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REVIEW

Defining High-Risk Disease Biology in Multiple Myeloma: A Narrative Review

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Abstract: Although modern therapies have significantly improved survival, multiple myeloma (MM) remains incurable and biologically heterogeneous, resulting in substantial variability in treatment response and outcomes. Effective risk stratification is therefore critical to guide therapy intensity, predict relapses, and inform prognosis. This review critically examines the current biological determinants of high-risk MM and their implications for treatment intensification, selection of novel therapeutic agents, and stratified clinical trial enrollment. High-risk MM is driven by three major biological determinants: (1) molecular and genomic abnormalities, including high-risk IgH translocations, del(17p), TP53 mutation, gain(1q), and high-risk gene expression signatures; (2) increased proliferative capacity, with an elevated plasma-cell S-phase fraction identifying a subgroup with markedly inferior survival independent of conventional staging; and (3) extramedullary dissemination biology, reflected by circulating tumor cells and soft-tissue extramedullary disease, both associated with marrow independence, clonal evolution, and poor outcomes. The 2024 IMS/IMWG framework integrates the genomic aspects of these biological markers and certain clinical factors into a more precisely defined disease. Complementing baseline classification, dynamic risk stratification using measurable residual disease (MRD) provides real-time prognostic refinement across the treatment course. Future advances will rely on comprehensive molecular profiling and AI-driven data integration to enable precision-guided treatment based on individualized disease biology.

Keywords: high-risk disease, outcomes, multiple myeloma

Background

Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by the proliferation of abnormal clonal plasma cells within the bone marrow that disrupt normal hematopoiesis and promote osteolysis. They also mostly secrete excessive amounts of monoclonal proteins, either whole immunoglobulins (ie, M-protein or spike) and/or light chain fragments. They ultimately lead to end-organ damage that can manifest clinically via the development of any of the following: lytic bone lesions, anemia, renal impairment, and hypercalcemia. The global burden of MM continues to grow, with an estimated almost 188,000 new cases and over 121,000 deaths reported in 2022.[1] In the United States, MM accounts for approximately 1% of all new cancer diagnoses and is the second most common hematologic malignancy.[2]

Despite advances in treatment—including proteasome inhibitors, immunomodulatory drugs, anti-CD38 monoclonal antibodies, and autologous stem cell transplantation (ASCT)—leading to an improvement in overall survival,[3,4] MM remains incurable for many patients and biologically heterogeneous where it is marked by cycles of remission and relapse.[5] This biological heterogeneity translates into considerable variability in clinical outcomes among patients with MM. As such, accurate risk stratification in MM is vital for tailoring treatment strategies to individual MM patients based on their disease biology. Current risk stratification frameworks attempt to classify MM patients as standard risk based on their expectation to follow a pattern of early and consistent response to therapy with longer periods of disease control. In contrast, patients with high-risk disease are expected to typically respond well to standard therapies but then later develop early drug resistance, necessitating frequent therapy changes due to frequent relapses resulting in an exhaustion of existing therapies and early mortality. Risk stratification in MM is critical because it enables clinicians to tailor therapy intensity, assess the timing of interventions like ASCT, and set realistic expectations about treatment outcomes, especially

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for those with high-risk disease who generally experience poorer long-term responses to standard therapies. Furthermore, as therapies continue to change leading to improved clinical outcomes for MM patients, the risk stratification criteria will need to continue to evolve to remain relevant.

Earlier staging frameworks, such as the International Staging System (ISS) relied primarily on serum biochemical markers such as serum β_2-microglobulin and serum albumin levels. While this model provided valuable prognostic information, it failed to capture the full spectrum of biological heterogeneity in MM as it did not account for key cytogenetic abnormalities associated with high-risk disease. The Revised International Staging System (R-ISS) and the second iteration of the R-ISS known as R2-ISS were improvements to the ISS by including the impact of adverse cytogenetic abnormalities. However, the therapeutic landscape of MM has once again shifted dramatically over the past decade via the utilization of anti-CD38 monoclonal antibodies, next-generation proteasome inhibitors, and the utilization of quadruplet induction regimens which have all improved outcomes across all risk groups, effectively rendering select previously defined high-risk features less clinically impactful. Thus, this evolution in therapy options necessitated yet another updated risk stratification system that recognized the entities of double- and triple-hit disease—defined by the co-occurrence of multiple adverse cytogenetic abnormalities. This need for a revised, biologically informed, and globally standardized definition of high-risk MM led to the development of the most recent 2025 IMS/IMWG framework for genomically high risk disease. This review will integrate molecular, proliferative, and extramedullary disease determinants within the context of the updated 2024 IMS/IMWG framework. The iterative refinements—from ISS to R-ISS to R2-ISS and now the IMS/IMWG consensus high risk definition—reflect a progressive integration of tumor burden, cytogenetic risk, and treatment-era–specific prognostic variables. This transition underscores the field's movement of its staging models toward a more biologically driven risk stratification approach that is contemporary to the therapeutic modalities available.

