“CAROL DAVILA”, UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST

SCHOOL OF DOCTORAL STUDIES

MEDICINE

*Monitoring the Therapeutic Response of Patients with Multiple Myeloma in the Era of Novel Therapies*DOCTORAL THESIS SUMMARY

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2025

Cuprins

GENERAL PART

CHAPTER 1 Multiple Myeloma – General Concepts, Diagnosis, Classification, and Treatment

1.1 Introduction

Multiple myeloma (MM) is a malignant hematologic neoplasm characterized by the uncontrolled proliferation of clonal plasma cells within the bone marrow. This proliferation is accompanied by the excessive production of monoclonal immunoglobulins, known as M protein, and leads to several severe complications such as lytic bone lesions, renal failure, anemia, and pronounced immunosuppression (1). The disease progresses through a series of pathological stages, beginning with an asymptomatic premalignant condition known as monoclonal gammopathy of undetermined significance (MGUS), which can evolve into smoldering myeloma and, eventually, into active myeloma (2)

1.2 Pathophysiology of Multiple Myeloma

The malignant transformation of plasma cells involves a series of genetic and epigenetic alterations. Among the most frequent are recurrent translocations of the IgH gene (14q32), often associated with the activation of oncogenes such as CCND1, MAF, or FGFR3 (3). These anomalies lead to unregulated cell proliferation, further exacerbated by point mutations in genes like NRAS, KRAS, BRAF, or in tumor suppressor genes such as TP53 (4). The prolonged survival of malignant cells is supported by the inhibition of apoptosis, mediated by anti-apoptotic proteins BCL-2 and MCL-1 (10), as well as by the activation of telomerase, which enables unlimited replication. Additionally, disruptions in the cell cycle caused by the overexpression of cyclins D1, D2, and D3 contribute to disease progression (5).

The bone marrow microenvironment plays a crucial role in the pathogenesis of multiple myeloma. It is composed of stromal cells, osteoclasts, osteoblasts, endothelial cells, and an extracellular matrix rich in growth factors and cytokines. These components promote the proliferation and survival of myeloma cells. Interactions between malignant plasma cells and the microenvironment stimulate the secretion of soluble factors such as IL-6, TNF-alpha, VEGF, and RANKL. IL-6 is considered the principal growth factor for myeloma cells, while VEGF stimulates angiogenesis and RANKL activates osteoclasts, resulting in bone resorption and the characteristic lytic lesions of MM (6–8). Furthermore, the imbalance between RANKL and OPG (osteoprotegerin) exacerbates bone destruction.

Immunosuppressive factors such as TGF-β and IL-10 inhibit the antitumor immune response, thereby facilitating disease progression (1,3).

1.3 Diagnostic Approach in Multiple Myeloma

The diagnosis of multiple myeloma requires the integration of clinical, laboratory, imaging, and histological data. According to international guidelines, the diagnosis is established by identifying at least 10% clonal plasma cells in the bone marrow, accompanied by signs of end-organ damage, known as the "CRAB" criteria (hypercalcemia, renal impairment, anemia, and lytic bone lesions), or by the presence of SLiM biomarkers that indicate active myeloma (≥60% clonal plasma cells, an abnormal κ/λ free light chain ratio, or focal lesions detected by MRI) (1,9). Imaging techniques such as MRI, CT, and PET-CT are essential for detecting bone involvement or extramedullary disease (3).

1.4 Classification of Multiple Myeloma

Based on severity and clinical-biological characteristics, multiple myeloma is classified into several forms: MGUS (monoclonal gammopathy of undetermined significance), smoldering myeloma, active myeloma, solitary bone plasmacytoma, extramedullary plasmacytoma, and non-secretory myeloma (10,11). This classification is complemented by the ISS (International Staging System) and R-ISS (Revised ISS) staging systems, which assess disease prognosis based on biological markers such as β2-microglobulin, albumin, LDH, and the presence of cytogenetic abnormalities (11). Genetic abnormalities such as del(17p), t(4;14), or t(14;16) are associated with poor prognosis, indicating the need for more aggressive therapeutic approaches (12).

