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Cardiac Biomarkers and Echocardiographic Findings in Patients with Multiple Myeloma With and Without Major Adverse Cardiovascular Events

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ABSTRACT

Background: Both disease- and treatment-related factors increase the risk of cardiovascular complications in multiple myeloma (MM) patients. The purpose of this study was to find parameters that are independently linked to major adverse cardiovascular events (MACE) by evaluating cardiac involvement using echocardiography and cardiac biomarkers in both MACE-and non-MACE patients.

Methods: This comparative cross-sectional analytical research included one hundred MM patients who were getting treatment at Cardiology Department, Al-Ahrar Teaching Hospital, GOTHI. Half of the patients were assigned to the MACE group and half to the non-MACE group. Clinical assessment, laboratory testing, and transthoracic echocardiography were all part of the protocol for all subjects. We used multivariate logistic regression and (ROC) curve analysis to find characteristics that were linked with MACE separately.

Results: In addition to being considerably older, patients with MACE exhibited lower hemoglobin and albumin levels, more frequent cardiovascular symptoms, decreased renal function, and higher levels of high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). The echocardiography results showed that the MACE group had larger cardiac chambers, a lower LVEF, and more severe diastolic dysfunction. The E/e′ ratio, age, creatinine, hs-cTnT, NT-proBNP, LVEF, and NT-proBNP were all separately linked to MACE. When it came to identifying individuals with MACE, NT-proBNP had the best diagnostic performance (AUC = 0.99), although high-sensitivity cardiac troponin (hs-cTnT) and E/e′ ratio were close behind (AUC = 0.88 and 0.79, respectively).

Conclusion: In MM patients with MACE, cardiac structural and functional abnormalities were more noticeable. An efficient method for stratifying cardiovascular risk is the combination of echocardiography with evaluation of cardiac biomarkers. Patients with MM may benefit from improved cardiovascular risk assessment and easier identification of those with more severe cardiac involvement if these non-invasive methods are routinely used together.

KEYWORDS: Multiple Myeloma; Cardiac Biomarkers; High-Sensitivity Cardiac Troponin T; Nt-Probnp; Transthoracic Echocardiography.

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INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal plasma-cell proliferation, affects several systems, and drastically reduces both survival rates and quality of life. Unfortunately, treatment-related morbidity is still a major therapeutic concern, and the majority of MM patients still do not have a cure, even with advancements in immunomodulatory drugs, monoclonal antibodies, proteasome inhibitors, and autologous stem cell transplantation. Among extra-hematologic consequences, cardiovascular involvement is now a strong predictor of prognosis **[1].**

Coexisting age-related cardiovascular diseases are common upon diagnosis of MM since the disease mostly affects older persons. In addition, various disease-related factors, including systemic inflammation, renal impairment, and a high tumour load, as well as therapeutic exposures like anthracyclines, carfilzomib, immunomodulatory drugs, and corticosteroids, can lead to cardiovascular adverse events (CVAEs) and worse outcomes. Hypertension, arrhythmias, pulmonary hypertension, ischaemic heart disease, venous thromboembolism (VTE), arterial thromboembolism (ATE), HF, and other cardiovascular adverse events (CVAEs) may occur in MM. A clinically relevant composite endpoint, major adverse cardiovascular events (MACE) capture serious occurrences that directly impact survival within this spectrum. Heart failure, cardiogenic shock, abnormal heart rhythms, acute coronary syndrome, and suddenly cardiac death are common occurrences in such cases **[2].**

Myocardial damage and haemodynamic stress may be easier to identify with the use of cardiac biomarkers. Although these results are useful for MM diagnosis, they might be difficult to interpret due to non-cardiac variables, especially renal impairment **[3].**

Noninvasive and easily accessible, transthoracic echocardiography may evaluate structural and functional cardiac complications; however, cardiac biomarkers like NT-proBNP and high-sensitivity cardiac troponin shed light on myocardial damage and ventricular stress. Combining echocardiographic examination with biomarker evaluation might help detect and better define cardiac involvement in persons with multiple myeloma **[4].**

The purpose of this study was to find parameters that are independently linked to major adverse cardiovascular events (MACE) by evaluating cardiac involvement using echocardiography and cardiac biomarkers in both individuals with and without MACE.

METHODS

This study was conducted at the Cardiology Department, Al-Ahrar Teaching Hospital, GOTHI from January 2022 to January 2023. Fifty patients were categorized as having MACE and fifty as not having MACE. MACE was defined as a composite of clinically documented heart failure requiring hospital admission or intravenous therapy, acute coronary syndrome confirmed by clinical, electrocardiographic, and biomarker criteria, clinically significant arrhythmia requiring medical or electrical intervention, cardiogenic shock, or sudden cardiac death. Researchers who weren't privy to the study's biomarker findings used patients' medical data to decide on events. In the predetermined one-year observation period, patients who did not have any recorded component of the composite endpoint were included in the non-MACE group.