This review will explore our current understanding of high-risk disease biology given its implications in clinical practice for determining optimal induction therapies and future clinical trial design.

Disease Biology-Related Factors Associated with Clinical Outcomes

Disease biology-related factors closely associate with determining outcomes in MM and can be categorized as 1) molecular and genomic abnormalities, 2) proliferative capacity and 3) extramedullary disease biology.

Molecular and Genomic Abnormalities

Cytogenetic abnormalities form the cornerstone of biological classification in MM.[6] Primary genetic events, which arise early—often during the precursor MGUS phase—include trisomies of odd-numbered chromosomes and IgH translocations involving the immunoglobulin heavy chain gene on the 14q32 locus with one of several different partner genes on other chromosomes such as CCND1 on chromosome 11, ie. t(11;14), or FGFR3/MMSET on chromosome 14, ie. t(4;14). These translocations, such as t(11;14), t(4;14), t(6;14), t(14;20) and t(14;16), dysregulate key oncogenes (eg, *CCND1, FGFR3/MMSET, MAF*), driving clonal plasma cell proliferation. These IgH translocation events are typically mutually exclusive and delineate distinct genomic subtypes with differing biological behaviors and initial therapeutic responses. In t(4;14), it is found that the NSD2 breakpoint location impacts prognosis, with "late-disruption" events within the gene associated with inferior survival.[7] Finally, in the 1–3% of MM patients with MAF translocations such as t(14;16) and t (14;20), it is observed that they are enriched for APOBEC mutational signatures,[8] and frequently co-occur with other secondary high risk cytogenetics such as 1q21+ and del(17p).

Secondary cytogenetic alterations, including gain or amplification of 1q, deletion of 1p, del(17p), del(13q), and MYC rearrangements, emerge later and are associated with disease progression, treatment resistance, and worse outcomes. Deletion of 17p or monosomy 17 which contains the TP53 gene is known to confer an adverse outcome as does TP53 mutations or inactivation.[9,10] Similarly, biallelic deletion of 1p32—driven primarily by CDKN2C loss—also confer a markedly poor prognosis.[11] Outcomes among patients with 1q21+ are heterogeneous, influenced by large-scale genomic events such as chromothripsis or co-occurring high-risk cytogenetic abnormalities, and the degree of 1q copy gain such as 4 or copies as in amplification.[12]

Gene expression profiling (GEP) has emerged as a powerful tool for risk stratification in MM, offering greater prognostic precision than traditional methods such as FISH or ISS/R-ISS. Signatures like GEP70 (UAMS-70) and EMC-92 (SKY92) evaluate the expression of genes involved in cell cycle control, apoptosis, and tumor–microenvironment interactions, effectively identifying high-risk patients—including those overlooked by conventional cytogenetics. EMC-92, in particular, has demonstrated superior predictive accuracy for progression-free and overall survival.[13] However, targeted GEP panels may miss emerging biomarkers detectable through whole-transcriptome or single-cell RNA sequencing. The advent of next-generation sequencing has identified additional prognostic biomarkers, such as mutations in *NRAS, KRAS, BRAF*, structural aberrations like chromothripsis, and MYC activation.[14–16]

