Mediterranean Journal of Hematology and Infectious Diseases

Review Article

Refining High-Risk Multiple Myeloma: Advancements in Genomic, Clinical, and Prognostic Criteria

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Competing interests: The authors declare no conflict of Interest.

Abstract. Multiple myeloma (MM) is a heterogeneous disease, with MM patients experiencing different clinical outcomes depending on the disease's biological features. Novel insights into the molecular mechanisms of MM have led to the introduction of sophisticated drugs, which dramatically improved patient treatment and survival. To date, young patients with newly diagnosed MM could experience a median overall survival (OS) of 10 years. Nevertheless, a small proportion of patients still undergoes early disease progression and death. Indeed, cases defined as ultra-high-risk MM (uHRMM) and high-risk MM (HRMM) are destined for a worse outcome, with an OS of 2-3 and 3-5 years, respectively. In this regard, current risk stratification systems failed to identify this subset of patients better. The application of existing risk models has led to the identification of extremely heterogeneous categories of patients, and they have not taken into account biological and clinical differences. The concept of HRMM was initially formalised in 2015. Since then, a great effort has been made to identify those parameters whose presence pone MM patients at higher risk of developing an early relapse. The simultaneous presence of 2 or more unfavourable cytogenetic abnormalities, the identification of an extramedullary disease or the detection of circulating plasma cells, as well as high-risk gene expression profiling (GEP) signature, have shown to be well related to a worse outcome and are going to be incorporated into new prognostic systems. The introduction of the Individualised Risk Model for Multiple Myeloma (IRMMa) marks a significant advancement in the management of HRMM by integrating genomic and clinical data to tailor treatment strategies. This model demonstrates improved prognostic accuracy compared to traditional staging systems and emphasises the importance of personalised treatment approaches. The implementation of these advanced tools is essential for enhancing precision medicine in MM and improving outcomes for patients in high-risk categories.

Keywords: High risk MM; Prognostic criteria; Genomics; Clinical classification.

Citation: Martino E.A., Mele G., Morabito F., Gentile M. Refining high-risk multiple myeloma: advancements in genomic, clinical, and prognostic criteria. Mediterr J Hematol Infect Dis 2025, 17(1): e2025006, DOI: http://dx.doi.org/10.4084/MJHID.2025.006

Published: January 01, 2025 **Received: October 31, 2024** **Accepted: December 16, 2024**

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Introduction. Multiple myeloma (MM) has been regarded as a single disease entity, characterised by an

inferior overall survival (OS) in patients compared to the general population. Nevertheless, considerable heterogeneity in clinical presentation, treatment response, and outcome is evident in daily clinical practice.[1] Event-free survival (EFS) can vary dramatically, ranging from barely three years for "ultra-high-risk" patients to up to ten years for "standard-risk" patients, who fortunately represent the majority of cases.[2] This underscores the critical importance of employing comprehensive risk stratification to accurately identify patients at the highest risk of disease progression, enabling them to benefit from tailored therapeutic regimens.[3]

The concept of high-risk multiple myeloma (HRMM) was initially formalised in 2015 with the introduction of the Revised International Staging System (R-ISS), which integrated parameters related to both tumour burden and disease biology.[4] Over the years, advances in understanding the pathogenic mechanisms of the disease, along with the development of seminal diagnostic tools, have led to the validation and incorporation of novel prognostic factors into clinical practice. These developments have further evolved the definition of "high-risk" MM (HR-MM) patients.

