14%). However, when Treg cells are specifically identified by FOXP3 expression, their numbers are significantly reduced in both MGUS and MM patients relative to healthy individuals. Furthermore, even when present at elevated levels, Treg cells from MGUS and MM patients fail to suppress anti-CD3–induced T-cell proliferation. This reduction in both the quantity and suppressive function of Treg cells may partially explain the nonspecific expansion of $CD4^+CD25^+$ T cells and contribute to impaired T-cell regulation in these conditions (20).

PD-1 expression on T cells suppresses anti-tumor immunity via interaction with PD-L1 on tumor cells, but its role in NK cells is less understood. We found that NK cells from multiple myeloma (MM) patients express PD-1, unlike those from healthy donors, and that primary MM cells express PD-L1. This interaction likely impairs NK-cell cytotoxicity against MM. CT-011, an anti-PD-1

antibody, enhances NK-cell activity against autologous MM cells by improving trafficking, immune synapse formation, and selective killing of PD-L1$^+$ MM cells without affecting normal cells. Lenalidomide further boosts this effect by downregulating PD-L1. These findings support targeting the PD-1/PD-L1 axis in MM and justify a phase 2 trial of CT-011 combined with lenalidomide (21).

Although B lymphocytes are less commonly highlighted in discussions of multiple myeloma (MM) pathogenesis, they may play a role in disease development. Evidence suggests that premalignant conditions such as monoclonal gammopathy of undetermined significance (MGUS) may arise from early B-cell precursors, with clonal evolution potentially involving the transformation of B cells into malignant plasma cells (14). Moreover, Multiple myeloma is a cancer of terminally differentiated B cells (plasma cells) marked by chromosomal translocations that activate oncogenes via immunoglobulin enhancers. Unlike most blood cancers, it shows complex chromosomal changes like those in epithelial tumors. Understanding what drives its progression and how this knowledge can guide prevention, and treatment remains a critical focus (22).

Natural killer (NK) cells are key players in tumor clearance, especially in leukemia, as shown by the success of KIR-mismatched allogeneic stem cell transplants. However, NK cells from patients with acute myeloid leukemia (AML) often show impaired cytotoxicity due to low expression of key activating receptors—NKp30, NKp44, and NKp46 (the NCRs). This NCR^dull phenotype is not an artifact of in vitro expansion and is observed across various AML subtypes and cytogenetic profiles. Longitudinal analysis revealed that the NCR^dull state develops during leukemia progression and is partially reversible upon remission, suggesting leukemia cells actively suppress NCR expression. Direct contact with leukemic blasts, but not their supernatants, downregulates NKp30 and NKp46 and inhibits IL-2–induced NKp44 expression. This effect is not driven by TGF-beta. While NK cells are proven effective in allogeneic transplants, their role in autologous settings remains unclear. Notably, the NCR dull phenotype correlates with poor survival in AML, indicating its potential as a prognostic marker and a target for future studies (23).

In summary, lymphocytes are deeply involved in the complex immunopathology of multiple myeloma. Dysregulated T cells, aberrant B-cell maturation, and impaired NK cell function all create a permissive niche that fosters myeloma cell survival and progression. Targeting these immune dysregulations, through therapies such as immune checkpoint inhibitors, CAR-T cells, and bispecific antibodies, represents a promising strategy for restoring anti-myeloma immunity and improving clinical outcomes (24).

Monocyte involvement

A deeper molecular view of multiple myeloma (MM) precursors and their microenvironment is key to better risk stratification. Using single-cell RNA sequencing bone marrow from healthy donors and patients with MGUS, SMM, and MM, we identify early immune changes. NK cells increase in early stages with altered chemokine receptor expression. SMM shows loss of GrK$^+$ memory cytotoxic T cells, crucial for MM immunosurveillance, and CD14$^+$ monocytes exhibit MHC class II dysregulation, suppressing T cells. These findings map immune shifts in MM progression and support immune-based patient stratification. (25)

A major challenge in multiple myeloma is drug resistance driven by interactions with bone marrow stromal cells. This study focused on macrophages, particularly tumor-associated macrophages (TAMs), and their role in supporting myeloma cell survival. We found that macrophages protect both myeloma cell lines and primary cells from spontaneous and drug-induced apoptosis through direct contact, suppressing caspase-dependent cell death pathways. Clinically, CD68$^+$ macrophages were abundant in the bone marrow of myeloma patients but not in controls, suggesting that macrophages contribute to chemoresistance and disease persistence in vivo (26).