The study included patients with a confirmed multiple myeloma diagnosis according to IMWG guidelines, and illness stage was determined using the Revised International Staging System **[5]**. All participants were at least eighteen years old, irrespective of the severity of their sickness or the efficacy of their treatment. We included patients with full clinical, biomarker, and echocardiographic data regardless whether they had cardiovascular symptoms or baseline ECG abnormalities.

Exclusion criteria included a patient's refusal to participate, a poor echocardiographic window, an active infection or sepsis, a history of diabetes mellitus, valvular or congenital cardiac disease, hypertension, chronic liver disease, diabetes mellitus, cardiomyopathy unrelated to multiple myeloma, or a stage 4 or 5 chronic kidney disease.

Every patient gave their written informed consent before they took part. Ethical guidelines for medical research involving human beings are outlined in the Declaration of Helsinki, which the study followed.

Clinical Assessment:

A comprehensive clinical evaluation was conducted on all participants. This included a comprehensive physical examination with an emphasis on cardiovascular findings, an evaluation of the duration of multiple myeloma and treatment history, and a detailed medical history regarding cardiac symptoms like dyspnoea, chest pain, palpitations, syncope and a standard 12-lead (ECG).

Laboratory Investigations:

Standard laboratory testing was conducted on all patients, including complete blood count (CBC), albumin, LDH, urea, creatinine, and liver function tests. Under aseptic conditions, venous blood samples were collected to assess cardiac biomarkers like hs-cTnT, which can detect myocardial injury, and NT-proBNP, which can indicate myocardial stress and ventricular dysfunction. The Clinical pathology Department, Al-Ahrar Teaching Hospital, GOTHI processed all samples in accordance with established laboratory procedures.

ECHOCARDIOGRAPHIC ASSESSMENT

Conventional Transthoracic Echocardiography

A commercial ultrasound machine (Vivid 7 US machine (GE-Vingmed Ultrasound AS, Horten, Norway) equipped with a 3.5 MHz transducer was used to do transthoracic echocardiography on all participants. An experienced cardiologist conducted the echocardiographic exams without knowledge of the results from the lab. Left ventricular dimensions, interventricular septal thickness, posterior wall thickness, and left atrial diameter were all measured during the echocardiographic evaluation. While diastolic function was determined by measuring mitral inflow velocities (E and A waves), the E/A ratio, deceleration duration, and isovolumetric relaxation time. Left ventricular systolic function was evaluated by calculating the LVEF using the modified Simpson's approach.

Doppler and Tissue Doppler Imaging (TDI):

The myocardial velocities at the mitral annulus were assessed at the beginning and end of each cardiac cycle. The E/e' ratio was used to determine the left ventricular filling pressures.

Assessment of Diastolic Dysfunction:
Standardised methods developed by the American Society of Echocardiography (ASE) were used to categorise left ventricular diastolic performance into three levels: normal, impaired relaxation (Grade I), and restricted filling (Grade II). Prior to the start of therapy for the cardiovascular event and the incidence of myocardial infarction, cardiac biomarkers and echocardiographic data were measured.

Statistical Analysis
SPSS (Statistical Package for Social Science) version 27.0 (IBM, 2020) was used to digitalize and analyze the collected data statistically. Qualitative data was presented using relative percentages and frequencies. The Chi-square test was used to find the difference between the qualitative variables. In cases where a number of the cells under examination was fewer than five, Fisher's exact test was used to determine if there were any differences in the qualitative characteristics between the groups. Quantitative data was expressed using the mean plus or minus the standard deviation. The purpose of using the independent T test was to compare two sets of normally distributed quantitative variables. The Mann Whitney (MW) test was used to assess quantitative variables between two groups with data that did not follow a normal distribution. Both Pearson's and Spearman's correlation coefficients may be used to demonstrate a link between quantitative variables. Using receiver operating characteristic (ROC) curve analysis, we find the best cut-off values for different features that have the maximum sensitivity and specificity for outcome-related risk variables.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of Multiple Myeloma Patients According to MACE Status

Variable		Group I (MACE, n = 50)	Group II (Non-MACE, n = 50)	P value
Age (years)	Mean ± SD	63.8 ± 5.6	58.6 ± 6.5	**<0.001***
	Range	51–78	42–71	
Sex	Male	32 (64%)	29 (58%)	0.53
	Female	18 (36%)	21 (42%)	
Smoking	Yes	21 (42%)	18 (36%)	0.53
	No	29 (58%)	32 (64%)	
MM status	Newly diagnosed	24 (48%)	27 (54%)	0.54
	On treatment	26 (52%)	23 (46%)	
MM duration (months)	Mean ± SD	18.2 ± 9.4	15.6 ± 8.1	0.11
	Range	2–40	1–36	
R-ISS stage	I	10 (20%)	14 (28%)	0.32
	II	25 (50%)	24 (48%)	
	III	15 (30%)	12 (24%)	

MM: Multiple Myeloma, MACE: Major Adverse Cardiovascular Events, R-ISS: Revised International Staging System, SD: Standard Deviation.