Cytogenetic Abnormalities. In 2003, the introduction of the International Staging System (ISS)[5] revolutionised the prognostication of MM, incorporating serum albumin and beta-2-microglobulin (β2-M) levels as surrogates of tumour burden and largely replacing the historical Durie-Salmon staging system.[6] As evidence accumulated on the significant role of cytogenetic abnormalities (CAs) in MM disease progression, particularly those detected by fluorescence *in situ* hybridisation (FISH), the ISS was empowered by the International Myeloma Working Group (IMWG) to include high-risk cytogenetic lesions, specifically translocation (4;14), translocation (14;16), and the deletion 17p (del17p)].[4] This led to the development of Revised-ISS (R-ISS), which also considered lactate dehydrogenase (LDH) serum levels, reflecting increased proliferation and more aggressive disease behaviour.[7]

The R-ISS stratified patients into three risk categories (stages I, II, and III), providing a more refined prognostic framework for both progression-free survival (PFS) and OS. Nevertheless, the R-ISS exhibits some limitations, including the exclusion of additional factors that negatively impact the disease course. One such factor is chromosome 1 aberrations, particularly gain or amplification of 1q (gain1q/amp1q). Gain1q refers to MM cells harbouring one extra copy of 1q, while amp1q involves more than three copies.[8] The prevalence of 1q abnormalities increases with disease progression, from monoclonal gammopathy of undetermined significance (MGUS) (0–20%) to relapsed/refractory (RR) MM (≥50%),[8] suggesting a role in the dynamic process of clonal evolution and drug resistance.[9] Gene expression profiling (GEP) studies have identified key genes within the 1q21 band, such as *CKS1B*, *ADAR*, *IL6R*, *ILF2*, *PSMD4*, and *MCL1*, which are implicated in MM pathogenesis and therapy resistance, even in the era of novel agents.[10]

With mounting evidence of the detrimental impact of 1q abnormalities on prognosis, 1q abnormalities are now recognised as high-risk features in newer staging systems. In 2019, the Intergroupe Francophone du Myelome (IFM) included +1q and other clinically relevant CAs in their definition of high-risk cytogenetics in MM.[11] The Myeloma Genome Project (MGP) also identified amp1q and bi-allelic *TP53* inactivation as high-risk factors in patients classified as ISS III.[12] In 2022, the Mayo Clinic proposed a new risk stratification model based on five factors, including +1q, to better stratify patients into three risk categories, building upon the R-ISS framework.[13] This system has improved discriminatory power, particularly in the R-ISS II group, which includes more than 60% of patients, further stratifying them into intermediate-low and intermediate-high risk categories.

Additionally, the European Myeloma Network (EMN) introduced the R2-ISS, a 6-factor, 4-tier risk system, including ISS II and III, del(17p), LDH levels, t(4;14), and +1q.[14] The strength of this scoring system lies in its enhanced discriminative capacity, especially within the R-ISS II group, which comprises over 60% of MM patients. This system further refines risk stratification by subdividing this large R-ISS II group into intermediate-low and intermediate-high categories. Such differentiation is critical because it allows for more tailored prognostic assessments and therapeutic strategies, addressing the heterogeneity within this sizeable subset of patients and offering a more precise prediction of clinical outcomes. The main risk stratification systems are shown in **Table 1**.

Despite these advancements, current definitions of high-risk profiles remain somewhat restrictive and oversimplified. Not all high-risk alterations carry the same prognostic weight. For instance, Perrot et al.[15] investigated the prognostic impact of del(17p), t(4;14), del(1 p32), 1q21 gain, and trisomies 3, 5, and 21 in a cohort of newly diagnosed MM patients (NDMM). Six key cytogenetic abnormalities were identified, and a prognostic index (PI) was developed, assigning weighted scores to each abnormality. The study highlighted the poor prognosis conferred by del(17p) abnormality, which is known to determine a poor prognosis either alone or in combination with other adverse cytogenetic lesions. Del(17p) is a recurrent cytogenetic abnormality detected in up to 80% of relapsed/refractory MM (RRMM) cases, but rarely at the disease onset, determining an aggressive disease course and poor outcomes.[16] While the adverse prognostic role of del(17p) is well-established, debates remain regarding the optimal threshold for its clinical significance. The

currently accepted 20% cut-off may not fully capture its prognostic relevance, with some studies suggesting that