1.5 Therapeutic Strategies in Multiple Myeloma

The therapeutic management of multiple myeloma is adapted according to the patient's eligibility for autologous stem cell transplantation (ASCT). For eligible patients, the treatment follows a standard sequential scheme: induction therapy with regimens such as VRd or VCD, followed by ASCT, consolidation, and maintenance with lenalidomide (10,11). For non-eligible patients, gentler drug combinations are used, with a focus on tolerability and maintaining quality of life. ASCT remains the standard of care for younger patients, offering significantly prolonged progression-free survival (10,13).

Although cellular therapies and bispecific antibodies are currently under development, autologous transplantation remains the only intervention that ensures a deep and early response, particularly in patients with standard-risk cytogenetics (10).

CHAPTER 2: Current Management of Multiple Myeloma

2.1 Evaluation of Treatment Response

The effectiveness of therapy is primarily monitored by assessing the biological response, defined by changes in M protein levels, bone marrow infiltration, and serum markers. The goal of treatment has evolved from achieving partial response to inducing complete remission, and more recently, to obtaining minimal residual disease (MRD) negativity. Advanced MRD assessment techniques, such as high-resolution flow cytometry and next-generation sequencing (NGS), offer increased sensitivity, being capable of detecting one malignant event among more than 100,000 normal cells (14).

Patients who achieve MRD negativity exhibit significantly longer survival compared to those with detectable disease (15). Moreover, this marker influences therapeutic decisions, allowing treatment discontinuation in certain cases or signaling the need for more intensive approaches (16).

Current challenges in the management of MM include the difficulty in achieving deep responses in patients with adverse cytogenetics, the lack of international standardization for MRD evaluation, and limited access to advanced therapies in certain regions (13,17). Furthermore, treatment with monoclonal antibodies such as daratumumab interferes with serological and immunophenotypic assessments, generating false-positive results in immunofixation tests or hindering surface marker detection (54). This issue is addressed by using alternative markers such as VS38C, which allow evaluation independent of CD38 interference (18,19).

2.2 Conclusions

In conclusion, multiple myeloma is a complex malignancy, in which recent progress in understanding molecular mechanisms and therapeutic development has led to prolonged survival and improved quality of life for patients. However, multiple challenges remain, especially in subgroups of high-risk patients, which justifies the need for further research to identify curative and personalized therapeutic strategies.

SPECIAL PART

Chapter 3 Working hypothesis and main objectives

3.1 Working assumptions

This doctoral thesis is part of a field of great topicality and clinical relevance, focusing on multiple myeloma, a complex malignant hematological condition, characterized by heterogeneity and a variable clinical evolution.

Considering the evolution of therapeutic strategies in recent decades in multiple myeloma, the paper rigorously analyzes their impact on the therapeutic response, emphasizing the evaluation of minimal residual disease (MRD), as a predictive marker of remission depth and long-term prognostic indicator. The research is part of a rigorous scientific approach, whose objectives are clearly formulated and aim to integrate MRD and simple but informative hematological indices (NLR and PLR), in the monitoring algorithms of patients with multiple myeloma treated mainly by ASCT.

Based on the hypotheses made, the study aims to highlight correlations between post-transplant therapeutic response and pre-existing clinical-paraclinical features, as well as to critically analyze the effects of new-generation therapeutic molecules on the likelihood of obtaining a negative MRD, currently considered the gold standard for assessing treatment efficacy (69). It is relevant to mention that the MRD evaluation was performed 100 days post-transplant, using the high-sensitivity flow cytometry technique (10^-5), allowing the identification of residual populations of myeloma plasmacytocytes, undetectable by conventional detection methods (20).

3.2 Main objectives of the doctoral thesis

Starting from the working hypotheses, the main objectives of the doctoral thesis were to characterize the studied population based on demographic, clinical-paraclinical criteria, to understand the basic characteristics and prognostic parameters, to evaluate the relationship between the parameters detected before transplantation and the profound response after therapy, to analyze the impact of various types of new treatments on the depth of minimal residual disease after ASCT. Also, the main objectives of the work included studies on the correlations between post-transplant MRD status and overall survival (OS) and progression-free survival (PFS) for the validation of MRD as a prognostic factor in MM, as well as repeated post-transplant monitoring through repeated evaluations of MRD in order to outline personalized therapies.

