

Review Article

Utility of Routine Hematological Parameters in Monitoring Multiple Myeloma Before and After Autologous Peripheral Blood Stem Cell Transplantation: A Narrative Review

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Abstract

Background: Multiple myeloma (MM) is a clonal plasma-cell malignancy, and its diagnosis and monitoring rely mainly on disease-specific investigations. Routine hematological tests remain widely available and are frequently performed before and after autologous peripheral blood stem cell transplantation (aPBSCT), particularly in resource-constrained settings. **Objective:** To evaluate the utility and limitations of complete blood count (CBC), absolute lymphocyte count (ALC), rouleaux formation and erythrocyte sedimentation rate (ESR) in MM before and after aPBSCT, in relation to disease-specific investigations. **Methods:** A narrative review was undertaken of published studies, international consensus recommendations, clinical trials, systematic reviews and major hematology publications. Evidence was synthesized according to whether each investigation provides disease-specific, prognostic, treatment-monitoring, hematopoietic-recovery or supportive information. **Results:** CBC parameters remain essential for assessing anemia, cytopenias, treatment-related toxicity and hematological recovery after transplantation. Early post-transplant ALC recovery is associated with improved progression-free and overall survival, but ALC reflects immune and hematological recovery rather than myeloma burden. Rouleaux formation and ESR may reflect altered plasma protein concentrations but are nonspecific. Serum protein electrophoresis, immunofixation, serum free light-chain analysis, bone marrow assessment, imaging and minimal residual disease testing provide substantially more disease-specific information. **Conclusions:** Routine hematological investigations remain clinically important, particularly for evaluating toxicity, marrow recovery and immune reconstitution. ALC may offer prognostic information after aPBSCT but cannot substitute for disease-specific monitoring, while rouleaux formation and ESR are only supportive. Prospective studies should assess whether ALC and other inexpensive parameters add prognostic value to established biomarkers.

1. Introduction

Multiple myeloma is a malignant plasma-cell disorder characterized by clonal expansion of plasma cells within the bone marrow and production of monoclonal immunoglobulin or immunoglobulin fragments. It represents approximately 10% of hematological malignancies and remains incurable for most patients despite substantial improvements in therapeutic strategies and survival [1–4].

The biological heterogeneity of MM results from multiple genetic and molecular abnormalities. Primary genetic events include immunoglobulin heavy-chain translocations and hyperdiploidy, while secondary abnormalities contribute to disease progression, treatment resistance and differences in clinical outcome [5–7].

The diagnosis of active MM is currently based on the presence of at least 10% clonal bone marrow plasma cells or a biopsy-proven plasmacytoma together with at least one myeloma-defining event. These include conventional CRAB manifestations, namely hypercalcemia, renal impairment, anemia and bone disease, as well as validated biomarkers associated with a very high probability of progression to symptomatic disease [8].

Risk stratification has also evolved considerably. The International Staging System (ISS), Revised International Staging System (R-ISS) and more recent second revision of the ISS (R2-ISS) incorporate clinical, biochemical and cytogenetic characteristics to improve prognostic classification [9–11].

Disease monitoring requires investigations capable of detecting and quantifying monoclonal disease. SPEP, IFE and sFLC analysis remain fundamental laboratory investigations, while bone marrow examination, imaging and MRD assessment provide complementary information regarding disease burden and treatment response [12–15].

Despite these advances, the CBC remains one of the most frequently performed investigations in patients with MM. Hemoglobin, leukocyte count, neutrophil count, platelet count and lymphocyte count provide information about marrow function, treatment-related toxicity and recovery.

Among these parameters, the ALC has attracted particular attention because post-transplant lymphocyte recovery has been associated with clinical outcomes in several hematological malignancies. In MM, early ALC recovery following autologous transplantation has been associated with improved survival [16–19].

Rouleaux formation and ESR are additional laboratory findings historically associated with plasma-cell disorders. Increased circulating immunoglobulins and other plasma proteins can promote erythrocyte aggregation and accelerate erythrocyte sedimentation [20–23]. However, neither parameter is sufficiently specific to serve as a stand-alone disease-monitoring biomarker.

This narrative review therefore examines the extent to which routine hematological investigations remain useful in monitoring MM before and after aPBSCT and clarifies their appropriate relationship with disease-specific investigations.