Proliferative Capacity

The S-phase represents the *synthetic phase* of the cell cycle, where DNA replication occurs—an indicator of cellular proliferation. In MM, the fraction of clonal plasma cells in S-phase reflects tumor growth kinetics. Thus, a higher S-phase proportion identifies plasma cells with more aggressive biological behavior.[17] Historically, the *plasma cell labeling index (PCLI)* performed at Mayo Clinic measured proliferation but was labor-intensive slide-based methodology. Recently, a flow cytometry–based *plasma cell proliferation (PCPRO)* assay has been developed, which is simple, scalable, and quantifies the proportion of clonal plasma cells with DNA content between G0/G1 and G2/M peaks using DAPI staining and immunophenotyping (CD19, CD38, CD45, CD138, cytoplasmic kappa and lambda). In a recent study, among 823 newly diagnosed MM patients, 16% had S-phase ≥2% at diagnosis.[18] These patients experienced markedly poorer outcomes with a median PFS of 1.4 years vs. 2.9 years for S-phase <2% (HR 1.6, $p<0.0001$) and a median OS of 3.9 years vs. 9.2 years (HR 2.2, $p<0.0001$). Furthermore, the S-phase ≥2% remained an independent predictor of inferior PFS (HR 1.56, $p=0.001$) and OS (HR 2.0, $p<0.0001$) even after adjusting for R2-ISS risk, age, renal function, and treatment strategy. Most importantly, an elevated S-phase provided complementary and additive prognostic value to established risk systems such that those with *both* S-phase ≥2% and high-risk cytogenetics had the worst outcomes (median OS 3.1 years) and two-thirds of patients with elevated S-phase were not classified as high-risk by R2-ISS or IMS models, identifying a previously unrecognized "functional high-risk" subgroup.

Extramedullary Disease Biology

Circulating Tumor Cells

Circulating tumor cells (CTCs) are clonal plasma cells that have egressed from the bone marrow into peripheral blood. Their detection initially evaluated by morphology on a peripheral smear but was not very sensitive or specific. However, now it's primarily assessed by *multiparametric flow cytometry*, which provides a sensitive and quantitative measure of disease dissemination and aggressiveness. CTCs possess unique biological characteristics—including reduced expression of adhesion and integrin molecules—that facilitate independence from the marrow microenvironment and enable systemic spread.[19] CTCs are enriched in patients with high-risk cytogenetic features, including TP53 inactivation and 1q gain as well as t(11;14).[20] Even very low CTC levels (≥0.01–0.07%) are associated with inferior progression-free and overall survival in newly diagnosed MM, independent of cytogenetic risk or ISS stage.[21,22] Primary plasma cell leukemia (pPCL) is the most aggressive plasma cell dyscrasia and has historically been defined by ≥20% circulating plasma cells or $\geq 2\times10^9$/L plasma cells in blood. Modern definitions now classify pPCL based on ≥5% circulating plasma cells by morphology.[23] However, recent flow cytometry–based studies have revealed that patients with ≥2% CTCs exhibit outcomes indistinguishable from pPCL—with median overall survival of roughly 14–15 months.[24] CTCs thus serve as a continuum marker between MM and pPCL. Patients with 2–20% CTCs, though not meeting the strict morphologic definition of pPCL, share similar transcriptomic signatures, poor clinical outcomes, and diminished response to therapy. This overlap supports redefining pPCL and tailoring therapies for "PCL-like" MM accordingly.[20] Elevated CTC levels at diagnosis are independently associated with inferior progression-free and overall survival, even when accounting for R-ISS and R2-ISS staging.[25,26]

Extramedullary Disease (EMD)

It is defined by myeloma infiltration outside the bone marrow—either as soft tissue plasmacytomas or visceral involvement—is associated with poor prognosis, particularly when present at relapse.[27] Detection relies on advanced imaging such as PET-CT or MRI, as conventional skeletal surveys often fail to identify these lesions. EMD frequently co-occurs with circulating tumor cells (CTCs), reflecting a biologically aggressive phenotype characterized by marrow independence, immune evasion, and enhanced clonal spread. EMD displays a distinct and genomically complex biology characterized by near-universal activation of the MAPK signaling pathway (NRAS, KRAS, and BRAF mutations in 94% of cases). Compared with matched bone marrow samples, EMD tumors show a higher tumor mutational burden and enrichment for 1q gain/amplifications, biallelic MAX and CDKN2C alterations, and frequent mutations in genes involved in chromatin remodeling (ARID1A, KMT2C/D, EP300) and cell adhesion/migration (ROBO1, ROBO2, FAT1).[28] These mutations are often clonal and suggest evolutionary selection for MAPK-driven, marrow-independent subclones capable of egressing from the bone marrow and soft-tissue infiltration. Thus, EMD biology reflects advanced MM evolution, with extensive genomic instability and loss of adhesion signaling, defining a tumor that is highly proliferative, genetically unstable, and resistant to conventional therapies.