Chapter 4 General Research Methodology

4.1 Introduction

The present paper presents two parts, the first being composed of general data from the literature on multiple myeloma (definition, classification, pathogenesis mechanisms and treatments used), techniques for assessing minimal residual disease post-ASCT and stratification of the prognostic risk associated with induction therapies. The second part of the paper outlines through stratified evaluations the associations between the evaluation of the profound response of minimal residual disease by the technique of immunophenotyping by flow cytometry following induction therapies and autotransplantation, certifying existing information in the literature on data on progression-free survival and overall survival. In the same part of the work, I tried to develop more accessible methods for assessing the risk of progression in patients diagnosed with multiple myeloma, being one of the proposed objectives. These methods required the evaluation of the ratios between commonly analyzed parameters (neutrophils/lymphocytes and platelets/lymphocytes). The aim of the second study was to implement methods using analyses accessible to all patients through which patients can be included in a prognostic score for the development of more elaborate monitoring and therapeutic strategies.

4.2 Study population

The study included two patient cohorts diagnosed with multiple myeloma. The first cohort, consisting of 55 patients who underwent autologous hematopoietic stem cell transplantation at SUUB, was used for minimal residual disease (MRD) analysis at 100 days post-transplant. The aim was to assess profound response to treatment and its correlation with previous treatments, as well as overall survival (OS) and progression-free survival (PFS).

The second cohort, comprising 87 patients treated or transplanted at SUUB, was analyzed for the correlation of paraclinical data, especially neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios, with the evolution of the disease. The objective was to identify accessible and effective prognostic methods for assessing the risk of progression or relapse.

4.3 MRD Monitoring

Minimal residual disease monitoring is performed at day +100 post-autotransplantation, in order to assess the depth of the therapeutic response obtained. The evaluation requires bone marrow aspiration, which is why this period is expected to stabilize the patient's biological parameters.

Chapter 5 Implementation of MRD monitoring by flow cytometry of patients with multiple myeloma post-autologous hematopoietic stem cell transplantation

5.1 Introduction

The optimal evaluation for post-transplant patients is performed at an interval of 100 days after, from bone marrow aspirate. The integration of minimal residual disease monitoring is, in addition to the prognostic marker, a way to establish the overall picture of individual subsequent therapies.

Information about the depth of response can guide subsequent therapeutic decisions, especially in the context of administration of strengthening or maintenance therapies.

5.2 Main objectives

The study "MRD analysis in relation to pre-transplant characteristics in patients with auto-stem cell transplantation" aims to evaluate the correlation between minimal residual disease (MRD) and different characteristics of patients with multiple myeloma. The objectives include: describing the demographic, clinical and paraclinical profile of patients according to post-transplant MRD status, as well as identifying therapeutic regimens that determine a profound response after autologous stem cell transplantation.

5.3 Materials and methods

The study is a retrospective, observational and single-center study, conducted at the Bucharest University Emergency Hospital, including 55 patients with multiple myeloma who benefited from autologous hematopoietic stem cell transplantation between January 1, 2019, and December 31, 2024. The data were extracted from the patients' electronic records. The inclusion criteria were confirmed diagnosis of multiple myeloma, age over 18 years, informed consent for the use of data for research purposes, and MRD analysis 100 days post-transplant.

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians and ranges. The Independent Median Test was used to compare continuous variables between groups. Categorical variables were reported as numbers and percentages. Associations between

categorical variables were analyzed using the Chi-Square test or Fisher's exact test. Survival analysis was conducted using the Log-rank test and illustrated with Kaplan-Meier curves.

To study minimal residual disease, the flow cytometry method was used, allowing the identification of specific surface antigens of malignant plasma cells (CD56, CD117, light chain clonality—kappa, lambda), following a gating procedure based on CD38++ and CD138+ expression. Bone marrow aspirate was used for the analysis, as the disease affects the hematopoietic marrow. A minimum of 2.5–4 mL of bone marrow aspirate was recommended to be collected in EDTA tubes, transported and stored at room temperature, with a maximum sample stability of 24 hours and an optimal processing time of 12 hours.

The analyzed samples were subjected to a panel of 10 reagents distributed across two tubes.

5.4 Results

The evaluation was conducted on a sample of 55 patients undergoing autologous stem cell transplantation, of which a significant proportion of 60% achieved post-ASCT MRD negativity.