Table 1. Risk Stratification Systems in Multiple Myeloma

Prognostic System	Laboratory Parameters	Genetic Abnormalities	High Risk Definition	Median PFS/OS (months)
R-ISS (4)	LDH Alb β2M	del(17p) t(4;14) t(14;16)	ISS III and LDH>ULN or HRCAs	29/43
R2-ISS (14)	ISS II=1 ISS III=1.5 LDH>ULN=1	del(17p)=1 t(4;14)=1 gain/ampl(1q)=0.5	Score 3-5	15/34
International Myeloma Working Group (IMWG) (71)	β2M Alb	del(17p) t(4;14) gain/ampl(1q)	ISS II-III and del(17p) or t(4;14)	NA/24
mSMART (72)	LDH Alb β2M	del(17p) gain/ampl(1q) t(4;14) *TP53* mutation t(14;16) High-Risk GEP t(14;20)	R-ISS III High-Risk GEP HRCAs High PC S-phase	NA/NA
Cytogenetic prognostic index (11)	None	del(17p)=1.2 gain(1q)=0.5 t(4;14)=0.4 tris 5=-0.3 del(1p32)=0.8 tris 12=0.3	Prognostic index score>1	NA/26-34
Myeloma Genome Project (12)	Alb β2M	*TP53* mutation ampl(1q)	ISS III and ampl(1q) or biallelic *TP53*	15/21
The Mayo Additive Staging System (13)	ISS III=1 LDH>ULN=1	del(17p)=1 t(14;20)=1 t(4;14)=1 gain/ampl(1q)=1 t(14;16)=1	Score≥2	29/54
Myeloma Prognostic Score System (MPSS) (73)	LDH>ULN=1 low platelet count=2 ISS III=2	del(17p) t(14;20) t(4;14), gain/ampl(1q) t(14;16),	MPSS score 4-7	20/35-50

Abbreviations: Alb=albumin; amp=amplification; β2M=beta-2-microglobuin, GEP=gene expression profiling, HCRA=high-risk cytogenetic abnormalities, ISS=International Staging System, LDH=lactate dehydrogenase, NA=not available, OS=overall survival, PC=plasma cell, PFS=progression-free survival, R-ISS=Revised International Staging System, ULN=upper limit of normal.

a higher threshold of 55-60% may be more appropriate.[15] A more refined understanding of the prognostic role of del(17p) considers not only the presence of the deletion but also the mutational status of the *TP53* gene, which is located on chromosome 17p(13.1) and encodes the tumour suppressor protein p53.[17] Mutations in *TP53*, particularly when occurring in a biallelic manner, significantly worsen prognosis, highlighting the need for comprehensive genetic assessment to inform risk better stratification.[17] Biallelic inactivation of *TP53*, a condition referred to as "double-hit" *TP53*, is a potent marker of adverse prognosis compared to wild-type or monoallelic inactivation.[18]

Circulating Plasma Cells. Plasma cell leukaemia (PCL), historically the most aggressive form of monoclonal gammopathy, was originally defined by the presence of both >20% circulating plasma cells (cPCs) and an absolute count >2×10^9/L of PCs.[19] However, in 2021, the evidence demonstrated that the presence of ≥5% circulating PCs in MM patients carried a similarly poor prognosis to PCL. This finding led to a redefinition of PCL, reducing the threshold for cPCs from 20% to 5%.[20] In 2023, the threshold was further lowered to 2%, as studies showed that MM patients with 2-20% cPCs had significantly shorter PFS and OS than those patients with <2%. Notably, patients with 2-5% cPCs exhibited outcomes similar to those with 5-20% cPCs, reinforcing the idea that elevated cPCs levels represent ultra-high-risk MM rather than a distinct clinical entity.[21] Over time, advances in laboratory techniques have underscored the prognostic value of cPCs. The slide-based immunofluorescence assay, which required fluorescence microscopy and was labour-intensive, has been largely replaced by multiparameter flow cytometry (MFC). This technique provides a more sensitive and reproducible method for quantifying cPCs.[22] Further advancements have come with next-generation flow cytometry (NGF), which could identify the presence of CPCs and enable the detection of cPCs at much lower thresholds of 10^{-5}-10^{-6}.[23] Several studies have already shown that the presence of cPCs has highlighted the association between the presence of cPCs and poor outcomes in both MM and related conditions, such as amyloidosis.[24,25] Similarly, patients with MGUS and smouldering MM (sMM) who harbour ≥5% cPCs are at an increased risk of progression to a symptomatic MM.[26] In a study by Garces et al.,[27] using NGF to measure cPCs in 374 MM patients enrolled in the GEM2012MENOS65 and GEM2014MAIN trials, higher percentages of cPCs were associated with inferior PFS. In multivariable analyses, the cut-off of 0.01% cPCs retained its independent prognostic value alongside other factors such as ISS, LDH, and cytogenetics. Similarly, a study by the Greek