Compared to the non-MACE group, patients with MACE tended to be older. There was no statistically significant difference, however, in terms of sex distribution, smoking status, multiple myeloma status, illness duration, or R-ISS staging (Table 1).

Table 2: Comparison of Treatment Exposure between MACE and Non-MACE Groups in Multiple Myeloma Patients

Variable	Group I (MACE, n = 50)	Group II (Non-MACE, n = 50)	P value
Proteasome inhibitor	33 (66%)	28 (56%)	0.29
IMiDs	31 (62%)	27 (54%)	0.41
Anthracycline	22 (44%)	14 (28%)	0.08
Steroids	40 (80%)	38 (76%)	0.63
ASCT history	15 (30%)	18 (36%)	0.52

IMiDs: Immunomodulatory drugs, ASCT: Autologous Stem Cell Transplantation, MACE: Major Adverse Cardiovascular Events.

Table 2 shows that there were no significant differences between the research groups with respect to treatment exposure, including proteasome inhibitors, IMiDs, anthracyclines, steroids, and history of ASCT.

Table 3: Clinical Presentation and Electrocardiographic Findings among Multiple Myeloma Patients According to MACE Status

Variable		Group I (MACE, n = 50)	Group II (Non-MACE, n = 50)	P value
Baseline ECG normal	Yes	30 (60%)	38 (76%)	0.08
Dyspnea	Yes	35 (70%)	10 (20%)	**<0.001***
Chest pain	Yes	22 (44%)	8 (16%)	**0.002***
Palpitations	Yes	18 (36%)	9 (18%)	**0.04***
Syncope	Yes	6 (12%)	2 (4%)	0.14

CV: Cardiovascular, ECG: Electrocardiogram, MACE: Major Adverse Cardiovascular Events.

There was an alarming increase in the prevalence of palpitations, dyspnoea, and chest discomfort in MACE patients. However, the incidence of syncope did not show significant difference across the groups (Table 3).

Table 4: Comparison of Laboratory Parameters between MACE and Non-MACE Groups in Multiple Myeloma Patients

Variable		Group I (MACE, n = 50)	Group II (Non-MACE, n = 50)	P value
Hemoglobin (g/dL)	Mean ± SD	9.8 ± 1.3	10.5 ± 1.4	**0.01***
WBC (×10³/µL)	Mean ± SD	6.4 ± 2.0	6.9 ± 2.3	0.28
Platelets (×10³/µL)	Mean ± SD	190 ± 60	215 ± 70	0.07
Creatinine (mg/dL)	Mean ± SD	1.5 ± 0.5	1.1 ± 0.4	**0.001***
Urea (mg/dL)	Mean ± SD	48 ± 18	35 ± 12	**<0.001***
Calcium (mg/dL)	Mean ± SD	10.7 ± 1.1	10.0 ± 0.9	**0.002***
Albumin (g/dL)	Mean ± SD	3.3 ± 0.5	3.7 ± 0.6	**0.002***
LDH (U/L)	Mean ± SD	305 ± 80	255 ± 65	**0.003***

WBC: White Blood Cells, LDH: Lactate Dehydrogenase, MACE: Major Adverse Cardiovascular Events, SD: Standard Deviation.

The MACE group showed much lower levels of haemoglobin and serum albumin compared to the non-MACE group, and significantly higher levels of serum creatinine, urea, calcium, and lactate dehydrogenase (LDH). However, when looking at the platelet and white blood cell counts, there were no notable variations between the groups (Table 4).

Table 5: Comparison of Cardiac Biomarkers between MACE and Non-MACE Groups in Multiple Myeloma Patients

Variable		Group I (MACE, n = 50)	Group II (Non-MACE, n = 50)	P value
hs-cTnT (ng/L)	Mean ± SD	39.7 ± 14.2	17.6 ± 7.8	**<0.001***
NT-proBNP (pg/mL)	Mean ± SD	1310 ± 540	410 ± 180	**<0.001***

hs-cTnT: High-sensitivity cardiac troponin T, NT-proBNP: N-terminal pro–B-type natriuretic peptide, MACE: Major Adverse Cardiovascular Events, SD: Standard Deviation.

Cardiac biomarkers were significantly greater in patients with MACE compared to those without. Both NT-proBNP and hs-cTnT were significantly higher in the MACE group, suggesting a higher degree of myocardial damage and haemodynamic stress throughout the evaluation (Table 5).