A trend towards higher survival was noted among MRD-negative patients. Similarly, patients who received daratumumab prior to HCT showed a trend toward better OS (p=0.274) (Figure 5.26), with no obvious difference in PFS (p=0.928) (Figure 5.27).

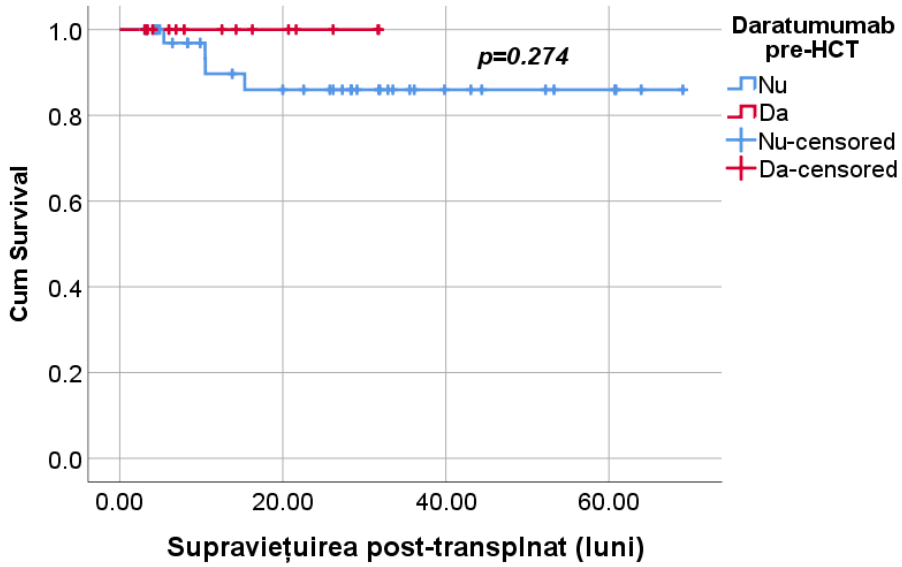

Figure 5.26. Post-transplant survival according to Daratumumab treatment

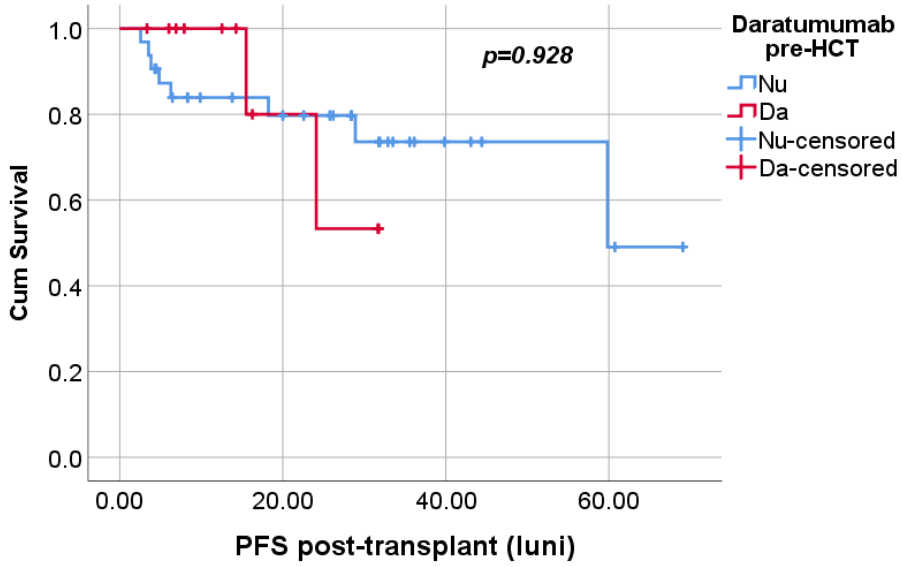

Figure 5.27. Post-transplant progression-free survival according to Daratumumab treatment

These results may be influenced by the small sample size, which limits the statistical power of the analysis. Also, the low number of deaths observed during the follow-up period may further reduce the ability to detect statistically significant differences in survival.