group found that patients with cPCs above 2 x 10^{-4} had a higher risk of progressing, irrespective of the ISS stage, cytogenetic abnormalities, or the induction therapy utilised.[28] Bertamini et al. further analysed the cPCs of 410 MM patients enrolled in the FORTE clinical trials, identifying a threshold of 0.07% as optimal for distinguishing patients at higher risk of poor outcomes.[29] Several efforts have been made to incorporate cPCs quantification into existing staging systems, such as the R-ISS. It has been demonstrated that the presence of ≥5 cPCs/μL, as detected by MFC, can identify patients classified as R-ISS I and II who are at risk of poor outcomes, comparable to those in stage III.[30] Similarly, Galieni et al. established that baseline cPCs detection serves as a useful tool for better stratifying R-ISS II patients.[31]

These findings firmly support the prognostic significance of cPCs as a remarkable prognostic marker for identifying high-risk MM patients.

Extramedullary Disease. Two distinct forms of extramedullary disease (EMD) are currently recognised in MM: 1) EMD involving soft tissues, such as the liver, lymph nodes, spleen, kidneys, breast, pleura, meninges, testes or skin, and 2) paraskeletal (PS) disease characterised by tumour masses arising from skeletal lesions. Only the EMD is recognised as a high-risk MM. Observational studies have reported an increased incidence of both forms of EMD during disease relapse[32] and following allogeneic transplantation with dose-reduced intensity conditioning regimens.[33,34] Regardless of when EMD occurs during the disease course, its presence is consistently associated with significantly worse outcomes.[35] Historically, in the era of chemotherapy, EMD was linked to significantly worse prognoses. However, the introduction of high-dose melphalan followed by autologous stem cell transplantation (ASCT) has shown survival benefits for patients with EMD, partially overcoming its adverse prognostic implications.[36] A study conducted by the EBMT Chronic Malignancies Working Party highlighted the differential prognosis between patients with EMD and those with PS disease.[37] Notably, patients with EMD had significantly shorter 3-year-PFS and OS rates after ASCT compared to those with PS disease or without plasmacytomas.

Furthermore, tandem transplantation did not confer any additional benefit in this patient population. Moreover, tandem transplantation did not confer any additional benefit in this setting of patients. The role of allogeneic stem cell transplantation (allo-SCT) in EMD has also been investigated. A study including 155 patients demonstrated that the presence of EMD prior to allo-SCT was significantly associated with an unfavourable prognosis, with a median OS of fewer than 8 months. However, allo-SCT was capable of inducing long-term remissions, even in patients harbouring high-risk cytogenetic lesions and multiorgan involvement.[38] In the era of novel therapies, further insights into the prognostic impact of EMD have emerged. A recent Italian meta-analysis, which included eight trials, investigated NDMM patients' clinical features, outcomes, and responses to new drug regimens. The analysis revealed no significant difference in median PFS between patients with and without EMD in a multivariable model. However, OS was worse in patients with EMD. This meta-analysis suggests that novel therapies may help mitigate the negative prognostic impact of extramedullary disease.[39]

