

Role of Composite Measurable Residual Disease Assessment with PET-CT and flow cytometry in Multiple Myeloma patients undergoing Autologous Transplant

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Abstract

Background: Bone marrow (BM) Measurable Residual Disease (MRD) assessments underestimate disease burden in multiple myeloma, as focal lesions can exist outside the marrow. Functional imaging, like positron emission tomography-computed tomography (PET-CT), offers valuable insights into residual disease beyond the marrow. Combining marrow flow cytometry (FCM) with PET-CT for a composite MRD (cMRD) assessment before and after autologous stem cell transplant (ASCT) is expected to provide prognostic information, particularly in settings where patients receive extended duration of anti-myeloma therapy prior to ASCT.

Methods: In this retrospective cohort study, we evaluated the prognostic impact of cMRD in newly diagnosed multiple myeloma (NDMM) patients who underwent triplet/quadruplet-based induction followed by ASCT from January 2017 to June 2023. cMRD was assessed before ASCT and again around day 100 post-transplant. cMRD negativity was defined as undetectable residual clonal plasma cells (sensitivity 1×10^{-5}) on multi coloured FCM and PET-CT negativity per The International Myeloma Working Group criteria.

Results: Among 106 patients undergoing ASCT, 82 had cMRD assessments before and on day 100 post-ASCT. Median pre-ASCT treatment duration was 11 months (interquartile range [IQR]: 4-18). At the pre-ASCT time point, sixty seven percent patients were bone marrow MRD negative (BM-MRD^{PRE}), while 38% were PET-CT negative (PET^{PRE}). Post-ASCT, these rates were 74% (BM-MRD^{POST}) and 49% (PET-CT^{POST}) respectively. At a median follow-up of 35 months (IQR: 23.5-58), median time to next treatment (TTNT) and overall survival (OS) were not reached. At three years, TTNT was significantly higher in patients who were cMRD-negative before ASCT compared to those who were cMRD-positive [91% (confidence interval (CI): 77-100) versus 67% (CI: 52-80); $p=0.027$]. BM-MRD^{PRE} and PET^{PRE} were both independently associated with improved TTNT on univariate analysis [Hazard Ratio: 0.32 (0.14-0.74) and 0.45 (0.23-0.94) respectively]. Post-ASCT cMRD status did not significantly impact TTNT [82% (CI: 68-96) versus 65% (CI: 51-69); $p=0.116$]. Three-year TTNT rates were similar among patients with and without baseline high-risk cytogenetic abnormalities (HRCA) if they maintained sequential cMRD negativity. In multivariate analysis, the absence of HRCA, complete response before ASCT, cMRD^{PRE}, and sustained cMRD negativity at both time points were independent predictors of longer TTNT.

Conclusions: Pre-ASCT cMRD assessment using both PET-CT and bone marrow FCM provides prognostic value in NDMM. This approach is particularly relevant in real-world settings where patients often receive prolonged induction therapy before ASCT.

Key words multiple myeloma, measurable residual disease, PET-CT, autologous transplant

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Introduction

Over the past decade, substantial advancements have significantly improved survival rates for patients with newly diagnosed multiple myeloma (NDMM)¹. These gains are attributed to enhanced diagnostic methods, the integration of novel therapeutic strategies, and the adoption of more sensitive techniques to monitor disease relapse. In this context, achieving bone marrow measurable residual disease (BM-MRD) negativity—assessed via flow cytometry (FCM) or molecular techniques—has become a critical prognostic indicator for long-term outcomes². Autologous stem cell transplant (ASCT) continues to be an effective strategy that improves outcomes in patients with NDMM³⁻⁶. Evidence shows that the depth of response prior to ASCT influences both survival and relapse patterns^{7,8}. However, while numerous studies have focused on MRD assessments after transplantation, data regarding the impact of pre-transplant MRD status on outcomes remains limited⁹⁻¹¹. Additionally, relying solely on bone marrow assessments may underestimate the disease burden due to the spatial heterogeneity of multiple myeloma, which often includes focal lesions outside the marrow^{2,12}. Functional imaging techniques, such as positron emission tomography-computed tomography (PET-CT) and MRI, provide valuable supplementary insights into MRD status, and their integration is now recommended by the International Myeloma Working Group (IMWG)¹³.

Most studies on bone marrow MRD have been conducted in Western settings, where stem cell mobilization typically occurs after four cycles of induction therapy, and stem cells are cryopreserved. In these cases, ASCT is performed either immediately or delayed, based on patient preference. In low- and middle-income countries (LMICs), however, stem cells are generally not cryopreserved. Due to out-of-pocket expenses, planned transplants are often delayed, and induction therapy is continued for longer periods. The relevance of composite MRD (cMRD) assessment in the context of extended induction therapy is not well understood. This study, therefore, aimed to assess the prognostic value of a composite response—integrating bone marrow MRD and PET-CT—conducted just before autologous ASCT and again at D+100 post-transplant in NDMM patients in a real-world LMIC setting.