Table 6: Comparison of Echocardiographic Parameters between MACE and Non-MACE Groups in Multiple Myeloma Patients

Variable		Group I (MACE, n = 50)	Group II (Non-MACE, n = 50)	P value
LVEDD (mm)	Mean ± SD	53.2 ± 5.1	49.8 ± 4.6	**<0.001***
IVS (mm)	Mean ± SD	11.5 ± 1.8	10.2 ± 1.5	**<0.001***
PW (mm)	Mean ± SD	11.3 ± 1.7	10.1 ± 1.4	**<0.001***
LA diameter (mm)	Mean ± SD	42.1 ± 5.4	37.0 ± 4.8	**<0.001***
LVEF (%)	Mean ± SD	49.2 ± 6.8	57.1 ± 5.9	**<0.001***
E wave (m/s)	Mean ± SD	0.68 ± 0.18	0.85 ± 0.20	**<0.001***
A wave (m/s)	Mean ± SD	0.82 ± 0.22	0.75 ± 0.18	**0.04***
E/A ratio	Mean ± SD	0.83 ± 0.25	1.13 ± 0.28	**<0.001***
DT (ms)	Mean ± SD	245 ± 45	210 ± 38	**<0.001***
IVRT (ms)	Mean ± SD	110 ± 18	92 ± 15	**<0.001***
e’ (cm/s)	Mean ± SD	5.8 ± 1.5	8.2 ± 1.7	**<0.001***
a’(cm/s)	Mean ± SD	7.5 ± 1.8	6.8 ± 1.5	**0.04***
E/e’	Mean ± SD	15.9 ± 3.8	10.8 ± 2.9	**<0.001***

LVEDD: Left Ventricular End-Diastolic Diameter, IVS: Interventricular Septum, PW: Posterior Wall, LA: Left Atrium, LVEF: Left Ventricular Ejection Fraction, DT: Deceleration Time, IVRT: Isovolumetric Relaxation Time, e’: Early

diastolic mitral annular velocity, a': Late diastolic mitral annular velocity, MACE: Major Adverse Cardiovascular Events, SD: Standard Deviation.

The left atrial diameter, interventricular septal thickness, and left ventricular dimensions were all significantly greater in the MACE group of patients. Furthermore, the MACE group showed a significant decrease in left ventricular systolic function as shown by reduced LVEF (Table 6).

Decreased E-wave velocity, longer deceleration and isovolumetric relaxation periods, decreased e′ velocity, and an elevated E/e′ ratio, all suggesting greater left ventricular filling pressure and were indicators of poor diastolic function in patients with MACE (Table 6).

Table 7: Distribution of Diastolic Dysfunction Grades among Multiple Myeloma Patients According to MACE Status

Grade	Group I (MACE, n = 50)	Group II (Non-MACE, n = 50)	P value
Normal	16 (32%)	32 (64%)	**<0.001***
Grade I	18 (36%)	12 (24%)	
Grade II	12 (24%)	5 (10%)	
Grade III	4 (8%)	1 (2%)	

MACE: Major Adverse Cardiovascular Events.

In terms of the distribution of diastolic dysfunction grades, the groups that were analyzed showed a statistically significant difference. The non-MACE group tended to have more individuals with normal diastolic function, while the MACE group had a greater frequency of patients with advanced diastolic dysfunction (Grades II and III) (Table 7).

Table 8: Distribution of first MACE component among patients with multiple myeloma who experienced MACE.

Event	Frequency
Heart failure	20 (40%)
ACS	13 (26%)
Arrhythmia	10 (20%)
Cardiogenic shock	4 (8%)
Sudden death	3 (6%)

MACE: Major Adverse Cardiovascular Events, ACS: Acute Coronary Syndrome. Data are presented as n (%) among the 50 patients with MACE.

Heart failure (40%), acute coronary syndrome (26%), and arrhythmia (20%) were the most common first events among the 50 patients who had MACE. Cardiogenic shock occurred in 8% and sudden cardiac death in 6% of patients with multiple myeloma who experienced MACE.

Table 9: Correlation between Cardiac Biomarkers and Echocardiographic Parameters in Multiple Myeloma Patients

Variable	hs-cTnT		NT-proBNP	
	(r)	(p value)	(r)	(p value)
LVEF (%)	-0.56	**<0.001***	-0.63	**<0.001***
E/e' ratio	0.52	**<0.001***	0.60	**<0.001***
LA diameter (mm)	0.48	**<0.001***	0.55	**<0.001***
IVS thickness (mm)	0.30	**0.003***	0.34	**0.001***
Posterior wall (mm)	0.28	**0.005***	0.31	**0.002***

hs-cTnT: High-sensitivity cardiac troponin T, NT-proBNP: N-terminal pro–B-type natriuretic peptide, LVEF: Left Ventricular Ejection Fraction, LA: Left Atrium, IVS: Interventricular Septum, MACE: Major Adverse Cardiovascular Events.

The correlation between cardiac biomarkers and echocardiographic parameters was statistically significant. As the levels of the biomarkers increase, systolic function declines, as LVEF and hs-cTnT and NT-proBNP were significantly inversely correlated. However, the E/e' ratio, left atrial diameter, interventricular septal thickness, and posterior wall thickness all exhibited positive associations with both biomarkers, suggesting that there were structural cardiac alterations and elevated

ventricular filling pressures (Table 9).

