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ARTICLE

Blood pressure variability as predictor of cancer therapy-related cardiovascular toxicity in patients with Multiple Myeloma

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Abstract

Blood pressure (BP) variability (BPV) is an independent predictor of cardiovascular (CV) events. The role of BPV in defining risk of cancer therapy-related cardiovascular toxicity (CTR-CVT) is currently unknown. The aims of this study were: (i) to evaluate BPV in a population of patients with Multiple Myeloma, undergoing proteasome inhibitors therapy; (ii) to assess the predictive value of BPV for CTR-CVT; (iii) to analyze clusters of subjects based on BPV. One hundred twenty-four patients underwent a baseline evaluation, including Ambulatory Blood Pressure Monitoring (ABPM), PWV, and Echocardiography. BPV was assessed through ABPM-based standard deviation (SD), weighted standard deviation (wSD), coefficient of variation (CoV), average real variability (ARV), and variability independent of the mean (VIM). Individuals who developed CTR-CVT had a higher baseline BPV. Furthermore, night-time BPV was associated with CTR-CVT, independently of age, smoking, BP, diabetes, dyslipidemia, and kidney function (night-time systolic CoV: adjusted OR 1.09 [1.01–1.21]; night-time systolic VIM: adjusted OR 1.18 [1.01–1.39]). Cut-offs for these BPV parameters were identified as predictors of CTR-CVT occurrence: 10.5 for night-time systolic CoV; 7.8 and 6.4 for systolic and diastolic night-time VIM. Clustering analysis identified subgroups of subjects characterized by the highest BPV, who had a greater prevalence of events, but no differences in other CV risk determinants. Short-term BPV is an independent predictor of CTR-CVT. BPV may enhance the precision of risk stratification in cancer patients, enabling identification of individuals at higher risk who would not be recognized, if traditional prognostic indicators were the sole applied criteria.

Keywords BPV · CadioOncology · Cardiovascular toxicity · Risk prediction

Introduction

Several antineoplastic therapies have been associated with cardiovascular (CV) side effects and the development of CV disease [1]. This has implications on cancer-related mortality, directly in terms of CV morbidity and in preventing and/or delaying anticancer therapy course. Cancer therapy-related cardiovascular toxicity (CTR-CVT) has been largely documented for proteasome inhibitors, used in the treatment of Multiple Myeloma [2, 3].

For these reasons, current European guidelines recommend CV baseline evaluation and regular follow-up to monitor for the occurrence of CTR-CVT, with the aim of improving both cancer and CV outcomes [4].

CV risk assessment is based on a multimodal approach including clinical examination, cardiac biomarkers (i.e., Troponin and BNP), electrocardiography, advanced echocardiography (with 3D and global longitudinal strain (GLS)

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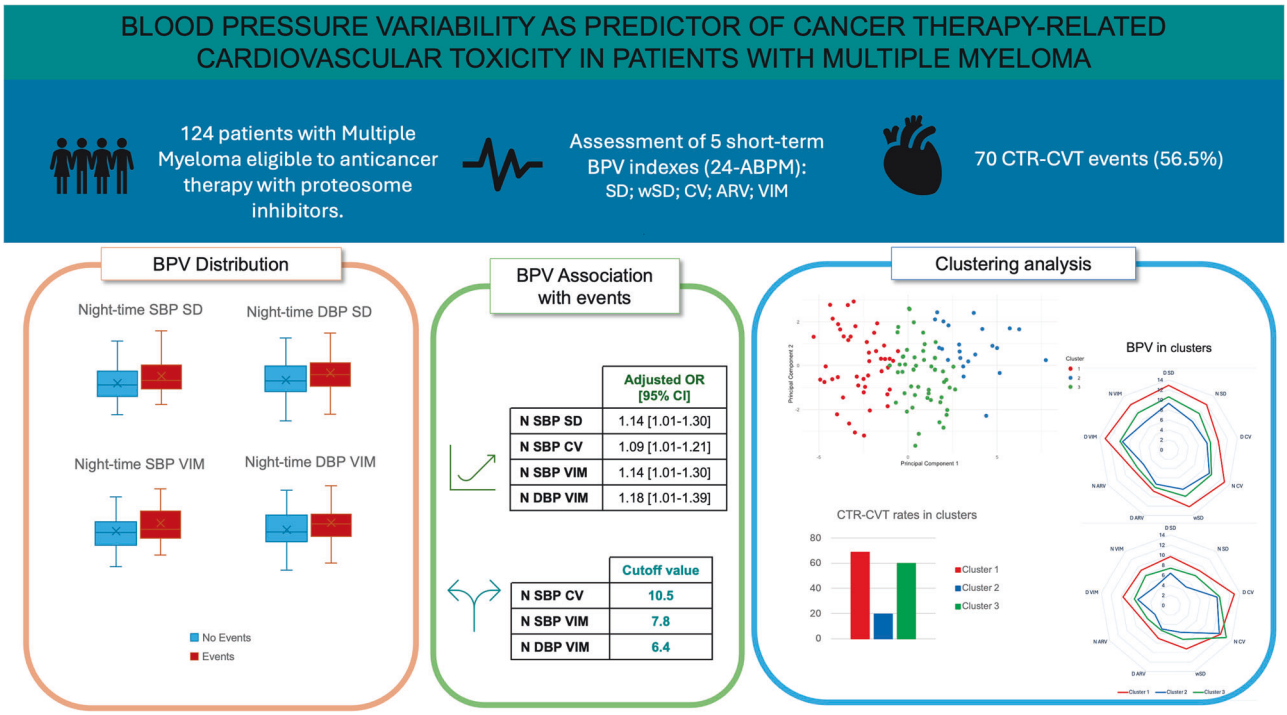
Graphical Abstract