Materials and Methods

This retrospective cohort study included adult patients (age > 18 years) with newly diagnosed multiple myeloma who underwent both PET-CT imaging and BM-MRD assessment immediately before ASCT at our centre from January 2017 to June 2023. The study was

approved by the Institutional Ethics Committee, PGI-MER, Chandigarh vide letter no. IEC-12/2020-1868. Informed consent was taken from each patient at the time of initiation of treatment regarding the use of their outcome data for publication. Patients achieving less than a Partial Response before ASCT, based on IMWG criteria, were excluded.

High-risk cytogenetic abnormalities (HRCA) were defined as the presence of t(4;14), t(14;16), del(17p), or 1q21 gain/amplification, identified by fluorescence in situ hybridization (FISH) at diagnosis. BM-MRD and PET-CT imaging were performed immediately before ASCT and again 100 days post-transplant.

BM-MRD detection utilised a two-tube FCM assay with a 10-color antibody panel (CD38, CD138, CD19, CD45, CD27, CD81, CD56, CD200, CD117, CD28). Approximately 3.2 million events were targeted to achieve a sensitivity of 0.001%, equating to one malignant cell per 100,000 cells (1 in 10⁵); this threshold defined BM-MRD negativity. PET-CT scans were evaluated per 2016 IMWG guidelines. PET negativity (PET-) was defined as complete resolution of all areas with increased tracer uptake from baseline or reduction of uptake below the standard uptake value of the mediastinal blood pool or adjacent normal tissue. All patients received ASCT according to the institutional protocol^{3,14}. Stem cell mobilization was conducted using granulocyte colony-stimulating factor (G-CSF), with plerixafor as needed. Peripheral blood stem cells were collected one day before a high dose of melphalan and stored at -4°C before infusion (day 0)¹⁵. Maintenance therapy with Lenalidomide or Bortezomib or both began 100 days post-ASCT after BM-MRD and PET-CT reassessment.

Baseline characteristics were summarised descriptively, with continuous variables as medians and interquartile ranges (IQRs) and categorical variables as percentages. Time to next treatment (TTNT) was defined as the interval from ASCT to initiation of new therapy due to disease progression, excluding maintenance changes due to side effects. Next treatment was initiated at the time of clinical relapse or significant paraprotein relapse based on IMWG criteria¹⁶. Overall survival was measured from diagnosis to death. Survival probabilities were estimated using Kaplan-Meier analysis, with group differences evaluated via log-rank tests. Cox proportional hazards regression models were applied for univariate and multivariate analyses to identify predictors, with a 5% significance level. Statistical analyses were conducted using SPSS version 24. The outcomes of patients who achieved both BM-MRD and PET negativity before ASCT i.e. composite MRD-negative (cMRD^{PRE-}), or who had positive results on either of the modalities, i.e. (cMRD^{PRE+}), those who achieved both BM-MRD and PET negativity at day 100

ASCT i.e. cMRD^{POST-} and those remaining positive on either/both modality i.e. cMRD^{POST+} were analysed and compared.

Results

Baseline characteristics of the study population

A total of 106 patients with NDMM underwent ASCT during the study period. Five patients with progressive disease, six who lacked pre-transplant cMRD assessment and 13 who lacked post-transplant cMRD assessments were excluded, and 82 patients were included in the analysis (**Supplementary Figure 1**). The median age of the study participants was 53.5 years (IQR 48-60), with a nearly equal gender distribution (M =1.1:1). The median follow-up duration for the entire cohort from the date of ASCT was 35 months (IQR 22-58). Baseline disease characteristics are summarized in **Table 1**. At diagnosis, 18 patients (21%) presented with HRCA. The median duration of induction therapy prior to ASCT was 11 (IQR 4-18)months. Majority of patients, 75 (91%), received a triplet combination, among which 34 (41.5%) received Bortezomib, Lenalidomide, and dexamethasone (VRd), while 30 (36.5%) received Bortezomib, cyclophosphamide, and dexamethasone (VCd) (**Table 1**). Prior to ASCT, 49 patients (60%) achieved complete remission (CR) or better, 23 (28%) achieved very good partial response (VGPR), and 10 (12%) had a partial response.