Regarding the therapeutic regimens administered before transplantation, the data suggest a direct correlation between the intensity of treatment and the depth of response. The VCD regimen (bortezomib, cyclophosphamide, dexamethasone) was shown to be effective in achieving a negative MRD status, while the quadruple DVTD regimen, which also includes Daratumumab, although theoretically considered superior, was paradoxically associated with a higher rate of positive MRD.

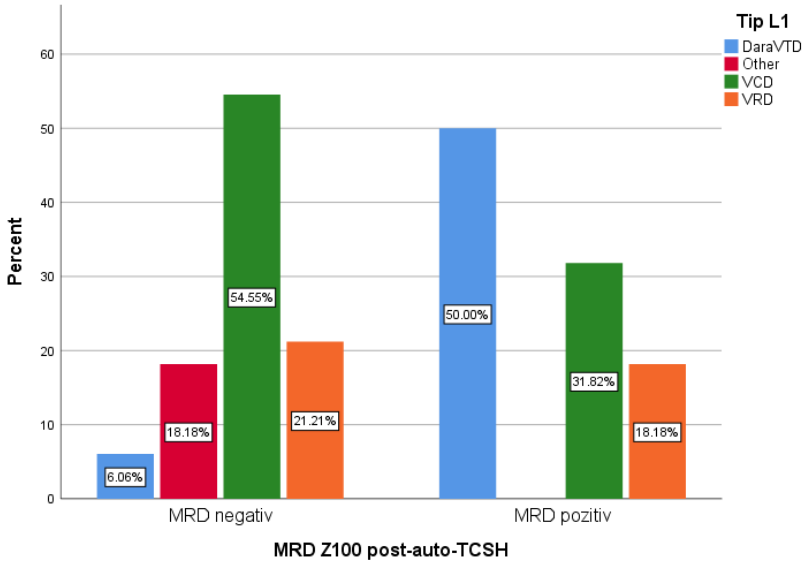

Figure 5.11. Post-transplant MRD according to first-line treatment

The MRD assessment on day +100 post-transplant also revealed that patients who achieved a complete response (CR) prior to ASCT consistently achieved MRD negativity, confirming the hypothesis that the depth of the therapeutic response to induction significantly influences subsequent transplant success.

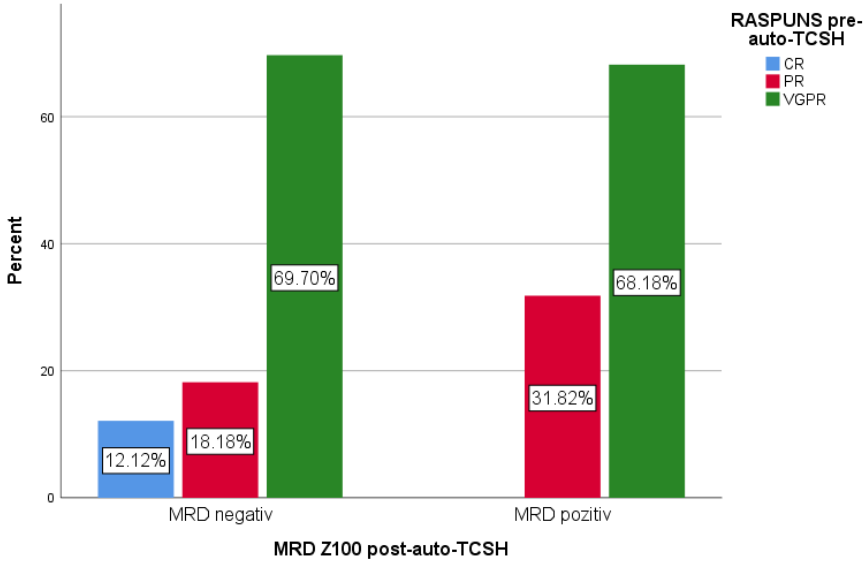

Figure 5.12. Post-transplant MRD according to treatment response before transplantation

5.5 Discussion

The paper highlights that achieving a negative MRD, even in the absence of a completely conventional response, is associated with longer progression-free survival (PFS) and superior overall survival (OS), which supports the integration of this marker into the response criteria proposed by the International Myeloma Working Group (IMWG) (21)

The evaluation was carried out on a sample of 55 patients undergoing autologous stem cell transplantation, of which a significant proportion, 60%, achieved post-ASCT MRD negativity. This rate, although below the levels reported in some controlled studies, closely reflects the clinical reality, given that most of the patients included had a poor functional status (ECOG ≥2 in more than 90% of cases) and were diagnosed in advanced stages of the disease (60% in stage 3 Salmon-Durie) (22).