Colla et al. highlights the role of osteopontin (OPN) and angiogenesis in the development and progression of hematologic cancers, particularly multiple myeloma (MM). Using in vitro assays, they show that MM cell-conditioned media promotes angiogenesis, with OPN being a key mediator. They identify RUNX2, a member of the Runt transcription factor family, as a critical regulator of OPN expression in MM cells. Silencing RUNX2 reduces OPN levels, confirming its role. Additionally, analysis of newly diagnosed MM patients shows a strong link between RUNX2 activation, OPN production, and bone marrow angiogenesis. OPN, a multifunctional glycoprotein found in bone and various cell types, is involved in processes like bone resorption, wound healing, and angiogenesis. Originally identified in bone and cancer cells, OPN is now recognized for its role

in MM progression through promoting angiogenesis and interacting with the bone marrow microenvironment (27). RT-PCR analysis showed that CCR1 and CCR5 are expressed in purified human osteoclast (OCL) precursors, myeloma cell lines, and marrow plasma cells from multiple myeloma (MM) patients. Blocking CCR1 or CCR5 with neutralizing antibodies reduced MIP-1α–induced OCL formation. Similarly, MCP-3 (which targets CCR1 but not CCR5) and the CCR1-specific antagonist BX471 significantly inhibited MIP-1α–stimulated OCL formation. In addition, anti-CCR1, anti-CCR5, and BX471 blocked MIP-1α–induced β1 integrin mRNA expression in myeloma cells, reduced their adhesion to stromal cells, and decreased stromal cell IL-6 production triggered by myeloma cells (28).

Thalidomide (Thal) and its analogs (IMiDs) were introduced in multiple myeloma (MM) due to their antiangiogenic and direct anti-MM effects. This study explored their immunomodulatory role, showing that while Thal/IMiDs don't directly stimulate T-cell proliferation, they enhance proliferation of anti-CD3–stimulated T cells and increase IFN-γ and IL-2 secretion. However, they did not boost T-cell killing of MM cells. Instead, Thal/IMiDs enhanced NK cell–mediated killing of MM cells. IL-2–primed PBMCs treated with Thal/IMiDs showed increased MM cell lysis, which was blocked by CD56(+) cell depletion, confirming NK cell involvement. This killing was MHC-independent. Importantly, increased NK activity against autologous MM cells was also observed. In patients responding to Thal, CD3(–)CD56(+) NK cells increased, supporting the idea that Thal's anti-MM effects are partly due to enhanced NK cell function (29).

Platelets microenvironment interactions

Platelets have been shown to have properties to interact with the neighbouring microenvironment. It has been confirmed that these cells interact with various growth factors, particularly with platelet-derived growth factor and platelet factor, determining cell proliferation and metastasis, through means of cell signal transduction and hemostasis pathways activation, blockade of the GP1b/IX/V, GPIIbIIIa and GPVI showing promising results in impeding the metastasis progression (7). Some studies investigating the megakaryocyte lineage reported that multiple myeloma patients display strong evidence of platelet activation, depicted by the cytokines secreted such as IL-6, VEGF,SDF-1α and IGF-1 (8).

The driving impact of the release of these cytokines might be influenced however by the natural course of the disease, as malignant plasma cells secrete the M protein which engages platelets in the bone marrow, therefore altering the normal hematopoiesis with potential negative regulatory effects, which might down-regulate the platelet activation and function (9). The balance between these two regulatory mechanisms might explain the various behaviours of the paltelets in the bone marrow niche and the conflicting results obtained in the studies which turned towards the platelet activation role in neoplasms.

Ratio	Elements of the ratio
Neutrophil-to-Lymphocyte Ratio (NLR)	NLR = Absolute Neutrophil Count (ANC)/ Absolute Lymphocyte Count (ALC)
Platelet-to-Lymphocyte Ratio (PLR)	PLR = Platelet Count (PLT)/ Absolute Lymphocyte Count (ALC)
Monocyte-to-Lymphocyte Ratio (MLR)	MLR = Absolute Monocyte Count (AMC) / Absolute Lymphocyte Count (ALC)

Ratios of promising clinical significance CBC ratios in Multiple myeloma

Platelets-to-Lymphocyte Ratio (PLR)

Another ratio in the marrow niche investigated by various other authors is the ratio between platelets and lymphocytes. Studies which have researched this topic outline that there might be a relationship between low PLR at diagnostic and a poorer overall survival (OS), particularly in high-risk myeloma cases, with strong evidence from a recent paper published by Zhang et. al(10). The implied cut-off value in this particular case is a PLR below 76.25 which corelated with worse outcomes in newly diagnosed myeloma patients treated using IMIDs.