On the left panel in the figure, the distribution of blood pressure variability (BPV) in the population according to cancer therapy-related cardiovascular toxicity occurrence; in the central panel, association of blood pressure variability with events and cutoffs values; in the right panel, clustering analysis results based on BPV levels. Histogram and radar plot represent events and BPV indexes distribution in the three clusters, respectively. ARV, average real variability; BPV, Blood Pressure Variability; CTR-CVT, cancer therapy-related cardiovascular toxicity; CoV, coefficient of variation; DBP, Diastolic blood pressure; SBP, Systolic blood pressure; SD, standard deviation; VIM, variability independent of the mean; wSD, weighted standard deviation



evaluation), and arterial stiffness. Left ventricular hypertrophy, GLS, and pulse wave velocity (PWV) have demonstrated a predictive value for CTR-CVT development in previous studies [5].

Nevertheless, the availability of these tests may vary among different cardio-oncological centers, influencing the ability to assess the CV risk prior to cancer therapy initiation.

Blood pressure (BP) variability (BPV) describes BP variation over time and may be considered a non-invasive technique for assessing BP regulation homeostasis, reflecting the complex interaction between BP regulation mechanisms [6]. BPV has been demonstrated to be an independent predictor of CV events and overall mortality in hypertensive individuals [7]. Furthermore, it has been shown to be a predictor of progression to hypertension in individuals with normal-high BP [8].

However, the potential role of BPV in defining CV risk of patients undergoing anticancer therapy with a potential CTR-CVT is currently unknown.

The aims of this study were: (i) to evaluate short-term BPV in a population of patients with Multiple Myeloma, undergoing therapy with proteasome inhibitors; (ii) to assess the predictive value of BPV indexes for CTR-CVT development; (iii) to analyze clusters of subjects based on BPV levels.

Methods

Study population

Patients with newly diagnosed, or relapsed-refractory, Multiple Myeloma, who were eligible for cancer therapy with proteasome inhibitors, were consecutively enrolled in the period between January 2015 and July 2023. Subjects underwent a multiparametric CV evaluation in the ESH Excellence Hypertension Center of A.O.U. Città della Salute e della Scienza di Torino, prior to initiation of cancer treatment and periodically on a 6-month basis, or earlier if CTR-CVT was suspected or occurred.

All the patients signed a written informed consent before inclusion in the study.

The presence of signs of cardiac amyloidosis at baseline assessment was an exclusion criterion for enrollment in the study.

The study was approved by the local Ethical Committee (protocol number 0038655) and was performed according to the principles of the Declaration of Helsinki and its subsequent modifications [9].

Multiparametric CV assessment

Baseline evaluation included past medical history collection, clinical examination, office BP measurement, 12-lead electrocardiography, 24-h Ambulatory Blood pressure Monitoring (ABPM), PWV, and transthoracic Echocardiography, according to current European guidelines [4].

Office BP measurements were performed through a validated oscillometric upper-arm cuff device Omron M10-IT (Omron, Hoofddorp, The Netherlands), with patients in resting condition and sitting position, using the mean of three consecutive measurements, according to current European recommendations [10].

Arterial stiffness was evaluated through carotid-femoral PWV measurement, with a SphygmoCor System (Atcor Medical, Sydney, Australia), averaging three consecutive recordings.

Transthoracic Echocardiography was performed with iE33, Affiniti 50, or EPIQ7C ultrasound systems (Philips Medical System, Andover, MA, USA), in accordance with current European standards, including speckle-tracking GLS assessment [11, 12]. Left ventricular (LV) hypertrophy was defined in the presence of indexed LV mass ≥115 g/m^2 and ≥95 g/m^2 in men and women, respectively [12]. Speckle-tracking analysis was performed with the software QLAB Cardiac Analysis (Philips, Andover, MA, USA), considering as normal a GLS value ≤ −20% [4].

Short-term BPV

ABPMs were performed through a validated oscillometric upper-arm cuff Spacelab model 90207 (Issaquah, Washington, USA), recording BP measurements every 15 min during day and night-time. Minimum quality levels of the ABPM for inclusion in the study were: recording of at least 64 measurements, maximum time interval without measurements of 2 h, minimum overall ABPM duration of 20 h, and a sleep quality rated as at least "sufficient", defined as a score of 6 or higher on a 10-point scale.