The increased rate of positive MRD with the DVTD regimen could be explained by the low tolerability of this treatment among patients with poor functional status, suggesting

the need to individualise therapy according to the biological reserve and comorbidities of each patient (23).

Also, although overall survival (OS) and progression-free survival (PFS) did not show statistically significant differences between the MRD-negative and MRD-positive groups, there was a clear trend of prolongation of survival in favor of MRD-negative patients. This observation is consistent with the literature, which indicates that maintaining a negative MRD for at least 12 months is associated with a favorable clinical outcome (24).

In summary, MRD negativity at 100 days post-ASCT was shown to be an early indicator of favorable prognosis, and the VCD regimen, remarkable for its tolerability, increased the likelihood of a profound response. Survival was negatively influenced by kidney damage and, to a lesser extent, by extramedullary disease, factors also recognized in the international literature. (24)

Chapter 6 NLR and PLR analysis in multiple myeloma patients from SUUB

6.1 Introduction

The need to develop efficient prognostic stratification methods that are cost-effective and easy to apply—especially in medical centers with limited resources—has led to growing interest in identifying simple, reproducible markers that are easy to integrate into routine clinical practice.

In this regard, numerous studies have explored the potential of hematological parameters derived from the complete blood count. Among these, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have been extensively investigated.

In this secondary study within the thesis, 87 patients with multiple myeloma were analyzed in terms of simple hematological indices derived from routine complete blood counts—namely, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR). The study aims to determine the prognostic significance of these indices in multiple myeloma patients in relation to survival. It seeks to highlight the clinical utility of these ratios, considering their low cost and easy accessibility for all healthcare professionals.

6.2 Special objectives

Previous studies have identified several validated prognostic markers in multiple myeloma, such as cytogenetic analysis, beta-2 microglobulin, LDH, the free light chain ratio, and gene expression profiling. Although NLR and PLR have been associated with poor prognosis in other types of malignancies, their role in multiple myeloma remains insufficiently explored and is supported by limited data. In this context, the present study aims to assess the prognostic value of the NLR and PLR indices in relation to the survival of patients with multiple myeloma, and to analyze the demographic characteristics of these patients based on these parameters.

6.3 Materials and methods

We conducted a single-center, retrospective, observational study on 87 patients who were either diagnosed with multiple myeloma at the Bucharest University Emergency

Hospital or who received autologous stem cell transplants at the same institution. Data were collected from the patients' electronic medical records.

Statistical analysis was performed using IBM SPSS Statistics software, version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as medians and ranges. The Independent Median Test was used to compare these variables between groups. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient (Spearman's rho). Categorical variables were reported as absolute numbers and percentages. Associations between categorical variables were analyzed using the Chi-Square test or Fisher's exact test, as appropriate. To identify threshold values of NLR and PLR predictive of early mortality (within 3 years), ROC curve analysis and area under the curve (AUC) evaluation were employed.

6.4 Results

Patients with bone lytic lesions had a lower NLR compared to those without bone lytic lesions. (p=0.013) (Figure 6.3).