Table 10: Multivariable Logistic Regression Analysis for Independent risk factors associated with MACE in Multiple Myeloma Patients

Variable	OR	95% CI	P value
Age	1.08	1.02–1.15	**0.01***
Creatinine	1.85	1.20–2.90	**0.005***
hs-cTnT	1.04	1.02–1.07	**<0.001***
NT-proBNP	1.002	1.001–1.003	**<0.001***
LVEF	0.90	0.85–0.95	**<0.001***
E/e'	1.18	1.08–1.30	**<0.001***

OR: Odds Ratio, CI: Confidence Interval, hs-cTnT: High-sensitivity cardiac troponin T, NT-proBNP: N-terminal pro–B-type natriuretic peptide, LVEF: Left Ventricular Ejection Fraction, MACE: Major Adverse Cardiovascular Events.

The independent risk variables related with MACE, as shown in multivariable logistic regression analysis were age, creatinine, hs-cTnT, NT-proBNP, LVEF, and the E/e' ratio (Table 10).

Table 11: Diagnostic Performance of NT-proBNP, hs-cTnT and E/e' Ratio as risk factors associated with MACE in Multiple Myeloma Patients

Variable	AUC	Cutoff	Sensitivity	Specificity	P value
NT-proBNP	0.99	>501 pg/mL	96%	98%	**<0.001***
hs-cTnT	0.88	>28 ng/L	82%	80%	**<0.001***
E/e'	0.79	>13.1	68%	80%	**<0.001***

AUC: Area Under the Curve, NT-proBNP: N-terminal pro–B-type natriuretic peptide, hs-cTnT: High-sensitivity cardiac troponin T, MACE: Major Adverse Cardiovascular Events.

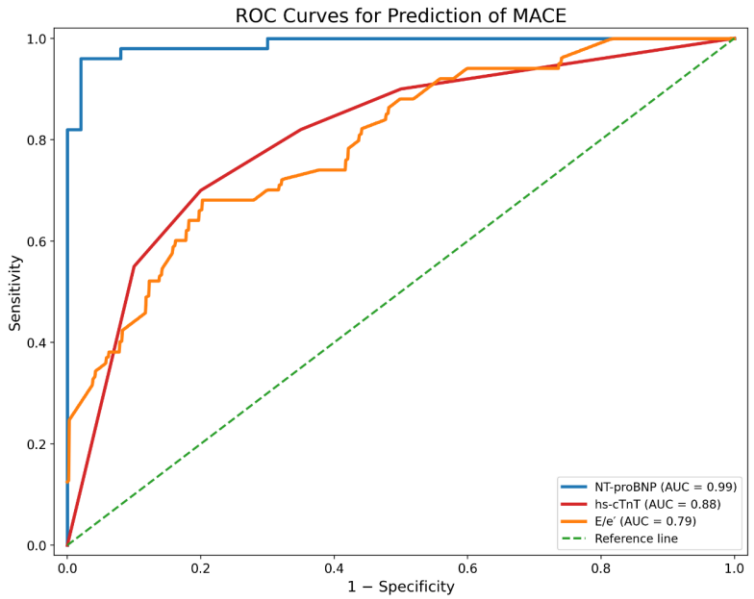

Figure (1): ROC Curves of NT-proBNP, hs-cTnT and E/e' as risk factors associated with MACE in Multiple Myeloma.

At a threshold value >501 pg/mL, NT-proBNP demonstrated exceptional diagnostic performance for association with MACE, with an AUC of 0.99, sensitivity of 96%, and specificity of 98%. It is important to use caution when interpreting the very high AUC of NT-proBNP. Acute or chronic heart failure, as well as renal function, affect NT-proBNP. It is also possible that the apparent diagnostic performance was overstated due to the balanced case-control sample and the cutoff being derived from the same cohort. Therefore, baseline measures taken before MACE incidence must be used for prospective validation (Table 11, Figure 1).

In terms of diagnosing MACE, hs-cTnT performed well, with an AUC of 0.88. With a threshold value greater than 28 ng/L, hs-cTnT demonstrated a sensitivity of 82% and specificity of 80%. Statistical significance of the connection indicates that hs-cTnT successfully distinguished study participants with and without MACE. (Figure 1 and Table 11).

When the cutoff value was more than 13.1, the E/e' ratio demonstrated acceptable to good discrimination with an area under the curve (AUC) of 0.79, sensitivity of 68%, and specificity of 80%. The accuracy was lower than NT-proBNP, even though it was statistically significant ($p < 0.001$) (Table 11, Figure 1).

DISCUSSION

In this study, patients in the MACE group had a much higher mean age (63.8 ± 5.6 years) compared to the non-MACE group (58.6 ± 6.5 years), with a p-value less than 0.001. When comparing the MACE and non-MACE groups, we did not find any statistically significant differences in terms of smoking status, MM status (newly diagnosed vs on treatment), illness duration, or R-ISS staging (all $p > 0.05$).