Accurate assessment of EMD, as well as response to treatment, requires advanced imaging techniques, such as magnetic resonance imaging (MRI) and 18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). MRI is particularly effective in detecting lesions and in assessing the extent of soft-tissue disease in both EMD and PS soft-tissue involvement, especially in cases of suspected spinal or central nervous system involvement. This radiological technique may accurately locate the level of the lesion and quantify its extent and the degree of damage.[40] PET/TC, known for its higher sensitivity, offers additional information on the metabolic activity of lesions and serves as a valuable prognostic tool. Several retrospective studies have demonstrated the detrimental impact of a positive PET/TC on survival. In 2011, Zamagni et al. conducted a prospective study evaluating the prognostic relevance of PET/CT in 192 NDMM patients who underwent thalidomide-dexamethasone induction followed by double ASCT. The analysis revealed that a standardised uptake value (SUV) greater than 4.2 and persistent pathologic uptake after ASCT were independent predictors of reduced PFS.[41] A subsequent prospective study by the French group in 2017 compared MRI and PET/TC in NDMM patients treated with lenalidomide-bortezomib-dexamethasone (RVD), with or without ASCT, followed by lenalidomide maintenance. This prospective analysis failed to demonstrate any difference in detecting bone lesions at diagnosis between the two image techniques but showed that PET/CT normalisation before maintenance was associated with improved PFS and OS.[42] The CASSIOPET trial, a companion study of the CASSIOPEIA trial,[43] investigated PFS differences between baseline PET-negative and PET-positive patients in both arms of the trial, confirming that baseline PET negativity is associated with better survival outcomes.[44]

Minimal Residual Disease. Clinical trials and meta-analyses have established that the achievement of minimal residual disease (MRD) is strongly linked to improved survival outcomes in MM. The concept of

MRD was first introduced by IMWG in 2015, referring to those patients who, despite achieving a complete response, still harbour a low level of residual disease.[45] MRD assessment is typically performed using MFC and molecular biology techniques with a sensitivity between 10^{-5} and 10^{-6}.[46] A meta-analysis including fourteen studies investigating the impact of MRD on PFS and 12 studies on OS was conducted to evaluate the clinical significance of MRD detection in NDMM patients.[47] The results confirmed the predictive value of MRD negativity, as it was associated with significantly better PFS. In a separate analysis, MRD negativity was also evaluated in patients with RRMM and NDMM patients who were transplant-ineligible and treated with daratumumab-based regimens. MRD-negative status. In this analysis, patients achieving a complete response or better (≥CR) who also reached MRD-negative status demonstrated superior outcomes in terms of PFS.[48] Sustained MRD negativity for at least 6 months, even in patients harbouring high-risk cytogenetic lesions, has been associated with significant improvements in both PFS and OS, reinforcing the idea that undetectable MRD can serve as a key treatment endpoint for this high-risk population.[49,50] Conversely, the loss of MRD negativity has been correlated with an increased risk of progression or death.[51] In light of these findings, several trials are now incorporating MRD negativity as a primary endpoint and are investigating treatment strategies tailored to MRD status. The MASTER trial, a multicentre phase II study, demonstrated that achieving MRD negativity after induction, ASCT, and consolidation allowed patients to avoid maintenance with lenalidomide.[52] Similarly, a British study[53] is investigating the potential for de-escalating therapy in patients who achieve MRD negativity post-ASCT. The phase III IFM MIDAS trial is evaluating the role of single *versus* double ASCT in the context of MRD-driven treatment strategies, while the DRAMMATIC trial (ClinicalTrials.gov Identifier: NCT04052880) is exploring the possibility of discontinuing maintenance therapy after 2 years if MRD negativity is achieved. These studies collectively support the growing role of MRD as a crucial endpoint in MM treatment, especially as novel therapies and personalised approaches continue to evolve.