2. Materials and Methods

2.1. Review Design

A narrative literature review was conducted to evaluate the utility of routine hematological investigations and disease-specific laboratory methods used in patients with MM before and after aPBSCT. The review focused on the biological characteristics and diagnosis of MM, laboratory methods used for disease monitoring, routine hematological parameters, ALC and post-transplant immune recovery, rouleaux formation, ESR, autologous transplantation, and the relationship between routine hematological findings and established disease-specific biomarkers.

2.2. Literature Identification

Relevant publications were identified through PubMed/MEDLINE and major hematology and oncology journals. Search concepts included combinations of the terms “multiple myeloma,” “absolute lymphocyte count,” “lymphocyte recovery,” “autologous stem cell transplantation,” “rouleaux,” “erythrocyte sedimentation rate,” “serum protein electrophoresis,” “immunofixation,” “serum free light chains,” and “minimal residual disease.”

Priority was given to international consensus criteria, laboratory recommendations, major randomized clinical trials, systematic reviews, meta-analyses and studies specifically investigating hematological recovery following autologous transplantation.

2.3. Narrative Synthesis

The identified evidence was synthesized narratively according to the clinical purpose of each investigation. Particular attention was given to whether an investigation provided disease-specific information, information regarding treatment-related toxicity, hematopoietic recovery, prognostic information or nonspecific supportive information. Because this study was designed as a narrative review, no quantitative meta-analysis was undertaken.

3. Results of the Narrative Synthesis

3.1. Current Approach to Diagnosis and Monitoring of Multiple Myeloma

Current diagnostic criteria distinguish active MM from precursor conditions such as monoclonal gammopathy of undetermined significance and smoldering MM. The SLiM-CRAB framework incorporates both conventional organ damage and biomarkers that identify patients at very high risk of progression [8].

Recent clinical updates continue to emphasize that diagnosis requires at least 10% clonal bone marrow plasma cells or a biopsy-proven plasmacytoma plus a myeloma-defining event, including CRAB features or validated biomarkers such as at least 60% clonal bone marrow plasma cells, an involved/uninvolved sFLC ratio of at least 100 under specified conditions, or more than one focal lesion on MRI [2–4, 8].

Disease monitoring requires an understanding of the biology of the monoclonal protein. SPEP provides quantitative assessment of an M-protein when measurable, whereas IFE identifies the immunoglobulin heavy- and light-chain type with greater analytical sensitivity [12, 24].

sFLC testing provides quantitative assessment of circulating free κ and λ light chains and their ratio. It is particularly valuable in patients with light-chain disease and contributes to diagnostic and response assessment [13, 25, 26].

The European Myeloma Network recommends appropriate integration of serum and urine monoclonal protein studies, sFLC analysis, bone marrow examination and other investigations according to disease characteristics and clinical circumstances [12]. Laboratory testing for monoclonal gammopathies should therefore be interpreted as an integrated diagnostic process rather than through reliance on a single assay [14].

Bone marrow examination remains important for diagnosis, cytogenetic assessment and response evaluation. MRD techniques, particularly next-generation flow cytometry and next-generation sequencing, provide substantially deeper assessment of residual clonal plasma cells than conventional morphology [15, 27–29].

Imaging is similarly important because skeletal and extramedullary disease cannot be adequately assessed using peripheral blood hematology alone. Whole-body low-dose CT, MRI and PET/CT have complementary roles in disease assessment [30, 31].

4. Routine Hematological Investigations

4.1. Complete Blood Count

The CBC remains a fundamental investigation throughout the MM treatment pathway. Anemia is frequently observed at diagnosis and may result from marrow infiltration, renal impairment, inflammatory mechanisms and other disease- or treatment-related factors. Leukopenia and thrombocytopenia may occur because of marrow involvement or chemotherapy-related myelosuppression [3, 4].

Following high-dose conditioning and aPBSCT, CBC monitoring becomes particularly important because it provides immediate information regarding neutrophil recovery, platelet recovery, anemia, transfusion requirements, infection risk, bleeding risk and treatment-related marrow suppression. Therefore, CBC parameters have substantial clinical value even though they do not directly quantify myeloma burden.