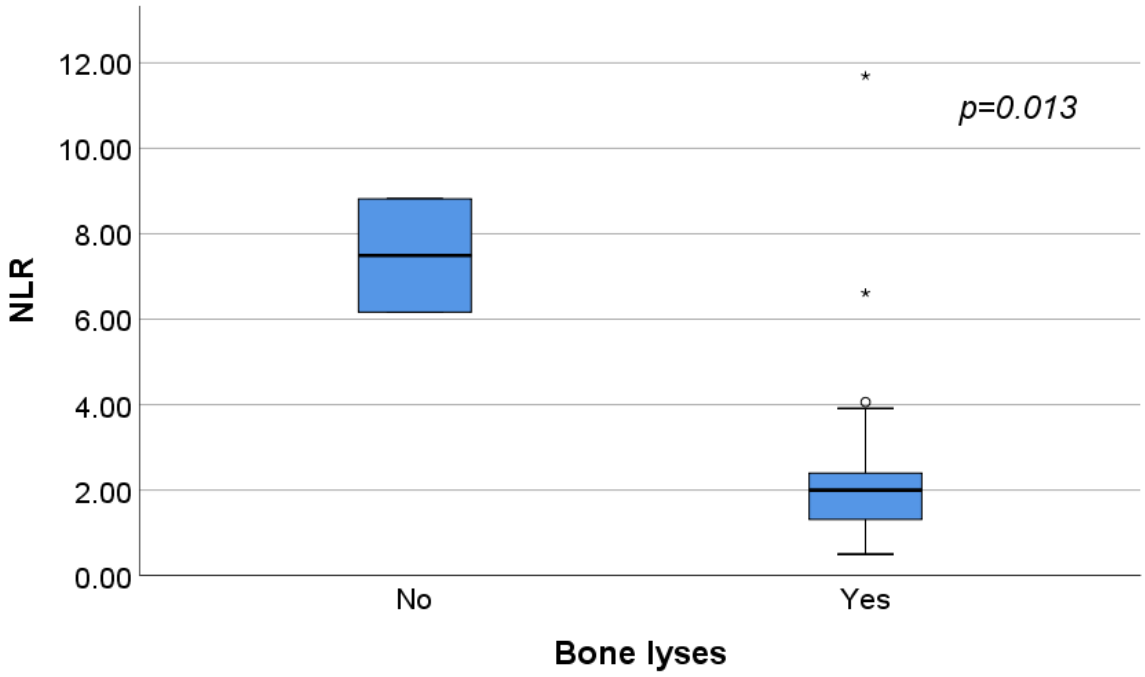

Figure 6.3. NLR based on the presence of bone lytic lesions

This figure illustrates the relationship between NLR values and the presence or absence of bone lytic lesions in patients with multiple myeloma. The results shown in the

figure indicate that patients without bone lesions had a significantly higher NLR (median ~7.5–8), whereas those with bone lesions had a lower NLR (median ~2). The statistical test indicates a significant difference between the two groups ($p = 0.013$). These differences suggest an inverse relationship between systemic inflammatory status (NLR) and localized bone involvement and may reflect a different immunological profile between patient subgroups—findings that warrant further investigation.