Statistical analysis pointed out that this relationship is a non-linear one, emphasizing the importance of this parameter, which can be easily generated using the data of the first blood counts obtained. Another study involving patients who received thalidomide as part of the treatment regimen also identified lower PLR at diagnostic to be of

predictive significance in terms of overall survival (OS) (11). However, strong data from previous meta-analyses by Xinwen Zhang et. al, which indeed showed some high heterogeneity between the studies, question this ratio as the evidence collected and analyzed failed to support the findings in the literature (12). Therefore, there is a strong need for more reports and larger cohorts to be analyzed to be able to assess the usefulness of platelets to lymphocytes ratio, as the biology empirically suggests promising theoretical basis that would explain the prognostic value of platelets and their proxy reflection of the microenvironment interactions caused by neoplastic cells.

Neutrophil-to-Lymphocyte Ratio (NLR)

Recent studies imply that neutrophil count values at the time of diagnosis might harbor a significant role in predicting the prognosis of patients with multiple myeloma. It has been shown that neutrophils can enhance tumor growth, angiogenesis and also can determine immune suppression (13).

Huaqin Zuo et al. studied this ratio on a cohort of 136 patients and the results consistently demonstrated that an elevated NLR translated into shorter overall survival (OS) (5). However, the value of this ratio and its robustness is well questioned by other observers in the literature as a high neutrophil count might not always be the result of the disease itself and could also be determined by a confounding concurrent process, independent from the myeloma. It seems that if the leukocytosis is caused by a paraneoplastic-process, with a raise in G-CSF levels, then it might have the sought predictive value (14).

Monocyte-to-Lymphocyte Ratio (MLR)

The monocyte-to-lymphocyte ratio (MLR) is a blood-based marker that reflects the balance between innate and adaptive immunity. In multiple myeloma (MM), elevated MLR may indicate increased monocyte activity and reduced lymphocyte-mediated tumor surveillance, both contributing to immune dysfunction and disease progression. (nota) Romano A, Parrinello NL, Vetro C, et al. Circulating myeloid-derived suppressor cells correlate with clinical outcome in multiple myeloma patients treated with novel agents (30).

Multiple studies have shown that a high monocyte-to-lymphocyte ratio (MLR) at diagnosis is linked to more aggressive multiple myeloma (MM), including advanced disease stage, greater tumor burden, and shorter overall survival (OS) and progression-free survival (PFS) (31). This may be attributed to the immunosuppressive effects of monocytes and their derivatives in the tumor microenvironment, along with lymphocyte depletion, which impairs the body's ability to generate an effective anti-myeloma immune response. Therefore, MLR reflects both systemic inflammation and the status of immune competence. (32)

MLR is a simple, cost-effective, and reproducible marker derived from routine CBC tests. As a non-invasive prognostic tool, it can complement existing risk models like R-ISS and cytogenetics. When combined with other inflammatory markers such as NLR and PLR, MLR may help refine risk assessment and guide treatment in newly diagnosed or relapsed MM. Further validation is needed to establish its role in routine clinical practice (33).

Conclusions

Multiple myeloma remains a clinically and biologically complex hematologic malignancy, with significant variability in disease presentation, progression, and response to treatment. While advanced scoring systems like the R-ISS have improved prognostication, their reliance on expensive or specialized diagnostic tools limits their applicability in resource-constrained settings. This review highlights the increasingly recognized value of standard hematological parameters—especially those derived from complete blood counts (CBC)—in stratifying risk and predicting outcomes in MM patients.

Among these, the red blood cell indices (e.g., RDW, MCV), neutrophil, lymphocyte, monocyte populations, and derived ratios such as NLR, PLR, and MLR have demonstrated clinical significance. These parameters not only reflect underlying pathophysiological processes such as inflammation, immune dysfunction, and marrow infiltration but also serve as potential cost-effective, accessible prognostic biomarkers.

In conclusion, while not yet a replacement for cytogenetics or advanced molecular profiling, CBC-derived markers represent promising adjunct tools for risk stratification in multiple myeloma. Further prospective studies and standardization of cut-off values are necessary to incorporate these simple, low-cost parameters into routine clinical practice, particularly for global settings with unequal access to specialized diagnostics.

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