The daytime and night-time periods were defined based on the sleeping and awakening times reported by each individual. Overall short-term BPV was assessed by standard deviation (SD), weighted standard deviation (wSD), coefficient of variation (CoV), average real variability (ARV), and variability independent of the mean (VIM), evaluated for both systolic and diastolic BP measurements during ABPM [13–16]. Furthermore, BPV indexes were evaluated on 24 h, daytime and night-time domains, with the exception of wSD for its definition.

CoV was calculated as SD normalized for the corresponding mean BP values, in order to reduce the influence of the mean on BPV estimation [13]. ARV was defined as the mean of absolute differences between consecutive measurements [14]. VIM was derived from SD, correcting for coefficients derived from a nonlinear regression analysis, plotting SD against the mean, in order to remove the influence of mean BP values on SD [15]. wSD was calculated as the mean of day and night SD corrected for the duration of these two periods in hours, to remove the contribution of night-to-day BP variation to the overall BPV estimation [16]. Extended formulas for the calculation of BPV indexes are reported in the Online Supplement material—Section 1.1.

CTR-CVT

CTR-CVT included CV and BP adverse events. CV events were defined as: acute coronary syndromes, heart failure, arrhythmias (including atrial fibrillation or flutter, atrial bigeminy, ventricular tachycardia, ventricular bigeminy/trigeminy, and grade ≥2 of atrioventricular block), typical chest pain, syncope, left ventricular dysfunction, sudden cardiac death. In particular, left ventricular dysfunction was defined as: (1) a new LV ejection fraction (LVEF) reduction to <40%; (2) a new LVEF reduction ≥10 percentage points to an LVEF of 40–49%; (3) a new LVEF reduction <10 percentage points to an LVEF < 40–49% and either new relative decline in GLS by 15% from baseline or new rise in cardiac biomarkers; (4) an LVEF ≥ 50% and new relative decline in GLS by 15% from baseline and/or a new rise in cardiac biomarkers [4].

BP events were defined by new diagnosis of arterial hypertension, worsening of known arterial hypertension, uncontrolled hypertension, and/or symptomatic uncontrolled BP (BP > 180/110 mmHg) with or without target acute organ damage. Specifically, uncontrolled hypertension was defined by BP levels ≥130/80 mmHg in hypertensive subjects on treatment, according to the European guidelines, which recommend this threshold for high-risk patients [17].

Details on CRT-CVT definition are provided in Online Supplementary—Section 1.2.

Statistical analysis

Shapiro–Wilk test was used to assess the distribution of continuous variables. Continuous variables are expressed as the mean ± SD or median and interquartile range, according to their distribution. Categorical variables are reported as absolute number and percentage.

Differences between two independent groups were evaluated using Student's *t*-test for continuous variables with normal distribution and the Mann–Whitney or Wilcoxon test for continuous variables with non-normal distribution; multiple comparisons (between more than two groups) were evaluated with the one-way ANOVA applying Bonferroni's correction. Categorical variables were compared using the chi-square test or Fisher's exact test according to the sampling number of analyzed groups. Differences in categorical variables among three or more groups were assessed using standardized adjusted residuals, considering as significant a residual of at least ±1.96.

The prognostic value of BPV was evaluated through logistic regression analysis, considering events as dependent variables and BPV indexes as independent variables. Associations were adjusted for age, sex, mean BP values, eGFR, diabetes and smoking habit by multivariate logistic regression.

Based on logistic regression, an ROC curve was calculated for each type of BPV, from which the most accurate prognostic cut-off value was defined by the highest Youden index.

Clustering K-means analysis was used to identify subgroups of subjects, based on BPV indexes. The *k* number of clusters in the population was defined through Silhouette and Elbow analyses. Prior to clustering analysis, BPV indexes were standardized and scaled; outliers were removed. Characteristics of different clusters were compared through ANOVA and Chi-square tests.

Statistical significance was set at a two-sided p value < 0.05 for all analyses. Sample size was based on a statistical power of 80%, a significance level of 0.05, a medium effect size (Cohen's $h = 0.3$), and the observed number of adverse events.

R Software v4.3.1 for Mac OS (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

Results

Clinical and hemodynamical characteristics

The study included 124 patients (12 patients with newly diagnosed and 112 patients with relapsed-refractory Multiple Myeloma) with 50% of women and a mean age of 63.3 ± 8.9 years. Nineteen (16.7%) patients had an at least stage III chronic kidney disease and 36 (29%) patients had obesity. Sixty-five (52.8%) individuals had a known history of arterial hypertension at baseline evaluation. Twelve (9.7%) subjects have been previously treated with an anthracycline agent. Mean follow-up time was 4.4 ± 1.6 years.

Mean office BP was 130.8 ± 17.9/76.9 ± 11.7 mmHg. Based on office BP measurement, 45 subjects with known hypertension had uncontrolled BP at baseline evaluation and 19 subjects were newly found hypertensive. Clinical and hemodynamic characteristics of the study population are summarized in Tables 1 and 2, respectively. Short-term BPV indexes, assessed in the 24-h, daytime, and night-time domains, are reported in Table 3. Patients with a known history of arterial hypertension had a higher BPV (Table 1s).