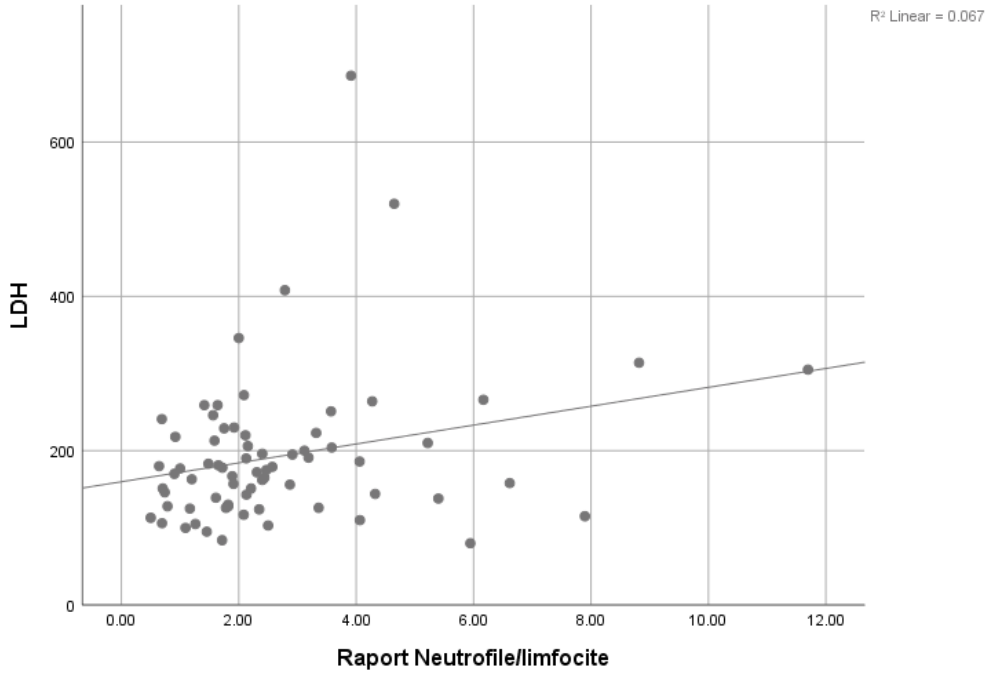

Figure 6.5. Correlation between NLR and LDH

Although the correlation is of lower intensity, the statistical significance suggests a true association between elevated NLR values and increased LDH levels, likely due to heightened inflammation or tumor-related stress. NLR could serve as an accessible and readily available marker with prognostic or severity stratification value, in correlation with LDH. Further analyses are needed to evaluate this relationship in different clinical contexts or in larger sample sizes.

6.5 Discussions

The results obtained indicate that a high NLR correlates positively with biological markers of tumor aggressiveness (LDH, white blood cell count), suggesting a negative prognostic role, while a low PLR was associated with a higher percentage of bone marrow plasma cell infiltration and elevated beta-2 microglobulin levels—findings consistent with more advanced disease and a poorer prognosis (8). Chronic inflammation, mediated by

cytokines such as IL-6 and TNF-α, is recognized as a facilitator of malignant plasma cell expansion and immune evasion, which explains why inflammatory hematologic markers are becoming increasingly important in prognostic evaluation (8).

The statistical analysis, conducted with methodological rigor, also included ROC curves to determine threshold values for NLR and PLR in predicting early mortality (within 3 years), with results confirming their utility in risk stratification. With the advantages of low cost and wide applicability, these indices can usefully complement traditional prognostic assessments and contribute to the individualization of treatment plans, particularly in resource-limited settings (8).

In conclusion, the above findings suggest that NLR may be considered a marker of systemic inflammation associated with more aggressive forms of multiple myeloma. On the other hand, PLR appears to be a marker with an inverse prognostic value. Both ratios, easily accessible and inexpensive, can provide complementary information in the prognostic evaluation of patients with multiple myeloma.

While the integration of NLR and PLR indices is promising, further validation is needed; nevertheless, their correlation with markers of tumor aggressiveness supports their utility, especially in centers with limited resources.

CHAPTER 7 Personal contributions and Conclusions

This work brings significant original contributions to both the scientific literature and national medical practice concerning multiple myeloma. At the University Emergency Hospital of Bucharest (UEHB), the systematic evaluation of minimal residual disease (MRD) at 100 days post-autologous transplant was implemented and validated using flow cytometry. The study demonstrated the feasibility and clinical relevance of this method, highlighting its prognostic value, particularly through the association of MRD-negative status with favorable trends in overall survival (OS) and progression-free survival (PFS).

Another important finding was the positive correlation between achieving complete response (CR) before transplantation and MRD negativity, supporting the importance of effective induction therapy. In this context, the VCD regimen (bortezomib, cyclophosphamide, dexamethasone) proved effective in achieving deep responses, showing that even more accessible therapies can yield favorable outcomes in real-world settings, especially in resource-limited centers.

The study also integrated the analysis of hematologic indices NLR (neutrophil-to-lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio), assessed at the time of diagnosis, demonstrating their potential as prognostic markers. Notably, elevated NLR values were associated with systemic inflammation and poorer prognosis. These parameters, being easy to obtain and low-cost, may become valuable tools for risk stratification when access to advanced molecular testing is limited.

Based on these findings, the paper proposes a practical and sustainable post-transplant monitoring model that combines MRD assessment with NLR/PLR analysis to support a personalized therapeutic strategy. This model is adaptable and can be implemented across various clinical settings in Romania, contributing to aligning local practices with international standards.

Additionally, the study contributed to the development of a relevant clinical database that can support future research and health policy initiatives, providing a solid perspective on the real-world applicability of modern methods within the Romanian healthcare system.

In conclusion, the Thesis demonstrates the feasibility of implementing modern MRD monitoring standards in Romanian clinical practice, contributing to the

standardization of care for patients with multiple myeloma and to the development of personalized algorithms that combine advanced molecular biomarkers with easily accessible hematologic indices, aiming for optimal risk stratification and judicious allocation of therapeutic resources.

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