4.2. Absolute Lymphocyte Count

ALC is calculated from the total leukocyte count and lymphocyte percentage. It is routinely available as part of the CBC and requires no additional laboratory testing.

The potential prognostic significance of ALC following autologous transplantation is thought to relate partly to immune reconstitution. Porrata et al. demonstrated an association between early lymphocyte recovery and survival following autologous hematopoietic stem cell transplantation [16].

Hiwase et al. subsequently demonstrated that ALC recovery following ASCT in MM was associated with clinical outcome and that early ALC could provide prognostic information [17]. In their study, an ALC of at least $1.0 \times 10^9/\text{L}$ at day 30 was associated with longer overall and progression-free survival [17].

The evidence was further strengthened by Jimenez-Zepeda et al., who evaluated 769 consecutive patients with MM undergoing single ASCT. An ALC of at least 1400 cells/ μL at specified post-transplant time points was associated with improved overall survival, and multivariable analysis demonstrated that ALC was an independent prognostic factor [18].

These findings support the hypothesis that ALC may reflect aspects of host immune competence and post-transplant recovery. However, ALC should not be interpreted as a direct measurement of residual myeloma. A patient may demonstrate excellent lymphocyte recovery while retaining measurable residual disease, whereas delayed lymphocyte recovery does not necessarily indicate persistent or progressive myeloma.

4.3. Lymphocyte Dose and Immune Recovery

The relationship between lymphocyte recovery and outcome may begin with the cellular composition of the autologous graft. Porrata et al. demonstrated that the infused lymphocyte dose correlated with subsequent ALC recovery and clinical outcomes following autologous transplantation in MM [19].

This observation provides biological support for the concept that post-transplant lymphocyte recovery is not simply a nonspecific hematological phenomenon but may reflect clinically relevant immune reconstitution. Nevertheless, immune recovery involves multiple lymphocyte populations, and total ALC does not distinguish between T cells, B cells and natural killer cells. Studies evaluating lymphocyte subsets have demonstrated that immune reconstitution following ASCT is heterogeneous [32].

5. Rouleaux Formation

Rouleaux formation refers to the arrangement of erythrocytes into stacked aggregates resembling a column of coins. The phenomenon is influenced by plasma protein concentration and the physicochemical forces acting between erythrocytes. Experimental studies have demonstrated that plasma proteins can markedly influence erythrocyte aggregation [20, 21].

Because MM may be associated with high concentrations of monoclonal immunoglobulins, rouleaux can be a prominent peripheral blood-film finding. However, rouleaux formation is not specific for MM and can occur in other conditions associated with increased plasma proteins or inflammatory states.

Therefore, rouleaux may provide a useful morphological clue, particularly when observed together with other findings suggestive of a plasma-cell disorder, but it cannot reliably quantify monoclonal protein burden. The potential value of standardized rouleaux grading

deserves further investigation. Prospective studies comparing rouleaux grade with SPEP, IFE, sFLC measurements and clinical outcomes could determine whether this inexpensive morphological finding has additional prognostic value.

6. Erythrocyte Sedimentation Rate

ESR is influenced by plasma protein concentration, erythrocyte aggregation, hematocrit and other physiological and pathological factors. Increased fibrinogen and immunoglobulin concentrations can enhance erythrocyte aggregation and accelerate sedimentation [22].

Historically, a markedly elevated ESR has been recognized as a supportive finding in plasma-cell disorders. However, ESR is inherently nonspecific. An increased ESR may occur because of anemia, infection, inflammation, age-related changes or increased plasma proteins [22, 23].

Consequently, ESR should not be used as an independent marker of active MM. Changes in ESR during treatment similarly cannot reliably distinguish between reduction in tumor burden and changes caused by other physiological factors. Its principal contemporary value is therefore as an inexpensive supportive investigation rather than a disease-specific monitoring test.

7. Disease-Specific Laboratory Investigations

7.1. Serum Protein Electrophoresis and Immunofixation Electrophoresis

SPEP is useful for identifying and quantifying monoclonal proteins in serum. IFE provides more sensitive characterization of monoclonal immunoglobulin type [12, 24]. These investigations are central to monitoring patients with measurable secretory disease because changes in monoclonal protein levels can be used to assess treatment response.