CTR-CVT

During follow-up, CTR-CVT occurred in 70 (56.5%) patients, with 46 subjects involved in BP events, 8 subjects in CV events, and 16 subjects involved both in BP and CV events (Table 4). Overall, 102 BP events and 37 CV events occurred. Median time to first CTR-CVT event was 3.6 [0.9–8.1] months for BP events and 3.5 [1.0–9.8] months for CV events.

When comparing patients who developed CTR-CVT to the rest of population, individuals with events showed higher office systolic BP and greater indexed left ventricular mass (LMVi) at baseline evaluation. On the contrary, no difference was observed in smoking habit, renal function, diabetes prevalence, and ABPM parameters (Tables 1 and 2).

Table 1 Clinical characteristics at baseline assessment of overall population and subgroups divided by development of cancer therapy-related cardiovascular toxicity

		Overall $n = 124$	CTR-CVT+ $n = 70$	CTR-CVT− $n = 54$	p value
Age [years]		63.3 ± 8.9	64 ± 9.5	62.4 ± 8.2	0.301
Female sex [*n*, (%)]		62 (50%)	31 (44.3%)	31 (57.4%)	0.147
BMI [kg/m^2]		27.7 ± 4.7	27.7 ± 4.8	27.6 ± 4.6	0.977
eGFR [mL/min/1.73 m^2]		80.1 ± 20.3	79.4 ± 18.9	80.8 ± 22.1	0.720
Smoking [*n*, (%)]	Non smoker	58 (46.8%)	30 (42.9%)	28 (51.9%)	0.320
	Former or current smokers	66 (53.2%)	40 (57.1%)	26 (48.1%)	
Diabetes [*n*, (%)]		11 (8.9%)	5 (7.1%)	6 (11.1%)	0.441
CHD [*n*, (%)]		3 (2.4%)	2 (2.9%)	1 (1.9%)	0.718
Previous cerebrovascular events [*n*, (%)]		4 (3.2%)	2 (2.9%)	2 (3.7%)	0.791

BMI body mass index, *CHD* coronary heart disease, *CTR-CVT* cancer therapy-related cardiovascular toxicity, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *SBP* systolic blood pressure

Table 2 Baseline assessment in overall population and subgroups divided by development of cancer therapy-related cardiovascular toxicity during follow-up

	Overall $n = 124$	CTR-CVT+ $n = 70$	CTR-CVT− $n = 54$	p value
Office SBP [mmHg]	130.8 ± 17.9	134.3 ± 17.3	126.3 ± 17.8	**0.013**
Office DBP [mmHg]	76.9 ± 11.7	78.1 ± 11.5	75.3 ± 11.8	0.195
24 h SBP [mmHg]	121.0 ± 12.2	122.4 ± 12.3	119.2 ± 11.9	0.146
24 h DBP [mmHg]	70.7 ± 9.0	71.2 ± 10.0	70.0 ± 7.6	0.451
Daytime SBP [mmHg]	125.7 ± 13.1	127.4 ± 12.7	123.5 ± 13.3	0.101
Daytime DBP [mmHg]	74.6 ± 9.7	75.5 ± 10.6	73.5 ± 8.5	0.231
Night-time SBP [mmHg]	111.9 ± 14.0	112.4 ± 14.4	111.3 ± 13.5	0.707
Night-time DBP [mmHg]	64.0 ± 10.2	64.2 ± 11.4	63.6 ± 8.5	0.736
LVMi [g/m^2]	90.7 ± 23.4	95.2 ± 24.8	85.0 ± 20.7	**0.014**
LVEF [%]	63.0 ± 7.2	62.6 ± 8.3	63.5 ± 5.7	0.477
GLS [%]	−21.5 ± 2.6	−21.4 ± 2.6	−21.6 ± 2.6	0.672
PWV [m/s]	8.3 ± 1.8	8.6 ± 1.8	7.9 ± 1.8	0.061

The bold is expressing when p value is < 0.05 (and so when statistically significant)

CTR-CVT cancer therapy-related cardiovascular toxicity, *DBP* Diastolic blood pressure, *GLS* global longitudinal strain, *LVEF* left ventricular ejection fraction, *LVMI* indexed left ventricular mass, *SBP* Systolic blood pressure, *PWV* pulse wave velocity

Table 3 Short-term blood pressure variability in overall population and subgroups divided by development of cancer therapy-related cardiovascular toxicity during follow-up