Functional High-Risk Myeloma. Functional high-risk MM (FHRMM) refers to patients who exhibit adverse disease biology that becomes evident after the failure of first-line therapy. This includes those who relapse within 18 months of treatment initiation and/or within 12 months of frontline ASCT,[54] encompassing both primary refractory patients and those with early relapse. In addition to R-ISS, other parameters, including a suboptimal response to first-line therapy or inappropriate induction therapy, should considered in identifying FHRMM patients, though these factors may underestimate the true risk. Emerging research highlights the role of the tumour micro-environment in both MM pathogenesis and treatment response. A recent study on bone marrow samples from NDMM patients revealed that the T-cell repertoire undergoes significant changes over time with treatment. In particular, a decrease in early memory T cells and an increase in senescent T-cell numbers were observed.[55] Alrasheed et al. examined bone marrow samples from NDMM patients before treatment induction and again 100 days post-ASCT, focusing on T-Regs. They found that a higher frequency of T-Regs was associated with poorer PFS and OS.[56]

Additionally, increased levels of naïve and terminally differentiated T cells post-ASCT were linked to worsening prognosis.[57] Disruptions in the immune microenvironment, including altered expression of inhibitory receptors on cytotoxic T cells and downregulation of costimulatory receptors, such as CD226, can contribute to disease progression.[58] Studies also show that NK cells play a pivotal role in preserving response to therapy, particularly in patients who undergo ASCT. Higher NK cell count is associated with better outcomes and a higher rate of MRD negativity, while impairments in NK cell number and function increase the risk of relapse.[59,60]

Gene expression profiling (GEP) assays represent valuable tools in predicting FHRMM. Several genes involved in MM cell metabolism and transduction signalling pathways, such as IL-6/JAK/STAT3,[61,62] were found to be overexpressed in FHRMM cases. Moreover, disruptions in DNA damage repair pathways and mutations in the *TP53* gene occur more frequently in FHRMM patients compared to those who relapse later in the disease course.[63] A recent study involving 104 NDMM patients used the GEP70/UAMS70 assay to predict relapse-free survival (RFS) and OS.[64] The main endpoints included relapse-free survival (RFS) and OS. An RNA microarray platform was used to identify low-risk and high-risk cohorts. The study demonstrated that patients with higher GEP scores experienced higher relapse rates within one year and poorer OS, regardless of their baseline FISH.

High-Risk Prediction in the Era of Artificial Intelligence. Recent advances in transcriptomic, exomic, and whole-genome sequencing have identified new genomic alterations and molecular signatures in MM. The CoMMpass study revealed distinct molecular subgroups, with approximately 25% of patients transitioning to high-risk categories at first relapse.[65] Similarly, Walker et al. emphasised the prognostic impact of single-nucleotide mutations (SNVs) and APOBEC mutational signatures alongside the International Staging System (ISS).[66] Whole-genome sequencing further highlighted the role of APOBEC

signatures and structural variants, such as chromothripsis, in driving MM progression and survival outcomes.[67,68]

Building on these findings, recent approaches in MM classification and individualised risk prediction now leverage artificial intelligence (AI)-based models that integrate clinical, genomic, and therapeutic data to generate more precise and adaptable risk classifiers.[69,70] These AI-driven models offer significant improvements over traditional systems, such as the ISS and its revisions (R-ISS, R2-ISS), by incorporating a broader array of variables, including genomic markers such as *TP53* mutations, 1q21 gain, chromothripsis, and NSD2 translocations. This allows for a more refined stratification of patients, offering a personalised approach to prognosis and treatment planning.[69,70] In the study by Maura et al., the Individualised Risk Model for Multiple Myeloma (IRMMa) was developed, integrating clinical, genomic, and therapeutic data from 1,933 newly diagnosed multiple myeloma (NDMM) patients to account for the heterogeneity of outcomes, where overall survival (OS) ranges from months to over a decade.[70] This model incorporates 20 key genomic features, such as 1q21 gain/amp, *TP53* loss, and APOBEC mutational signatures, and demonstrated superior accuracy compared to existing models like the ISS, R-ISS, and R2-ISS, with a concordance index (c-index) for OS of 0.726. Furthermore, the study identified 12 distinct genomic clusters, validated using data from the GMMG-HD6 clinical trial, allowing the IRMMa model to predict treatment efficacy, particularly regarding high-dose melphalan followed by ASCT.[70]