Bone marrow measurable residual disease and PET-CT response before and after ASCT

In the study cohort of 82 patients, 55 (67%) were negative for bone marrow measurable residual disease (BM-MRD^{PRE-}) before ASCT, while 31 (38%) were negative on PET-CT (PET^{PRE-}). A comparison of baseline disease characteristics between the cMRD^{PRE-} versus cMRD^{PRE+} and cMRD^{POST-} versus cMRD^{POST+} cohorts did not reveal any significant differences with respect to age, International Staging System, HRCA or renal involvement or duration of anti-myeloma therapy (**Supplementary Table 1**). Twenty-five patients (30%) achieved a composite MRD-negative (cMRD^{PRE-}) state prior to ASCT. Among the 57 patients (70%) who were cMRD^{PRE+}, 19 (23%) were double-positive (BM-MRD+ and PET+), 30 (37%) were BM-MRD negative but PET positive (BM-MRD- and PET+), and 8 (10%) were BM-MRD positive and PET negative (BM-MRD+ and PET-). There was a 47% discordance between BM-MRD and PET-CT results at the pre-ASCT time point, with a Cohen’s kappa of 0.1, indicating very low agreement (**Supplementary Figure 2(A)**). Post-ASCT, this discordance decreased to 39%, with a Cohen’s kappa of 0.23, suggesting a fair level of agreement (**Supplemen-**

Table 1. Baseline characteristics of study population

Baseline characteristics		n=82
Median Age (IQR)		53.5 (48-60)
Gender (n, %)	Male	45 (55)
	Female	37 (45)
Anemia (n, %)		50 (61)
Renal impairment at diagnosis (n, %)		31 (37.8)
Skeletal involvement (n, %)		74 (90)
HRCA at diagnosis * (n, %)		18 (21)
ISS (n, %)	I	14 (17)
	II	28 (34)
	III	40 (49)
Initial treatment (n, %)	VRd	34 (41.5)
	VCd	30 (36.5)
	VTd	9 (11)
	Dara-VRd	7 (8.5)
	Others	2 (2)
Median duration of treatment in month prior to ASCT (IQR)		11 (4-18)
Prior line Treatment (n, %)		
1		65 (80)
2or more		17 (20)
Response pre-ASCT (n, %)		
CR		49 (60)
VGPR		23 (28)
PR		10 (12)
Maintenance (n, %)		
Singlet (IMiD or PI)		68 (83)
Doublet (IMiD and PI)		14 (17)

HRCA, high-risk cytogenetic abnormalities; ISS, international staging system; VRd, bortezomib, ienalidomide, and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VTd, bortezomib, thalidomide, and dexamethasone; Dara VRd, daratumumab + VRd; CR, complete response; VGPR, very good partial response; PR, partial response; IMiD, imunomodulatory drug; PI, proteosome inhibitor; ASCT, autologous stem cell transplant; IQR, interquartile range

* High-risk cytogenetic abnormalities (HRCA) were defined as the presence of t(4;14), t(14;16), del(17p), or 1q21 gain/amplification, identified by fluorescence in situ hybridization (FISH) at diagnosis.

tary Figure 2(B)). The proportion of patients who attained a cMRD^{POST-} were 48% (n=39). One-fifth (n=5, 20%) patients who were cMRD^{PRE-} progressed to cMRD^{POST+} at day 100 post-ASCT time point. **Figure 1** illustrates the conversion patterns of different response categories pre- and post-ASCT among the 82 patients who underwent sequential cMRD assessments.

Prognostic impact of composite MRD assessment at pre-ASCT and post-ASCT time points

TTNT and overall survival were not reached for the entire study population. At three years, the TTNT was significantly longer for the cMRD^{PRE-} cohort compared to the cMRD^{PRE+} cohort [91% (C.I. 77-100) versus 67% (C.I. 52-80); *p*=0.027] while statistically significant dif-

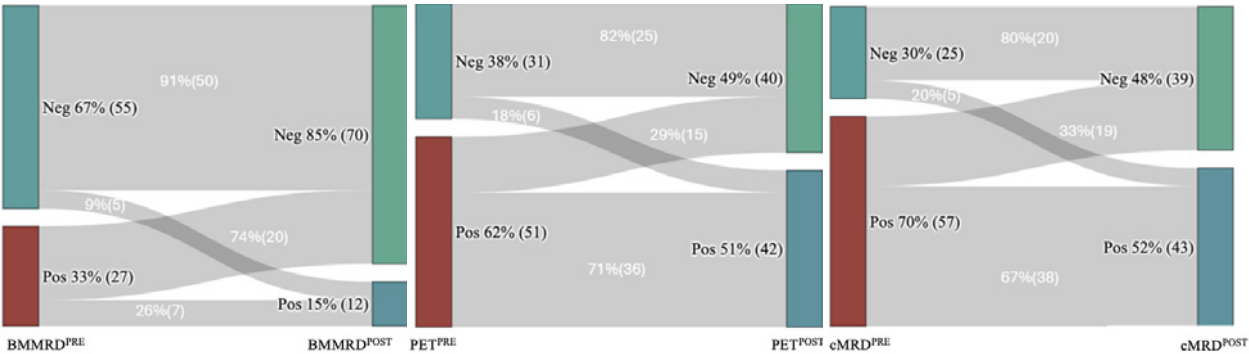


Figure 1. MRD Conversion Pre and Post-Autologous Stem Cell Transplant using both modalities (BM-MRD and PET-CT)
Numbers in solid black indicate the response status before and after ASCT. Numbers in solid white indicate proportion of patients transitioning from one MRD category to another after ASCT.
Pos, positive; Neg, negative; BM-MRD, bone marrow measurable residual disease; cMRD, composite measurable residual disease using BM-MRD and PET-CT)