7.2. Serum Free Light Chains

sFLC analysis measures free κ and λ light chains and provides the involved-to-uninvolved FLC ratio. The assay is particularly important in light-chain MM and contributes to both diagnosis and disease monitoring [13, 25, 26]. Unlike ALC, rouleaux or ESR, the sFLC assay provides information more directly related to monoclonal plasma-cell activity.

However, interpretation of sFLC results should consider renal function and the clinical context because altered renal clearance can influence circulating free light-chain concentrations [13]. Serum FLC testing may be particularly valuable in oligosecretory disease and in circumstances where conventional monoclonal protein assessment is less informative [13, 26].

7.3. Bone Marrow Examination

Bone marrow aspiration and biopsy remain important for determining the proportion and phenotype of clonal plasma cells and for performing cytogenetic and molecular investigations. Bone marrow examination is also essential for many MRD strategies [15, 27–29]. Its major limitation is invasiveness, which makes repeated assessment less convenient than peripheral blood testing.

7.4. Minimal Residual Disease

MRD assessment has become one of the most sensitive measures of treatment response in MM. The IMWG has established standardized criteria for MRD assessment and response evaluation [15, 33]. Next-generation flow cytometry can detect residual clonal plasma cells at very low levels, while next-generation sequencing provides another highly sensitive approach [27, 28].

A large meta-analysis demonstrated a strong association between MRD negativity and improved survival outcomes [29]. Therefore, although routine hematological parameters may provide supportive prognostic information, MRD currently provides much more direct information about residual malignant disease.

8. Autologous Peripheral Blood Stem Cell Transplantation

High-dose chemotherapy followed by autologous stem cell rescue remains an important treatment strategy for eligible patients with multiple myeloma. Early randomized trials demonstrated improved disease control with high-dose therapy and autologous transplantation compared with conventional treatment [34, 35]. Subsequent systematic reviews and meta-analyses have confirmed the role of autologous transplantation in appropriately selected patients, although its optimal timing and integration with contemporary induction and maintenance strategies continue to evolve [33, 36–39].

High-dose melphalan remains the principal conditioning regimen used before autologous peripheral blood stem cell transplantation (aPBSCT) [40]. Modern induction therapy commonly incorporates combinations of proteasome inhibitors, immunomodulatory drugs, and corticosteroids. Bortezomib-containing triplet regimens have been extensively evaluated, while more recent clinical trials have incorporated daratumumab into transplant-based treatment strategies [41–45].

Maintenance therapy, particularly with lenalidomide, has further improved outcomes following transplantation [46–50]. These therapeutic developments highlight the importance of interpreting routine hematological parameters within the broader context of contemporary multiple myeloma management. Although routine hematological investigations remain readily available and clinically valuable, they primarily provide information on hematopoietic recovery, treatment-related toxicity, and immune status rather than directly measuring residual myeloma burden Table 1.

Table 1: Comparison of routine hematological and disease-specific investigations used in the monitoring of multiple myeloma before and after autologous peripheral blood stem cell transplantation

Investigation	Main information	Clinical value	Main limitation
Hemoglobin	Red-cell status	Assessment of anemia and marrow function	Nonspecific
Total WBC count	Leukocyte status	Infection risk and marrow recovery	Nonspecific
Neutrophil count	Myeloid recovery	Infection risk and engraftment	Not disease-specific
ALC	Lymphocyte recovery	Prognostic and immune-recovery information	Does not directly measure tumor burden
Platelet count	Megakaryocytic recovery	Marrow recovery and bleeding risk	Nonspecific
Rouleaux	Plasma protein-related erythrocyte aggregation	Supportive morphological clue	Nonspecific
ESR	Plasma protein and inflammatory effects	Supportive finding	Poor specificity
SPEP	M-protein	Disease monitoring	Limited in some low-secretory/nonsecretory disease
IFE	Monoclonal protein characterization	Sensitive response assessment	Less quantitative
sFLC/ λ : κ ratio	Free light-chain production	Diagnosis and monitoring	Interpretation affected by renal function
Bone marrow examination	Clonal plasma cells	Diagnosis and MRD assessment	Invasive
Imaging	Bone and extramedullary disease	Disease assessment	Cost and access considerations
MRD	Residual clonal disease	Deep response assessment and prognostic information	Requires specialized testing

The table illustrates that routine hematological parameters and disease-specific investigations provide complementary information. In particular, complete blood count parameters are valuable for evaluating hematopoietic recovery and treatment-related complications following aPBSCT, whereas investigations such as SPEP, IFE, sFLC analysis, bone marrow assessment, imaging, and MRD testing provide more direct information regarding disease status. ALC may have additional prognostic relevance because lymphocyte recovery following transplantation has been associated with clinical outcomes; however, its role should be interpreted as complementary rather than as a replacement for established disease-specific investigations.