One key finding from this study was the IRMMa model's ability to incorporate time-dependent factors, including treatment strategies such as ASCT and maintenance therapies, to predict patient outcomes better. Patients with high-risk genomic profiles showed a poorer response to these therapies, highlighting the need for personalised treatment approaches based on genomic insights. Additionally, patients classified as high-risk by the IRMMa model - especially those harbouring *TP53* mutations, 1q21 gains, or chromothripsis - were found to have a significantly increased risk of death. These high-risk patients often experienced relapse within 18 months of initial treatment, and their OS was substantially lower compared to those with lower-risk profiles. In these cases, the IRMMa model predicted that the likelihood of death within three years was markedly higher in patients classified as having high-risk genomic signatures. For example, patients with *TP53* loss or chromothripsis had a more than 50% higher risk of death compared to those without these mutations.

The IRMMa model is not only more accurate than traditional staging systems but also adaptable, providing clinicians with tools to tailor therapies based on each patient's genomic profile, significantly reducing the risk of death for those in higher-risk categories.

Table 2. Proposed Parameters for Risk Stratification in Multiple Myeloma.

Standard Risk: - Hyperdiploidy - t(11;14) - Decreased level of albumin
High Risk: - Isolated HRCA [del(17p), gain(1q), del(1p32), amp(1q), t(14;16), t(14;20), t(4;14)] - High tumor burdern (elevated β2M, elevated LDH)
Ultra High-Risk: - ≥2 HRCAs - Biallelic *TP53* mutation - Extramedullary disease - High-Risk GEP - ≥2% cPCs - Early relapse (<12 months) or primary refractoriness

Abbreviations: β2M=beta-2-microglobuin, GEP=gene expression profiling, HCRA=high-risk cytogenetic abnormalities, LDH=lactate dehydrogenase, cPCs=circulating plasma cells.

Conclusions. Multiple myeloma is an extremely complex disease, with clinical outcomes that are strictly dependent on its underlying biological characteristics. Advances in our understanding of the molecular mechanisms driving MM have significantly improved patient treatment and survival. Nevertheless, further effort is needed to standardise the definition of high-risk patients and identify therapeutic strategies aimed at improving outcomes. Current risk stratification systems, such as R-ISS, do not fully capture all high-risk MM cases. Therefore, integration with novel prognostic factors is expected to enhance risk identification (**Table 2**). Chromosome 1 abnormalities, for example, have been shown to exert an unfavourable prognostic impact, and FISH cytogenetics at baseline should routinely include these disruptions.

The detection of cPCs rate using MFC has emerged as a useful parameter in identifying patients with aggressive disease, as demonstrated by many retrospective analyses.[21,29] However, validation and standardisation of this technique, especially within

prospective clinical trials, are recommended. Additionally, FDG-PET/CT should be incorporated into routine baseline prognostic evaluations, given its ability to provide topographic, quantitative, and metabolic information about EMD, which is known to contribute to an unfavourable prognosis.[41]

In this regard, most data regarding FDG-PET/CT are derived from retrospective studies with small populations, highlighting the need for prospective evaluations.

There has also been growing interest in MRD assessment, particularly due to the deeper responses obtained with novel agents. MRD assessment, detected via NGS or NGF, has proven to be a strong prognostic marker, serving as a good surrogate for both PFS and OS. Open issues remain concerning the standardisation of NGF, the optimal threshold for MRD negativity, the appropriate time points for analysis, and the definition of sustained MRD negativity and loss of MRD-negative status. Ongoing prospective clinical trials will undoubtedly address these questions.

The development of the IRMMa[69,70] is a promising step forward in the management of HRMM. By integrating genomic data with clinical and treatment variables, the model offers a more personalised approach to prognosis and treatment planning, significantly improving the limitations of traditional systems like the R-ISS.

It could lead to improved outcomes for patients, particularly those who may not benefit from standard treatment protocols. However, implementing such a model in clinical practice will require widespread access to genomic testing and the integration of these data into clinical workflows. While the IRMMa model shows significant potential, further validation in diverse patient populations and real-world settings is crucial to confirm its utility and accuracy. The integration of these advanced tools will be key to advancing precision medicine in MM and improving outcomes for those in the highest-risk categories.

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