	Overall $n = 124$	CTR-CVT+ $n = 70$	CTR-CVT− $n = 54$	p value
24 h SBP SD [mmHg]	13.5 ± 4.1	13.8 ± 3.5	13.1 ± 4.8	0.382
24 h DBP SD [mmHg]	10.1 ± 2.8	10.4 ± 2.3	9.7 ± 3.4	0.200
Daytime SBP SD [mmHg]	11.6 ± 4	11.8 ± 2.9	11.2 ± 5.0	0.390
Daytime DBP SD [mmHg]	8.3 ± 2.6	8.5 ± 1.9	8.0 ± 3.2	0.334
Night-time SBP SD [mmHg]	10.2 ± 3.4	10.8 ± 3.5	9.5 ± 3.1	**0.033**
Night-time DBP SD [mmHg]	7.8 ± 2.5	8.2 ± 2.4	7.3 ± 2.5	**0.050**
24 h SBP CoV	11.2 ± 3.4	11.4 ± 3.0	11.0 ± 3.9	0.579
24 h DBP CoV	14.4 ± 4.1	14.8 ± 3.7	13.8 ± 4.6	0.202
Daytime SBP CoV	9.2 ± 3.3	9.3 ± 2.4	9.1 ± 4.2	0.682
Daytime DBP CoV	11.2 ± 3.6	11.5 ± 3.1	10.9 ± 4.2	0.414
Night-time SBP CoV	12.5 ± 4.4	13.1 ± 4.5	11.7 ± 4.2	0.068
Night-time DBP CoV	12.3 ± 4.7	12.0 ± 4.0	12.7 ± 5.6	0.439
SBP wSD [mmHg]	11.1 ± 3.2	11.5 ± 2.6	10.6 ± 3.8	0.167
DBP wSD [mmHg]	8.1 ± 2.1	8.4 ± 1.6	7.8 ± 2.5	0.141
24 h SBP ARV [mmHg]	7.8 ± 1.4	7.9 ± 1.4	7.7 ± 1.4	0.489
24 h DBP ARV [mmHg]	5.7 ± 1.2	5.7 ± 1.1	5.6 ± 1.3	0.737
Daytime SBP ARV [mmHg]	8.2 ± 1.6	8.2 ± 1.6	8.1 ± 1.7	0.773
Daytime DBP ARV [mmHg]	5.9 ± 1.4	5.9 ± 1.2	5.9 ± 1.5	0.867
Night-time SBP ARV [mmHg]	7.3 ± 2.0	7.5 ± 1.8	7.1 ± 2.2	0.360
Night-time DBP ARV [mmHg]	5.4 ± 1.7	5.5 ± 1.6	5.2 ± 1.8	0.387
24 h SBP VIM	13.6 ± 4.0	13.8 ± 3.5	13.3 ± 4.7	0.479
24 h DBP VIM	10.1 ± 2.8	10.4 ± 2.3	9.7 ± 3.3	0.200
Daytime SBP VIM	11.6 ± 4.0	11.8 ± 2.9	11.3 ± 5.1	0.556
Daytime DBP VIM	8.3 ± 2.5	8.5 ± 1.9	8.1 ± 3.2	0.370
Night-time SBP VIM	10.3 ± 3.4	10.8 ± 3.5	9.6 ± 3.1	**0.037**
Night-time DBP VIM	7.8 ± 2.5	8.2 ± 2.4	7.3 ± 2.5	**0.050**

The bold is expressing when p value is < 0.05 (and so when statistically significant)

ARV average real variability, *CTR-CVT* cancer therapy-related cardiovascular toxicity, *CoV* coefficient of variation, *DBP* Diastolic blood pressure, *SBP* Systolic blood pressure, *SD* standard deviation, *VIM* variability independent of the mean, *wSD* weighted standard deviation

Table 4 Cancer therapy-related cardiovascular toxicity during follow-up

	Population, $n = 124$
Total CTR-CVTs	70 (56.5%)
Blood pressure CTR-CVTs	62 (50%)
New onset/uncontrolled HTN	51 (41.1%)
HTN prior or after protesome inhibitor infusion	37 (29.8%)
Severe uncontrolled HTN (> 180/100) with symptoms	5 (6%)
HTN Emergency	0 (0%)
Cardiovascular CTR-CVTs	24 (19.4%)
Acute coronary syndrome	6 (4.9%)
Heart failure	10 (8.1%)
Arrhythmia	10 (8.1%)
EF reduction	2 (1.6%)
GLS decline	5 (4%)
Sudden cardiac death	1 (0.8%)
Others	10 (8.1%)

CTR-CVT cancer therapy-related cardiovascular toxicity, *EF* ejection fraction, *GLS* global longitudinal strain, *HTN* hypertension

Association of BPV with CTR-CVT

A higher night-time BPV was observed in subjects who subsequently developed CTR-CVT during follow-up. This evidence was demonstrated both for indexes dependent by mean BP, as SD (systolic night-time SD: 10.8 ± 3.5 Vs. 9.5 ± 3.1 mmHg, $p = 0.033$; diastolic night-time SD: 8.2 ± 2.4 Vs. 7.3 ± 2.5 mmHg, $p = 0.050$), both for indexes independent by mean BP, as VIM (systolic night-time VIM: 10.8 ± 3.5 Vs. 9.6 ± 3.1, $p = 0.037$; diastolic night-time VIM: 8.2 ± 2.4 Vs. 7.3 ± 2.5, $p = 0.050$).

Furthermore, an association between night-time BPV and CTR-CVT was demonstrated, independently by mean BP, age, smoking, and comorbidities as diabetes and renal dysfunction (night-time systolic SD: unadjusted OR 1.13 [95% CI 1.01–1.28], adjusted OR 1.14 [95% CI 1.01–1.30]; night-time systolic CoV: unadjusted OR 1.08 [95% CI 1.01–1.18], adjusted OR 1.09 [95% CI 1.01–1.21]; night-time systolic VIM unadjusted OR 1.13 [95% CI 1.01–1.28], adjusted OR 1.14 [95% CI 1.01–1.30]; night-time diastolic VIM unadjusted OR 1.16 [95% CI 1.01–1.37], adjusted OR 1.18 [95% CI 1.01–1.39]).