9. Hematological Recovery Following aPBSCT

High-dose conditioning produces profound temporary bone marrow suppression. During the early post-transplant period, serial CBC testing is essential for evaluating neutrophil and platelet recovery and identifying complications.

ALC recovery occurs alongside broader immune reconstitution but may follow a different pattern from neutrophil and platelet engraftment. The association between early ALC recovery and outcome is particularly relevant because ALC is automatically available from the CBC and does not require specialized testing [16–19, 32].

However, the evidence should not be overinterpreted. Different studies have examined different time points and thresholds, and ALC is affected by several factors, including disease status, conditioning, graft composition, infection and treatment. Consequently, a universal ALC cutoff for routine MM disease monitoring cannot currently be recommended.

10. Routine Hematological Parameters Versus Disease-Specific Monitoring

The principal distinction between routine and disease-specific investigations is the biological process being measured. Routine hematological parameters primarily provide information regarding hematopoiesis, treatment toxicity, immune recovery and nonspecific systemic effects, whereas disease-specific investigations more directly assess monoclonal protein production, clonal plasma cells, skeletal disease and residual malignant disease.

The table illustrates that routine and disease-specific investigations should not be viewed as competing approaches. Rather, they answer different clinical questions and are most informative when interpreted together.

11. Potential Role of ALC in Resource-Constrained Settings

The potential clinical relevance of ALC is particularly important in healthcare systems where specialized MM investigations may not be consistently available. CBC testing is generally inexpensive and widely accessible, giving ALC an important practical advantage over specialized investigations.

However, affordability and availability do not establish diagnostic specificity. The appropriate approach is therefore to use ALC as a complementary prognostic or immune-recovery marker while maintaining disease-specific tests whenever possible.

For example, a patient with improved ALC following transplantation may be considered to have favorable hematological and immune recovery, but confirmation of disease response should still rely on SPEP, IFE, sFLC, bone marrow/MRD and imaging as clinically indicated [12, 15, 30, 51].

This distinction is particularly important in resource-limited settings, where an inexpensive test can easily be overinterpreted when more specific tests are unavailable. International recommendations emphasize adapting essential diagnostic and monitoring strategies to local resource availability while retaining appropriate standards of care [51]. Contemporary experience from resource-constrained settings similarly illustrates the challenges posed by access, cost and transplant infrastructure [39].

12. Potential Relationship Between ALC, Rouleaux and Monoclonal Protein

The three routine parameters considered in this review—ALC, rouleaux formation and ESR—reflect different biological processes. ALC primarily reflects the number of circulating lymphocytes and may provide information about immune recovery and prognosis. Rouleaux formation reflects erythrocyte aggregation influenced by plasma protein composition, while ESR reflects the combined effects of plasma proteins, erythrocyte aggregation and other physiological variables.

In contrast, SPEP, IFE and sFLC analysis provide information regarding monoclonal immunoglobulin production, while bone marrow examination and MRD directly assess residual clonal plasma cells [12–15, 27–29]. Consequently, routine hematological parameters should be interpreted primarily as supportive or prognostic measures, whereas disease-specific investigations should remain the principal tools for evaluating disease burden and treatment response.

13. Clinical Implications

The evidence reviewed in this narrative indicates that routine hematological investigations remain important throughout the treatment pathway of patients with MM. CBC parameters provide continuous information regarding anemia, treatment-related cytopenias, neutrophil and platelet recovery, infection risk, bleeding risk and hematopoietic recovery following transplantation. These parameters therefore retain substantial clinical value despite their inability to directly quantify the underlying myeloma burden.