Consistent with a previous retrospective study of 162 MM patients conducted by 6. Plummer et al. [6], our finding supports the hypothesis. In order to evaluate the efficacy of an external risk-score-based categorization, the study's authors aimed to identify MACE risk indicators in MM patients. Age at diagnosis was determined to be an independent risk factor for MACE (OR = 1.059 per year) using multivariable logistic regression, alongside cigarette smoking, anthracycline exposure, and ISS stage III.

Cardiovascular risk factors and comorbidities were not significantly different in individuals with and without MACE, according to Fontes et al. [7]. There was no significant difference between the two groups with respect to age, sex, cardiovascular risk factors, or cardiovascular comorbidities in their prospective study of 126 high-risk patients who were recently diagnosed with MM.

According to Plummer et al. [6], patients in the non-MACE group did not have as many cardiovascular comorbidities as those in the MACE group. As a surrogate for cardiovascular risk, cigarette smoking was shown to be an independent predictor of major adverse cardiac events (MACE) in their multivariable model (OR = 3.652, 95% CI: 1.392-9.578, $p = 0.008$).

Our results show that patients with MACE are more likely to have palpitations, dyspnoea, and chest discomfort. In terms of urea, serum creatinine, calcium, and lactate dehydrogenase levels, our study found statistically significant differences between the MACE and non-MACE groups.

Consistent with these results, Plummer et al. [6] discovered that the MACE group had a higher creatinine and a poorer estimated glomerular filtration rate (eGFR) compared to the non-MACE group. Furthermore, NT-proBNP levels were shown to be significantly inversely correlated with renal function (glomerular filtration rate) ($r = -0.43$, $p < 0.001$), according to Fontes et al. [7].

We found that cardiac biomarkers (hs-cTnT and NT-proBNP) were significantly greater in individuals with MACE compared to those without MACE.

Fontes et al. [7] also discovered that patients with cardiac dysfunction (heart failure, LVEF decline, and/or diastolic dysfunction) tended to have higher baseline NT-proBNP levels, which is in line with our findings. However, they asserted that baseline NT-proBNP levels did not predict the development of CVAE.

We also found the same thing as Finke et al. [8], who evaluated the predictive value of high-sensitivity cardiac troponin T (hs-cTnT) in cancer patients. Their single-center cohort study demonstrated that hs-cTnT plasma concentration was a better predictor of patient outcomes than NT-proBNP or functional cardiac measurements, with a greater concentration of hs-cTnT being associated with a higher all-cause mortality (ACM). They found that hs-cTnT was a useful risk categorisation tool for cardio-oncology patients, although it missed very few patients whose LV function had declined, and that death rates were already greater than 7 ng/L.

Not only that, but Samuel et al. [9] shown that increased troponin levels independently predicted death in solid tumours. There was a clear upward increase in mortality risk across all troponin groups.

Our results are at odds with those of Fontes et al. [7], who discovered that NT-proBNP did not predict the incidence of CVAE. About 76% of their high-risk MM patients had higher NT-proBNP levels (> 125 pg/mL) at baseline, with a median of 229 pg/mL and an interquartile range (IQR) of 129-504 pg/mL. Thus, higher NT-proBNP is probably not a good predictor of cardiovascular risk, yet it is quite common in this group.

The left ventricular dimensions (LVEDD 53.2 ± 5.1 versus 49.8 ± 4.6 mm, $p < 0.001$), interventricular septal thickness (IVS 11.5 ± 1.8 versus 10.2 ± 1.5 mm, $p < 0.001$), posterior wall thickness (PW 11.3 ± 1.7 versus 10.1 ± 1.4 mm, $p < 0.001$), and left atrial diameter (42.1 ± 5.4 versus 37.0 ± 4.8 mm, $p < 0.001$) were significantly more impaired in the MACE group compared to the non-MACE group. The MACE group showed a substantial decrease in left ventricular systolic function as seen by a lower LVEF (49.2 ± 6.8 vs 57.1 ± 5.9%, $p < 0.001$).

This result is consistent with that of Bae et al. [10], who found that MACE is associated with advancing age, decreased left ventricular ejection fraction (LVEF), increased left atrial diameter, increased E/E' ratio, and increased frequency of increasing severity diastolic dysfunction.

In contrast to our findings, Plummer et al. [6] discovered that whereas patients with MACE had a higher left ventricular mass index (LVMI) ($p < 0.05$), there was no significant difference in the LVEF between the MACE and non-MACE groups. Patients with MACE had significantly impaired diastolic function, as evidenced by lower E wave velocity (0.68 ± 0.18 versus 0.85 ± 0.20 m/s, $p < 0.001$), greater A wave velocity (0.82 ± 0.22 vs 0.75 ± 0.18 m/s, $p = 0.04$), lower E/A ratio (0.83 ± 0.25 versus 1.13 ± 0.28, $p < 0.001$), longer DT (245 ± 45 versus 210 ± 38 ms, $p < 0.001$), and IVRT (isovolumetric relaxation time) (110 ± 18 versus 92 ± 15 ms, $p < 0.001$). Furthermore, there was a statistically significant difference ($p < 0.001$) in the distribution of diastolic dysfunction grades across the groups, with a greater incidence of advanced diastolic dysfunction (Grades II and III) among patients in the MACE group.