The IMS/IMWG Definition of "High Risk" in 2025

With the advent of novel therapies, certain high-risk features have been able to be overcome necessitating a realignment with what constitutes high risk disease in today rather than 10 years ago. A newly recognized high-risk subset, double-hit and triple-hit myeloma, is defined by the accumulation of two or more high-risk cytogenetic abnormalities, including del(17p), t(4;14), gain (1q), and TP53 mutations. These patients exhibit markedly inferior progression-free and overall survival, along with an increased risk of early extramedullary relapse. Incorporating double- and triple-hit status into revised staging systems such as R2-ISS and RW-ISS enhances risk stratification and supports the implementation of precision-guided therapeutic strategies. Thus, the International Myeloma Society (IMS) and International Myeloma Working Group (IMWG) recently introduced a revised risk stratification framework in 2025 for MM.[29] This model defined high-risk MM by the presence of del(17p), TP53 mutation, or biallelic deletion of 1p32 as independent high-risk features. An elevated β_2-microglobulin (>5.5 mg/L) with normal serum creatinine (<1.2 mg/dL) was also recognized as an adverse, independent prognostic factor. In addition, patients with two or more intermediate-risk lesions—including 1q21 gain/amplification, t(4;14), t(14;16), or monoallelic del(1p32)—were classified as high-risk but not stand-alone individual abnormalities. Using this new schema, approximately 20% of newly diagnosed patients fall into the high-risk category. Adoption of the IMS/IMWG 2025 framework is recommended to ensure standardized, reproducible risk assessment and to facilitate harmonized clinical trial design for high-risk MM. The mSMART guidelines (www.msmart.org), developed at Mayo Clinic, incorporate these IMS/IMWG criteria for high risk in addition to the other aforementioned biological determinants of high risk disease such as high proliferative capacity and extramedullary disease biology as listed in BOX 1 making it the most biologically comprehensive risk stratification tool for newly diagnosed MM.

Currently, this risk stratification can be utilized to inform clinical decision-making at every stage of management. For newly diagnosed MM patients classified as high-risk, an intensive induction therapy is preferable with the use of quadruplet regimens, which have demonstrated superior depth and duration of hematologica response compared to less intensive therapies such as triplets or doublets. Autologous stem cell transplantation remains a critical consolidation strategy for all eligible patients, but even more so in high-risk patients. During maintenance, extended or continuous therapy—particularly with doublet-based therapies containing any two different classes of drugs such as proteasome inhibitors, immunomodulators or anti-CD38 monoclonal antibodies given their higher risk of early relapse and clonal evolution. Furthermore, high-risk classification should actively guide clinical trial enrollment, as these patients represent the population most likely to benefit from novel agents including T-cell engagers and CAR-T cell therapies. Aligning risk classification with therapeutic strategy is therefore essential to translating biological insight into improved patient outcomes.

Dynamic Risk Stratification

MM risk stratification progressed from static, diagnosis-based models to dynamic frameworks that incorporate treatment response and disease evolution over time. Dynamic risk assessment, particularly through measurable residual disease (MRD) monitoring, offers real-time prognostic insight. MRD in MM refers to the presence of malignant plasma cells below the threshold of

BOX 1 Summary of Criteria Used to Identify High-Risk Disease Biology in Newly Diagnosed Multiple Myeloma (NDMM) (Adapted from mSMART v2024)

High Risk Cytogenetic/Genomic Abnormalities ▪ Del 17p[a] and/or *TP53* mutation[b] ▪ Bi-allelic del 1p[b] ▪ t(4;14), (14;16), or t(14;20) *plus* either Gain/Amp 1q or Del 1p ▪ Gain/Amp 1q *plus* Del 1p
β2M >5.5 with normal renal function
High Proliferative Capacity ▪ High Plasma Cell S-phase percentage
Extramedullary Biology ▪ Primary plasma cell leukemia (defined by >5% circulating tumor/plasma cells by morphology on a peripheral smear) ▪ Newly diagnosed myeloma with extramedullary disease