A cut-off value of 10.5 was identified for night-time systolic CoV as predictive of CTR-CVT (sensibility 73% and specificity 46%), while cut-off values of 7.8 and 6.4 were identified for systolic and diastolic night-time VIM, respectively (sensibility 86% and 83%; specificity 33% and 37%). A cut-off value of 7 was identified for night-time systolic SD (sensibility 94% and specificity 24%).

Clustering analysis

Clustering analysis identified three different clusters of subjects in the overall sample, based on BPV indexes. Two clusters (Clusters 1 and 3—Fig. 1) were characterized by the highest levels of night-time BPV. Those two subgroups had a higher rate of CTR-CVT, without significant differences in age, sex, renal function, left ventricular mass, and GLS (Table 5). BPV indexes in different clusters are reported in Table 6.

Discussion

BP regulation is the result of the complex interaction among hormonal, neural, cardiac, and vascular factors. The alteration of BP homeostasis has been associated in previous studies with increased CV morbidity and mortality, independently of mean BP values and conventional CV risk factors [7, 18].

In the present study, the prognostic role of BPV was investigated for the first time in cancer patients, considering its relevance in predicting CTR-CVT by itself. The night-time BPV demonstrated an association with CV and BP events, independently from baseline mean BP, age, renal function, and other CV risk factors, such as diabetes and smoking. Namely, a 9–18% increase in relative risk was shown for each one-unit increase in SD in different BPV indexes. This is a very significant finding considering the independence from the known predictive variables previously reported. This point was further confirmed through a cluster analysis, which was able to distinguish groups of subjects with similar hemodynamic and demographic characteristics, differing only in BPV levels, to which corresponded a different probability of adverse events occurrence.

This study is part of the framework of CV risk prediction in cancer patients going through cardiotoxic therapies, given the need to identify higher-risk categories and reduce the risk of developing CTR-CVT [19]. At present, office BP, left ventricular EF, GLS, and PWV are recognized parameters used for assessing CV risk in oncologic patients, with an established prognostic value [4].

Only selected centers have easy access to all potential tests to stratify individuals for CV toxicity (e.g., GLS and PWV). ABPM is a simple, inexpensive, and widely available tool that allows the evaluation of mean BP outside office assessment, together with a more accurate definition of BP profile during daily life and night-time period, hence the possibility of targeting pharmacological therapy at specific times of the day. Furthermore, ABPM allows the assessment of overall short-term BPV.