Among routine hematological parameters, ALC may provide additional prognostic information following aPBSCT. Several studies have reported associations between early post-transplant lymphocyte recovery and improved clinical outcomes [16–19]. This finding may reflect the contribution of immune reconstitution to disease control and survival. Nevertheless, ALC should be interpreted as a prognostic or immune-recovery parameter rather than as a direct marker of residual myeloma.

Rouleaux formation and ESR may also provide supportive laboratory information. Rouleaux can reflect alterations in plasma protein concentrations, particularly increased immunoglobulins, while ESR is influenced by plasma proteins, erythrocyte aggregation, hematocrit and inflammatory processes [20–23]. However, both parameters lack sufficient specificity to be used independently for assessment of disease activity or treatment response.

The most appropriate approach is therefore an integrated laboratory strategy in which routine hematological investigations complement, rather than replace, disease-specific investigations. SPEP, IFE, sFLC analysis, bone marrow examination, imaging and MRD assessment provide substantially more direct information regarding monoclonal disease, residual clonal plasma cells and treatment response [12–15, 27–31]. In patients with relapsed or refractory disease, contemporary treatment recommendations further emphasize the importance of disease-specific response assessment and appropriate selection of subsequent therapy [52].

14. Future Research

Further prospective studies are warranted to evaluate routine hematological parameters alongside established biomarkers of MM. Future investigations should simultaneously assess CBC parameters, ALC, neutrophil and platelet recovery, rouleaux grade, ESR, SPEP, IFE, sFLC concentrations and κ/λ ratio, bone marrow plasma-cell percentage, MRD status and relevant imaging findings, while also examining progression-free survival and overall survival. Such studies could determine whether ALC provides prognostic information that is independent of established disease-risk factors, treatment response and transplant-related variables.

The relationship between rouleaux formation and monoclonal protein concentration also warrants systematic investigation. Standardized microscopic or digital assessment of rouleaux could be compared with quantitative SPEP, IFE and sFLC measurements to determine whether the degree of erythrocyte aggregation provides additional clinical or prognostic information. Similarly, longitudinal assessment of ESR could clarify whether changes following treatment provide any incremental information when interpreted alongside disease-specific biomarkers.

Importantly, future studies should distinguish between prognostic association and biological surrogacy. Although ALC may be associated with survival following aPBSCT, this does not establish that ALC directly reflects myeloma tumor burden. Prospective studies with standardized ALC measurement time points, predefined thresholds and concurrent assessment of MRD and monoclonal protein response will be necessary before ALC can be considered for incorporation into validated disease-monitoring algorithms.

15. Strengths and Limitations

This review has several strengths. First, it considers routine hematological parameters within the context of contemporary MM laboratory monitoring rather than treating them as independent diagnostic tests. Second, it incorporates evidence concerning post-transplant lymphocyte recovery and the prognostic significance of ALC. Third, it emphasizes the distinction between inexpensive routine laboratory investigations and specialized disease-specific tests.

However, this review has limitations. It is a narrative rather than systematic review and therefore does not provide a formal PRISMA-based systematic search or quantitative meta-analysis. The literature concerning ALC includes retrospective studies using different assessment time points and thresholds. Evidence concerning rouleaux and ESR as MM monitoring markers is also considerably weaker than the evidence supporting SPEP, IFE, sFLC and MRD.

Consequently, the potential role of ALC should be regarded as prognostic and hypothesis-generating rather than as a replacement for established response criteria.

16. Conclusions

Routine hematological investigations remain clinically relevant in patients with MM before and after aPBSCT. CBC parameters are indispensable for monitoring anemia, treatment-related cytopenias, infection risk and hematological recovery.

Among CBC-derived parameters, ALC is particularly promising because several studies have demonstrated an association between early post-transplant lymphocyte recovery and survival [16–19]. Nevertheless, ALC does not directly measure myeloma burden and should not replace SPEP, IFE, sFLC analysis, bone marrow assessment, imaging or MRD.

Rouleaux formation and ESR may provide supportive clues related to increased plasma protein concentrations, but both are nonspecific. The appropriate role of routine hematological investigations is therefore complementary rather than substitutive. Future prospective research should determine whether combinations of ALC, rouleaux grading and other routine laboratory parameters can provide additional prognostic information when integrated with established disease-specific biomarkers.

Article Information

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