Notes: [a]The threshold for considering del(17p) positivity on FISH is if the abnormality is detected in ≥ 20% of clonal plasma cells assessed. [b]Assessments for TP53 mutations and biallelic deletion of 1p require genomic sequencing techniques.

conventional detection, assessed using highly sensitive techniques such as next-generation flow cytometry (NGF) and next-generation sequencing (NGS), often in combination with PET/CT for extramedullary disease. The IMWG has standardized MRD assessment, validating NGF and NGS assays with sensitivities up to 10^{-6}, though sample quality and reproducibility remain challenges.

Achieving a deep response, particularly MRD negativity, is a strong prognostic factor in multiple myeloma—surpassing even cytogenetic risk in predictive value. In a pooled analysis of three different, GEM (Grupo Español de Mieloma) 2000 and GEM2005MENOS65 studies for transplant-eligible MM and the GEM2010MAS65 clinical trial for elderly patients with MM who had MRD assessments performed, patients who attained MRD negativity at a sensitivity of 10^{-6} had minimal risk of progression, regardless of high-risk cytogenetics, suggesting that deep molecular remission may mitigate the impact of adverse genomic features.[30] In addition, sustained MRD negativity further reduces relapse risk, while MRD resurgence often precedes clinical relapse.[31] MRD tracking can also detect clonal evolution linked to therapeutic resistance. However, data from the MASTER trial reveal that patients with ≥2 high-risk FISH abnormalities are more likely to experience MRD resurgence or progression after treatment discontinuation, despite initially achieving MRD negativity.[32] This underscores the importance of dynamic risk assessment, which enhances prognostication and guides clinical decisions but should complement—not replace—baseline risk stratification at diagnosis.

Future Directions

The future of MM risk stratification lies in a deeper, more granular understanding of disease biology and patient-specific characteristics. Comprehensive molecular profiling—encompassing genomics, transcriptomics, proteomics, and epigenomics—is poised to replace static cytogenetic-based risk models. High-throughput sequencing and single-cell technologies could potentially identify driver mutations, subclonal evolution, and tumor heterogeneity, which can better predict outcomes and response to treatment. Integrating these tools into routine clinical practice will require standardization, cost reduction, and collaborative efforts across centers. Artificial intelligence (AI) and machine learning (ML) are also revolutionizing MM research by enabling multidimensional data integration.[33] Predictive algorithms trained on large patient cohorts will soon personalize treatment regimens and help allocate novel therapies to those most likely to benefit. Emerging technologies—including single-cell multi-omics, spatial proteomics, and circulating tumor DNA (ctDNA) profiling—are poised to further refine risk stratification by capturing clonal heterogeneity, spatial tumor–microenvironment interactions, and low-level systemic dissemination beyond current detection platforms.

Conclusion

The tools used to identify high-risk MM should be actively applied in routine clinical practice. The 2025 IMS/IMWG framework offers a standardized, reproducible definition of high-risk MM. In addition, cytogenetic profiling by FISH or next generation sequencing, S-phase fraction quantification, circulating tumor cell assessment by multiparametric flow cytometry, and advanced imaging for detecting extramedullary disease collectively provide a comprehensive biological picture of high-risk disease that goes well beyond conventional staging. This rigorous biological characterization can directly impact treatment decisions rather than serving purely as a prognostic exercise.

The following practical recommendations apply to current clinical practice:

- Classify all newly diagnosed MM patients using the 2025 IMS/IMWG risk stratification criteria as these patients experience a poor prognosis and require the most intensive therapeutic approach.
- Extending risk assessment beyond genomics by routinely incorporating assessments of the S-phase fraction, circulating tumor cell quantification, and imaging-based evaluation for extramedullary disease, as these identify a biologically high-risk population frequently missed by standard staging systems.
- Apart from baseline risk stratification at diagnosis, dynamic risk assessment throughout the disease course enhances prognostication and aids in clinical decision making.

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Author Contributions

Mohammad Aljumaa and Hasan Hamam Refai are co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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