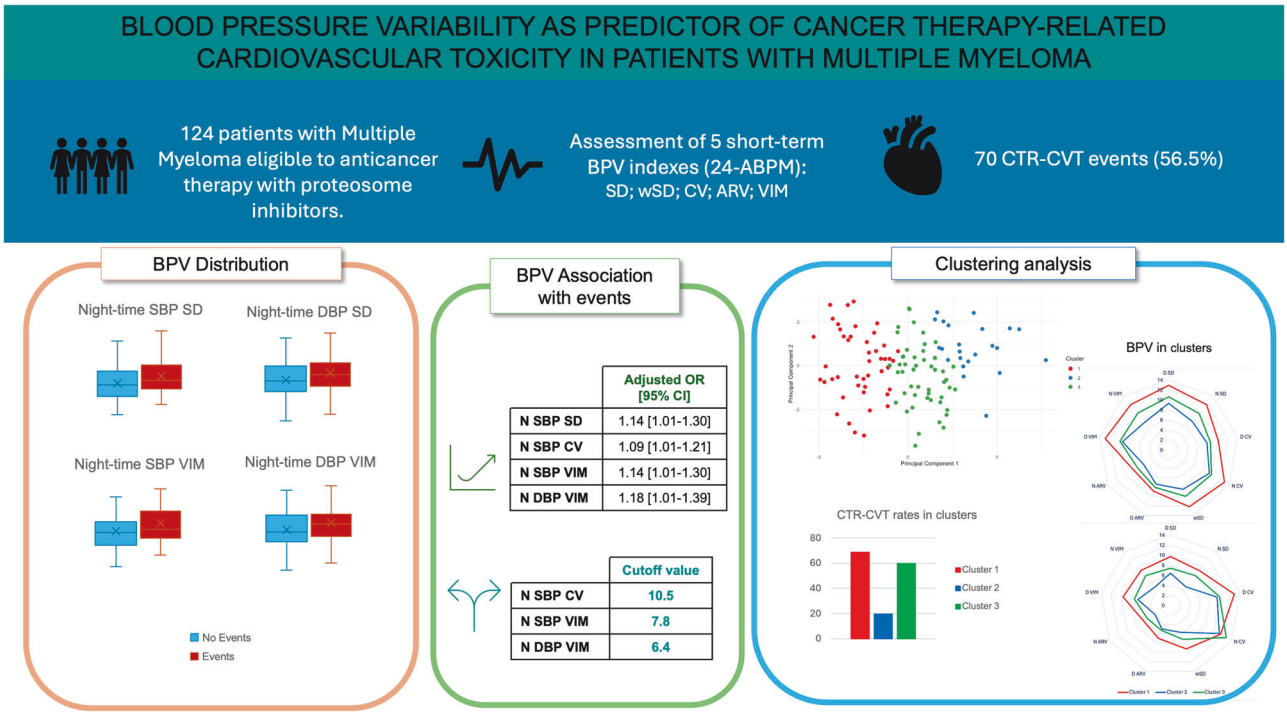


Fig. 1 On the left panel in the figure, the distribution of blood pressure variability (BPV) in the population according to cancer therapy-related cardiovascular toxicity occurrence; in the central panel, association of blood pressure variability with events and cut-offs values; in the right panel, clustering analysis results based on BPV levels. Histogram and radar plot represent events and BPV indexes distribution in the three clusters, respectively. ARV average real variability, BPV Blood Pressure Variability, CTR-CVT cancer therapy-related cardiovascular toxicity, CoV coefficient of variation, DBP Diastolic blood pressure, SBP Systolic blood pressure, SD standard deviation, VIM variability independent of the mean, wSD weighted standard deviation

BPV indexes have proven to be significantly associated with adverse outcomes in our population were night-time systolic SD, night-time systolic CoV, night-time systolic VIM, and night-time diastolic VIM. The association of events with BPV of nocturnal period presumably reflects a higher stability of night-time BP, more closely influenced by BP regulation itself, through the autonomic nervous system, and less by daily life exercise and emotional stressors. In this regard, high night-time BP values and BPV in patients with synucleinopathies and related autonomic dysfunction are well known [20–22]. In the only study on cancer patients in which BPV was incorporated into a prognostic risk score, it was still an index extrapolated from the nocturnal period, namely the night-time systolic SD [5].

Comparison of systolic and diastolic BPV indexes has traditionally been discussed in the literature, with occasional conflicting data. In our analysis, systolic BPV indexes, for which associations with more advanced organ damage were previously described [16, 23], are more represented. Among indices of diastolic BPV, only night-time diastolic VIM was predictive in our cohort; these data, although not fully comparable, are in slight contrast to previous studies in which diastolic BPV was at least as relevant as, if not greater than, systolic BPV [24–26].

In our study, individuals with known history of arterial hypertension had higher BPV, similar to what was described in several previous studies [27]. Nevertheless, the association between BPV and CVT-CRT was independent of mean BP and no difference in predictive value of BPV was observed between hypertensive and normotensive subjects.

Cut-off levels were identified based on the occurrence of outcomes. Previous studies mainly on hypertensive individuals have proposed reference values based on population distribution, which are limited by poor reproducibility among different populations and low prognostic value. Only few studies have evaluated cut-off values driven by outcomes, as in the present study, with evidence mainly on SD, wSD, and systolic Dipping [28–30]. The high sensitivity of the selected cut-offs makes the method a good screening test to select patients who deserve more attention in follow-up, as explained below.

In clustering analysis, an unsupervised machine learning process identified clusters of subjects characterized by the highest levels of BPV and also by higher rate of events. BPV was a distinctive feature of these subgroups of individuals, being the other demographical and hemodynamic characteristics, such as age, renal function, left ventricular EF, LVMi, and GLS, not different among the groups. This

Table 5 Comparison of clustering subgroups characteristics

	Cluster 1 $n = 45$	Cluster 2 $n = 23$	Cluster 3 $n = 50$	p value
Age [years]	62.5 ± 10.7	65.5 ± 7.2	64.0 ± 7.5	0.424
Female sex [n, (%)]	28 (62.2)	12 (52.2)	20 (40)	0.095
BMI [kg/m^2]	27.5 ± 4.8	28.2 ± 4.5	27.9 ± 4.7	0.670
eGFR [mL/min/1.73 m^2]	82.9 ± 21.1	69.2 ± 22.8	80.6 ± 16.4	0.628
Office SBP [mmHg]	133.9 ± 17.3	125.5 ± 16.6	131 ± 18.8	0.451
Office DBP [mmHg]	79.8 ± 8.8	71.3 ± 15	77.1 ± 11.2	0.288
LVMi [g/m^2]	92.2 ± 23	86.9 ± 16.8	90.2 ± 26.4	0.692
LVEF [%]	62.3 ± 6.8	65.5 ± 6.6	61.9 ± 7.4	0.738
GLS [%]	−21.4 ± 2.4	−21.8 ± 2.6	−21.3 ± 2.9	0.796
PWV [m/s]	8.4 ± 1.8	8.6 ± 2.3	8.1 ± 1.7	0.511
Total CTR-CVTs [n, (%)]	31 (68.9)	7 (19.5)	30 (60)	**0.009*#§**

The bold is expressing when p value is < 0.05 (and so when statistically significant)

BMI body mass index, *CTR-CVT* cancer therapy-related cardiovascular toxicity, *DBP* Diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *GLS* global longitudinal strain, *LVEF* left ventricular ejection fraction, *LVMI* indexed left ventricular mass, *PWV* pulse wave velocity, *SBP* Systolic blood pressure

* for $p < 0.05$ between Clusters 1 and 2; # for $p < 0.05$ between Clusters 1 and 3; § for $p < 0.05$ between Clusters 2 and 3

provides additional support to the evidence that BPV may be an indicator of an elevated risk for developing CTR-CVT, even when conventional CV risk factors would not classify individuals as at higher risk.