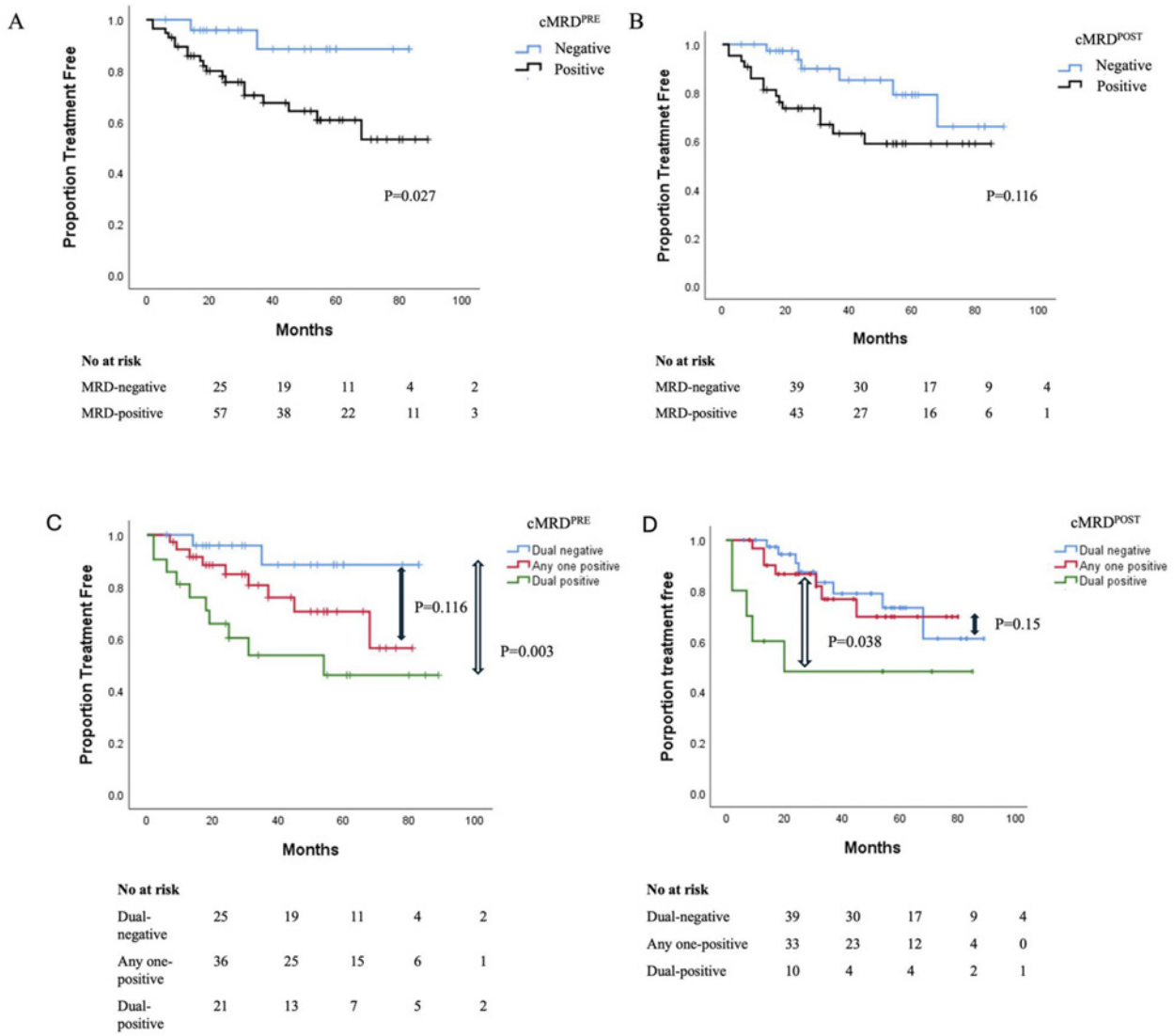


Figure 2. Kaplan Meier survival analysis showing TTNT plots between (A) cMRD^{PRE} Positive vs Negative, (B) cMRD^{POST} Positive vs Negative, (C) cMRD^{PRE} stratified by status of Both modalities (BM MRD and PET CT), and (D) cMRD^{POST} stratified by status of both modalities (BM MRD and PET CT)