This finding is consistent with that of Kozelj et al. [11], who found that diastolic cardiac failure patients had significantly lower values for metrics such E wave velocity, E/A ratio, lateral e' velocity, and septal e' velocity.

Makris et al. [12] found that in individuals with cardiac dysfunction, decreasing segmental LV longitudinal strain and worsening left atrial function and structure occurred before declines in LVEF, which is in line with our results. These changes were in line with the hypothesis that diastolic mechanics were compromised in patients exposed to carfilzomib.

Consistent with what is known about diastolic dysfunction in heart failure, our investigation found an E/e' ratio association value of 0.79 with MACE (cutoff > 13.1, sensitivity 68%, specificity 80%). In a review of the pros and cons of E/e' in HFpEF, Nauta et al. [13] found that, in most studies, it was associated with outcome (mortality and/or composite endpoint), and the cumulative hazard ratio for each unit increase was 1.05 (1.03-1.06). They found that E/e' was the most accurate echocardiographic index for assessing left ventricular filling pressure, despite the poor relationships between filling pressures and findings.

In our study, heart failure was the most prevalent incidence among patients with MACE (40%), followed by acute coronary syndrome (26%), and arrhythmia (20%). The incidence of cardiogenic shock (8% of cases) and sudden cardiac death (6% of cases) was lower.

Iqbal et al. [14] also discovered that 68% of MM patients had cardiac comorbidities, significantly increasing the risk of mortality; our findings are consistent with theirs. Congestive heart failure (21%), atrial fibrillation (18%), and ventricular arrhythmias (3%), among others, were associated with a higher risk of death (OR 1.5, $p < 0.001$ for CHF, OR 1.1, $p = 0.001$ for atrial fibrillation, and OR 3.2, $p < 0.001$ for ventricular arrhythmias).

However, a different pattern of cardiovascular adverse events was seen in the group of high-risk newly diagnosed MM patients studied by Fontes et al. [7]. The most common adverse events noted in cardiovascular systems were heart failure in 5% of patients with cardiac dysfunction, diastolic dysfunction in 2%, and a decrease in left ventricular ejection fraction (LVEF) in 2%. Other common CVAEs included thromboembolic events in 7% of patients, arterial hypertension in 19% of patients, and CTCAE grade ≥ 3 in 14%.

The correlation between cardiac biomarkers and echocardiographic parameters was statistically significant. The levels of hs-cTnT and NT-proBNP were significantly inversely related to LVEF. However, the E/e' ratio, interventricular septal thickness, left atrial diameter, and posterior wall thickness were all positively correlated with both biomarkers.

Consistent with this finding is the work of Hinrichs et al. [15], who assessed the diagnostic utility of cTnI and NT-proBNP in 485 cancer patients referred to their cardio-oncology clinic for the purpose of monitoring cardiomyopathy produced by cancer treatment. Increased NT-proBNP was associated with abnormal global longitudinal strain (GLS) and reduced LVEF. The results of the Spearman rank correlation analysis showed a significant relationship between a decline in LVEF and improvements in cTnI ($p < 0.001$, $r = 0.234$) and raised NT-proBNP ($p < 0.001$, $r = 0.406$). In addition, correlations between NT-proBNP and troponin alterations and LVEF changes during follow-up studies were seen in 116 individuals with serial measurements.

We also discovered a high link between a drop in LVEF and hs-cTnT levels in our sample of cancer patients, which is consistent with the findings of Finke et al. [8]. At the established hs-cTnT threshold (≥ 7 ng/L), they found that ROC curves had a rather good sensitivity rate for predicting the deterioration of left ventricular function. Although hs-cTnT was superior on its own for identifying patients at high risk, they still found a robust association between echocardiography findings and hs-cTnT.

Fontes et al. [7] contradicted this, finding no correlation between pre-treatment biomarker levels and post-treatment echocardiographic changes. Early changes in hs-cTnT from baseline were only associated with a tendency toward an

enhanced risk for CVAE occurrence (hazard ratio 1.11, p = 0.053), and neither baseline levels nor variations in NT-proBNP levels during early induction cycles were predictive of the occurrence of CVAE.

The following factors were found to be independent risk factors associated with MACE: age (OR = 1.08, 95% CI: 1.02-1.15, p = 0.01), creatinine (OR = 1.85, 95% CI: 1.20-2.90, p = 0.005), hs-cTnT (OR = 1.04, 95% CI: 1.02-1.07, p < 0.001), NT-proBNP (OR = 1.002, 95% CI: 1.001-1.003, p < 0.001), LVEF (OR = 0.90, 95% CI: 0.85-0.95, p < 0.001), and E/e' ratio (OR = 1.18, 95% CI: 1.08-1.30, p < 0.001). There was a direct correlation between greater LVEF and reduced odds of MACE, but a stronger correlation between higher hs-cTnT and NT-proBNP levels and an increased risk of adverse cardiovascular events (ACEs).