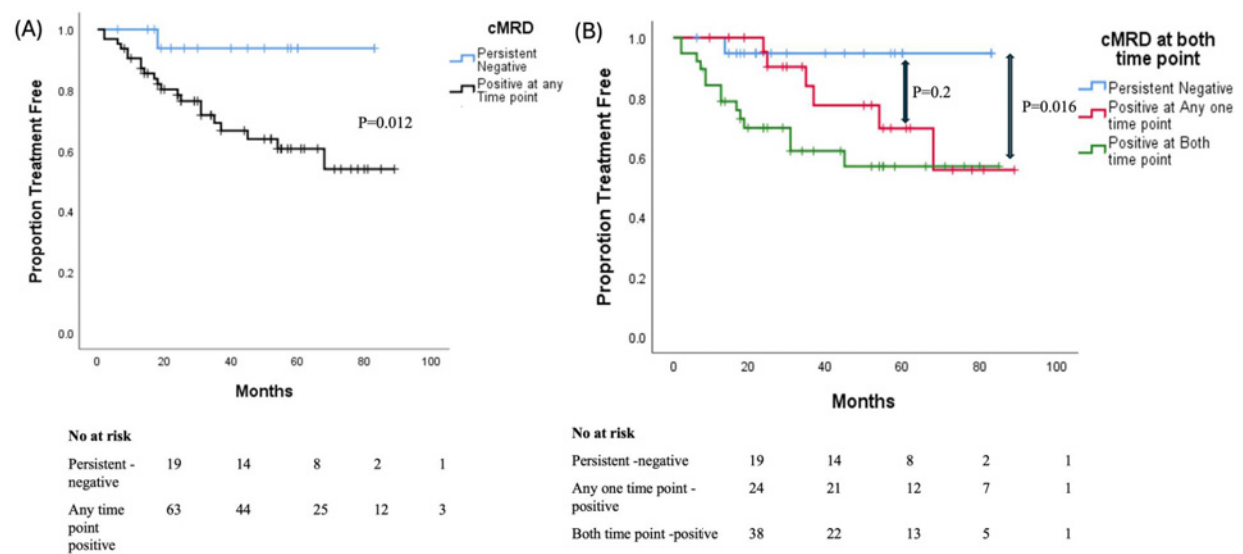


Figure 3. Kaplan Meier survival analysis showing TTNT plots stratified by groups based on Pre-ASCT and Post-ASCT cMRD status

ference was not observed at the post-ASCT time point [82% (C.I. 68-96) versus 65% (C.I. 51-69); $p=0.116$] (**Figure 2(A)-(D)**, **Supplementary Table 2**). Moreover, patients who were cMRD-negative at both time points had a significantly longer TTNT compared to those who were cMRD positive at both time points or any one of the time points (**Figure 3**). However, the Overall Survival (OS) did not differ significantly between the cMRD-positive and cMRD-negative groups at either time point. Patients who achieved early cMRD negativity (cMRD^{PRE-}) demonstrated a trend towards longer TTNT compared to those who were cMRD negative at a later time point (initially cMRD^{PRE+} but converted to cMRD^{POST-} following ASCT). The 3-year TTNT rates were 89% for the early cMRD negative group and 78% for the late cMRD negative group ($p=0.198$) (**Supplementary Figure 3**).

Among patients with HRCA at diagnosis, the proportion achieving cMRD^{PRE-} was 27.8% (5 out of 18) before ASCT, which increased to 44.5% (8 out of 18) after ASCT. The three-year TTNT was comparable between patients with and without baseline HRCA who attained cMRD-negative status at both time points. However, for patients who remained cMRD-positive at either time point, the presence of HRCA continued to negatively impact TTNT (**Supplementary Figure 4 (A)-(D)**).

On the Cox univariate analysis, the absence of HRCA at diagnosis, pre-ASCT BM-MRD negativity, pre-ASCT PET negativity, cMRD-negative status before ASCT (cMRD^{PRE-}), and cMRD negativity at both time points (cMRD^{PRE-}cMRD^{POST-}) were identified as predictors of a longer TTNT: while the duration of anti-multiple myeloma therapy pre-ASCT and the choice of maintenance

therapy post-ASCT did not impact TTNT (**Table 2**). In the multivariate analysis, the absence of HRCA at diagnosis was associated longer TTNT [Hazard Ratio (HR) of 0.16 (Confidence interval (CI) 0.06-0.41; $p<0.001$)]. Additionally, achieving CR before ASCT had an HR of 0.37 (CI 0.15-0.89; $p=0.027$), cMRD negativity before ASCT had an HR of 0.19 (CI 0.04-0.63; $p=0.018$), and sustained MRD negativity at both time point (cMRD^{PRE-}cMRD^{POST-}) had HR of 0.17 (CI 0.02-0.31; $p=0.019$), indicating that these were independent predictors of longer TTNT (**Figure 4**).

In contrast, cMRD^{POST-} was not a significant predictor of longer TTNT in the multivariate analysis (**Figure 4 (A)**). Among all the factors analysed, only the presence of HRCA was significantly associated with overall survival in the multivariate analysis (**Figure 4(B)**).

Discussion

MRD has become a critical surrogate marker for progression-free and overall survival in patients with multiple myeloma, serving as an essential endpoint in treatment^{17,18}. However, the differential prognostic impact of various time points of achieving MRD negativity in the bone marrow and imaging negativity remains unclear. Most prior studies have relied on bone marrow MRD assessments conducted three months post-ASCT for prognostic predictions^{10,19}. Our findings indicate that among patients with newly diagnosed multiple myeloma (NDMM) undergoing ASCT, TTNT varied based on when cMRD negativity was achieved. Specifically, those who maintained sequential cMRD negativity at both the time points had the most favourable prognosis. Additionally, cMRD negativity before ASCT

Table 2. Univariate analysis of various factors impacting TTNT and overall survival study

Covariates	Univariate analysis for TTNT		Univariate analysis for OS	
	HR (95% CI)	p=	HR (95% CI)	p=
Age	1.02 (0.97-1.08)	0.44	1.1 (0.99-1.22)	0.06
Renal involvement	1.37 (0.76-3.9)	0.48	1.81 (0.36-8.96)	0.449
ISS				
I	Ref			
II	1.16 (0.59-2.36)	0.8		
III	1.9 (0.67-5.42)	0.23		
HRCA		0.003		0.046
Positive	Ref		Ref	
Negative	0.27 (0.12-0.66)		0.26 (0.07-0.96)	
Pre-ASCT		0.11		0.205
Not in CR	Ref		Ref	
CR	0.51 (0.22-1.19)		0.4 (0.09-1.66)	
Pre ASCT cMRD		0.028		0.58
cMRD Positive	Ref		Ref	
cMRD Negative	0.24 (0.06-0.77)		0.65 (0.13-3.23)	
Pre ASCT MRD by FCM		0.008		0.26
Positive	Ref		Ref	
Negative	0.32 (0.14-0.74)		0.45 (0.11-1.8)	
Pre ASCT PET CT		0.047		0.29
Positive	Ref		Ref	
Negative	0.45 (0.23-0.94)		0.44 (0.09-2.2)	
Day 100 Post-ASCT MRD by FCM		0.42		0.48
Positive	Ref		Ref	
Negative	0.71 (0.3-1.67)		0.59 (0.14-2.48)	
Day 100 Post ASCT PET CT		0.377		0.319
Positive	Ref		Ref	
Negative	0.68 (0.29-1.62)		0.44 (0.09-2.2)	
Day 100 post ASCT cMRD		0.239		0.33
cMRD Positive	Ref		Ref	
cMRD Negative	0.59 (0.24-1.45)		0.47 (0.1-2.34)	
Sequential cMRD		0.036		0.48
Positive at any or both time point	Ref		Ref	
Persistent Negative	0.16 (0.02-0.61)		0.48 (0.06-3.87)	

CR, complete response; ISS, international staging system; ASCT, autologous stem cell transplant; TTNT, time to next treatment; OS, overall survival; HR, hazard ratio; CI, confidence interval; MRD, measurable residual disease; PET CT, positron emission tomography computed tomography; FCM, flow cytometry; cMRD, composite measurable residual disease; HRCA, high-risk cytogenetic abnormalities, Ref, reference

was predictive of longer TTNT, with both BM-MRD^{PRE} and pre ASCT PET negativity independently predictive of longer TTNT on univariate analysis. These results suggest that assessing cMRD negativity prior to ASCT may help identify a subgroup of patients who will have a longer time to next treatment following ASCT consolidation with standard immunomodulatory (IMiD) drug and/or proteasome inhibitor (PI) maintenance in the setting where prolonged inductions are given prior to ASCT consolidation.

Unlike patients with most lymphomas where the time points for interim and follow-up image based response assessments are well validated, the timing and frequency of BM-MRD and imaging for response assess-

ment in multiple myeloma remains uncertain. Most data suggest that sequential evaluations are more informative from a prognostic stand point²⁰. IMWG defines sustained MRD negativity as consecutive negative MRD result in bone marrow, confirmed ≥ 1 year apart¹³. Sequential MRD studies using bone marrow and PET-CT before and after ASCT have a potential to analyse the efficacy of ASCT in the eradication of residual disease. In the current study patients who attain an early cMRD negativity had the longest time to next treatment, cMRD^{PRE} was a stronger predictor of TTNT as compared to cMRD^{POST}. Contrary to these findings the PRIMeR study reported, that patients achieving BM-MRD^{neg} by multiparametric flow cytometry (MFC) at 1-