The results are in line with the multivariate analysis conducted by Plummer et al. [6]. In their study of 162 newly diagnosed MM patients, they found that factors such as age at diagnosis (OR = 1.059 per year), Anthracycline exposure (OR = 5.850), ISS stage III (OR = 2.593), and cigarette smoking (OR = 3.652) were independent risk factors for major adverse cardiac events (MACE). Consistent with our findings is the prospective study conducted by Finke et al. [8]. This study demonstrated that hs-cTnT was a distinct predictor of all-cause mortality in cancer patients, even after accounting for established confounding variables such as GFR and cardiac risk factors (gender, age, hypertension, diabetes, and obesity). Logistic regression study revealed solid relationships between increased hs-cTnT levels and cardiac parameters, including reduced LVEF and increased NT-proBNP. It seems that hs-cTnT may be the most dependable biomarker for risk stratification, since neither lower GLS nor greater NT-proBNP levels could predict all-cause mortality in their group on their own.

We found that baseline NT-proBNP and hs-cTnT were not independent predictors of CVAE in the Cox regression analysis by Fontes et al. [7]. A tendency toward an elevated risk for CVAE incidence was associated with an early shift from baseline (Δ hs-cTnT) rather than absolute hs-cTnT levels at baseline, even after the researchers controlled for possible confounders (HR 1.11, p = 0.053).

Our investigation found that NT-proBNP had excellent diagnostic performance for association with MACE, with an AUC of 0.99, sensitivity of 96%, and specificity of 98% at a threshold value > 501 pg/mL. With an area under the curve (AUC) of 0.79, sensitivity of 68%, and specificity of 80% at a threshold value > 13.1, the E/e' ratio showed excellent diagnostic performance. At a threshold value > 28 ng/L, hs-cTnT again showed wonderful diagnostic performance, with an AUC of 0.88, sensitivity of 82%, and specificity of 80%.

The results are in line with those of Pan et al. [16], who evaluated the diagnosis accuracy of NT-proBNP for chronic heart failure in 436 outpatients suspected of having the condition. They discovered an area under the curve (AUC) of 0.926 at a threshold value of 257.4 pg/mL (specificity 74.2%, sensitivity 93.0%). Incorporating age, eGFR, body mass index (BMI), atrial fibrillation, and sex into a diagnostic model resulted in an AUC of 0.955 (sensitivity 94.2%, specificity 86.7%).

Finke et al. [8] found that hs-cTnT was better at predicting adverse outcomes in cancer patients than NT-proBNP and functional cardiac measures. Our study's good diagnostic performance of hs-cTnT (AUC 0.88) is in line with these findings. Over 7 ng/L, they found that mortality rates began to rise. By using hs-cTnT to categorise risk, only few individuals with a decrease in LV function were overlooked.

Although NT-proBNP levels were often elevated at baseline (76% of patients had levels > 125 pg/mL), they were not a predictor of the occurrence of CVAE, according to Fontes et al. [7], contradicting our findings. Despite the low predictive value, they did find that patients whose baseline hs-cTnT levels were 2.9 ng/L or above were much more likely to get CVAE while undergoing treatment (p = 0.0023).

This study has some limitations. Because it was a single-center study with a small sample size, the findings may not be generalizable. The assessment of changes in heart function over time was further hindered by the absence of repeated biomarker testing and longitudinal echocardiographic follow-up. Furthermore, there was a lack of evaluation of contemporary echocardiographic techniques such as global longitudinal strain (GLS) for the early detection of cardiac dysfunction, and different treatment plans made it difficult to conduct therapy-specific cardiovascular risk analyses. Additionally, the exclusion of individuals with hypertension and diabetes mellitus may have chosen a cardiovascular group with a lower risk, limiting the results' applicability to the larger multiple myeloma community.

CONCLUSION

In MM patients with MACE, cardiac structural and functional abnormalities were more noticeable. Independently related with MACE were advanced age, renal impairment, elevated hs-cTnT and NT-proBNP levels, reduced left ventricular ejection fraction (LVEF), and elevated E/e' ratio. While NT-proBNP showed strong discriminating performance in this population, predictive interpretation is hindered by the balanced group allocation and the unknown temporal link between biomarker testing and MACE. These findings highlight the significance of routinely evaluating the cardiovascular risk of MM patients using cardiac biomarkers and comprehensive echocardiographic examination. Improved clinical outcomes

and faster initiation of cardioprotective treatments may result from earlier identification of high-risk people. To confirm these results, prospective multicenter trials are needed that include baseline and serial evaluations.

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