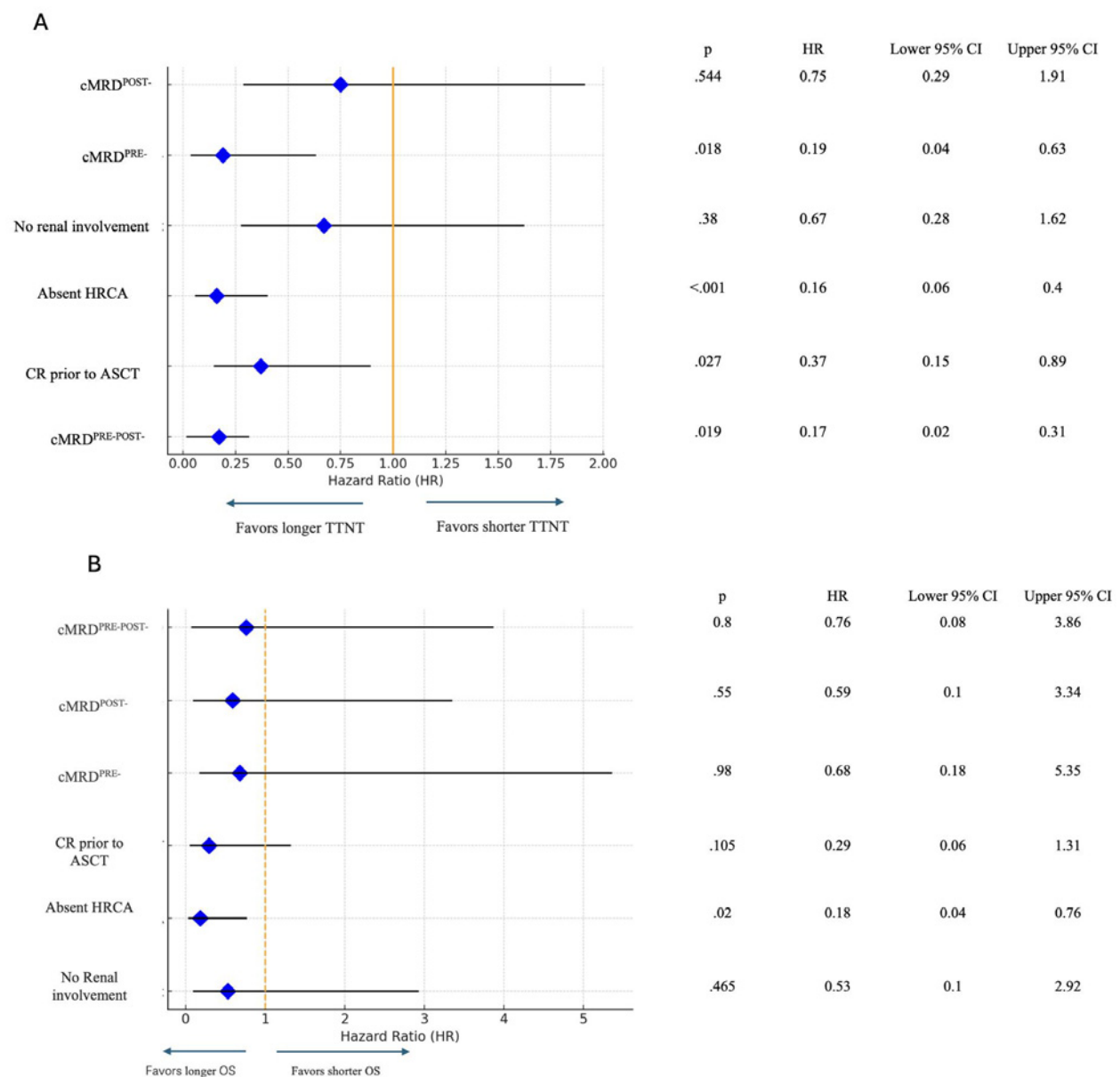


Figure 4. Multivariate analysis for (A) TTNT among patients who had sequential cMRD assessment at two time points and (B) multivariate analysis for overall survival among patients who had sequential cMRD assessment at two time points

year post-ASCT had the best outcomes rather than pre-maintenance and pre-ASCT time points. In the PRIMeR cohort, 42% of patients attained BM-MRD negativity at pre ASCT time point compared to 67% BM-MRD negativity in the current cohort. The long median duration of induction (~11 months in the current study compared to ~6 months in the PRIMeR cohort) may have led to a higher proportion of patients who were already MRD-negative at the pre-ASCT time point²¹. This extended induction period is particularly common in LMIC settings, where patients generally lack health insurance, and treatment costs are out-of-pocket, often resulting in delayed autologous transplants and the pre-ASCT time point may be particularly significant for

prognostication in such settings. While the additional costs of BM-MRD and PET-CT imaging are significant, this needs to be viewed against the costs of subsequent lines of treatment. Majority of patients who relapse after IMiD and Proteasome inhibitor exposure have limited treatment options in the real world. Given the ability of sequential cMRD to identify a subgroup of patients who have dismal outcome (**Figure 3**), a careful consideration needs to be given on the choice of maintenance strategies (single versus doublet maintenance) as well as the frequency of follow-up investigations and surveillance strategies for disease monitoring in patients who remain cMRD positive. However the utility of these strategies based on cMRD results need validation

in prospective studies.

It is well known that while BM-MRD provides disease assessment at single cell resolution level at a medullary level, imaging modalities like PET-CT are a reflection of a global marrow activity and also extramedullary disease status. Therefore the two modalities have a potential of being discordant and the same was observed in the current and various other studies that have simultaneously analysed BM-MRD and PET-CT²². In the IMAJEM study that reported outcomes based on imaging response in patients receiving VRd based induction, the discordance between the BM-MRD and PET modalities at the pre-ASCT time point was 39.5%, compared to 44% in our study²³. Similar high discordance rates between BM-MRD and PET were also reported in trials that utilised quadruplet combinations²⁴. However, in other studies that used next-generation sequencing with a cut off 1 in 10⁶ clonal plasma cells to define BM-MRD negativity, this discordance reduced to ~10%²⁵. These finding suggests the complementary utility of PET for response assessment in the real world setting until more sensitive methods of BM-MRD assessment become widely available.

The current study also reported the comparative impact of ASCT on BM-MRD versus PET conversion rates in a real world patient population predominantly treated with a Proteasome Inhibitor -Immunomodulatory Drug (PI-IMiD) triplet combination. Previous studies have suggested that ASCT leads to clearance of BM-MRD in nearly half of patients who are BM-MRD positive pre-ASCT, 74% patients cleared their BM-MRD in the current study with ASCT⁸. The impact of ASCT on PET responses has been variably reported depending on the type of criteria used to define PET negativity and the timing of PET scans²⁶⁻²⁸. A significant proportion of patients were PET negative (36.5%) and BM-MRD negative (67%) pre-ASCT in the current study, likely because of long duration of pre-ASCT induction (median 11 months). The PET negativity rate was 49% at the post ASCT time point in the current study. In the CASSIOPET study that utilised a quadruplet induction, 64% of patients achieved PET negativity (defined by uptake < mediastinal blood pool) at the post consolidation time point. On the contrary Kadoura M et al reported a lower PET-negativity rate of 35% at day 100 post-ASCT in a heterogeneously treated population over a period ranging from 2003 to 2016^{7,29}. Both these studies have utilised similar PET response criteria as the current study. In contrast, Zamagni et al reported higher rates of PET negativity (70%), and the IMAJEM study noted a 75% PET-negativity rate, using different PET interpretation criteria^{23,30,31}. **Supplementary Table 3** summarises the findings of salient studies that have analysed the PET-CT

responses at various time points. Most of these studies suggested that attainment of PET negativity post ASCT was associated with nearly halving the risk of progression^{7,30,32}. In the current study while pre-ASCT PET was prognostic for TTNT, the prognostic impact of day 100 PET negativity did not reach a statistical significance. Whether a more distant time point rather than a repeat day 100 PET-CT may be useful for predicting long-term outcomes particularly when a long induction is used and a Pre-ASCT PET-CT has been done needs further studies.

The presence of HRCAs remained a significant factor for overall survival in the current study, as previously reported^{33,34}. However, the TTNT and OS for patients who maintained sequential cMRD negativity at both assessment points were comparable amongst patients with and without HRCAs in the current study. This suggests that achieving cMRD negativity in both bone marrow MFC and PET-CT may help offset the adverse prognostic effect of HRCAs. A cMRD-guided approach before ASCT, including intensified treatment for MRD-positive patients with HRCAs, could improve outcomes and is currently being tested in several ongoing trials^{35,36}.

The findings of this study should be interpreted considering the inherent limitations of a retrospective analysis with a small sample size, as well as the strengths of the real-world setting in which the data were collected outside of a clinical trial. Given the retrospective nature of the study with lack of consistent follow up intervals, the current study utilised TTNT rather than Progression-Free Survival for the comparison of outcomes. Although MRD detection sensitivity was 1 in 100,000 cells, baseline PET status was not included in the analysis, These limitations reflect scenarios commonly encountered in most real-world settings. Additionally, only a limited number of patients received the more effective quadruplet regimens, now considered the standard of care for frontline treatment of NDMM in high-income countries. This limitation, however, underscores the relevance of studying outcomes in settings where resource constraints necessitate the use of triplet regimens. Furthermore, most patients underwent ASCT later than usual, after receiving a higher median number of induction cycles. While this might have influenced pre-ASCT and subsequent response assessments, it also provides a unique opportunity to evaluate the prognostic impact of bone marrow and imaging MRD in the context of extended induction therapy - a scenario more commonly encountered in LMICs due to delayed access to transplants. By addressing the gaps in composite response assessments at multiple time points, future prospective research can better guide treatment strategies in resource-limited settings, enhancing global equity in myeloma care.

In summary, our findings highlight the importance of PET-CT and BM-MRD in assessing residual disease in NDMM patients. Additionally, the pre-ASCT time point may be particularly crucial for sequential MRD evaluation and future prognostication, especially in settings where longer initial treatments are administered before ASCT.

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Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the web-site.

DL is one of the editors of Blood Cell Therapy. He was not involved in the editorial evaluation or decision to accept this article for publication.

Author Contribution

RNS and AJ analyzed the data and wrote the initial draft of the manuscript. All authors were involved in patient recruitment, reviewing, and approving the final manuscript. RNS and AJ have equally contributed to the manuscript.

Data availability statement

Data will be made available on reasonable request by contacting the corresponding author.

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