It is important to note that currently, no direct evidence links the action of proteasome inhibitors to increased BPV. Nevertheless, proteasome inhibitors have been linked to endothelial dysfunction [31], with subsequent increased arterial stiffness, that may contribute to elevation in BPV [32]. Furthermore, a relation between proteasome inhibitors and damage in peripheral and autonomic nervous systems is well established [33]. Autonomic nervous system alterations are known to disrupt normal BP circadian rhythm and contribute to an increase in BPV, as observed in patients with neurological conditions involving autonomic dysfunction [34]. For these reasons, a drug-related effect through these mechanisms cannot be excluded.

On the other hand, Multiple Myeloma has been associated with variable rates of autonomic dysfunction [35].

On this basis, it is essential to make it clear that we cannot definitively attribute elevated BPV solely to proteasome inhibitors or the diagnosis of Multiple Myeloma itself.

While our study demonstrates a significant association between night-time BPV and CTR-CVT, further research is necessary to elucidate the specific contributions of treatment-related and disease-related factors. In addition, it is not possible from this study to determine whether high BPV is only a marker of higher risk of CTR-CVT or plays itself a direct role in causing CV adverse events.

Limitations

The present study was conducted on a sample of patients with Multiple Myeloma, undergoing therapy with proteasome inhibitors. The generalizability of the prognostic value of BPV deserves to be assessed also in other populations of cancer patients, because involvement of the autonomic system has been described in patients with myeloma [36, 37], and therefore they may be prone to have greater BPV than patients with other types of malignancies.

It is important to note that the criterion used for determining BP events, based on office BP measurements, does not completely exclude the possibility of white coat effects; however, recognizing these events as CTR-CVT underscores the importance of achieving good BP control in this patient population.

In addition, there is a lack of evidence on the actual effectiveness in reducing adverse outcomes from more rigorous management of the high BPV; at the same time, highlighting the role of BPV on the risk of developing CTR-CVT in these patients invites further investigation of this aspect as well. Future studies should address these open questions, evaluating BPV prognostic value in larger and wider cohorts of cancer patients and the effect of a personalized management in subjects with signs of BP regulation impairment. At the same time, ad hoc studies should be designed to distinguish the contribution of cardiotoxic therapy from that of high BPV itself in determining adverse outcomes.

Conclusion

Night-time short-term BPV is a risk factor for development of CTR-CVT in patients with Multiple Myeloma undergoing therapy with proteasome inhibitors, independently by the other conventional prognostic factors. The use of some BPV indexes, such as night-time systolic SD, night-time systolic CoV, night-time systolic VIM, and night-time diastolic VIM, improves CV baseline prediction risk and allows the identification of a category of patients to be followed more closely during follow-up, with the eventual assistance of a CV specialist.

Clinical perspectives

BPV proved to be an independent predictor of CTR-CVT in patients with Multiple Myeloma undergoing therapy with

Table 6 Blood pressure variability indexes in different clustering subgroups

	Cluster 1 $n = 45$	Cluster 2 $n = 23$	Cluster 3 $n = 50$	p value
Daytime SBP SD [mmHg]	12.9 ± 2.9	9.3 ± 2.3	10.6 ± 2.4	**<0.001*#**
Daytime DBP SD [mmHg]	9.7 ± 1.3	6.4 ± 1.4	7.4 ± 1.3	**<0.001*#§**
Night-time SBP SD [mmHg]	11.8 ± 2.9	7.4 ± 2	9.5 ± 2.4	**<0.001*#§**
Night-time DBP SD [mmHg]	9 ± 1.9	4.8 ± 1.3	7.7 ± 1.5	**0.003*#§**
Daytime SBP CoV	10.1 ± 2.3	7.8 ± 1.7	8.5 ± 1.8	**<0.001*#**
Daytime DBP CoV	12.9 ± 2.7	9.4 ± 1.8	9.9 ± 2.1	**<0.001*#**
Night-time SBP CoV	12.9 ± 2.7	9.4 ± 1.8	9.9 ± 2.1	**0.004*#§**
Night-time DBP CoV	11.5 ± 3.4	11.2 ± 3.9	12.8 ± 4.6	0.119
SBP wSD [mmHg]	12.1 ± 2.5	8.4 ± 1.9	9.9 ± 1.9	**<0.001*#§**
DBP wSD [mmHg]	9.2 ± 1.0	5.7 ± 1.2	7.2 ± 0.8	**<0.001*#§**
Daytime SBP ARV [mmHg]	8.8 ± 1.4	7.3 ± 1.4	8.0 ± 1.6	**0.013*#**
Daytime DBP ARV [mmHg]	7.0 ± 1.0	5.0 ± 0.9	5.3 ± 0.9	**<0.001*#**
Night-time SBP ARV [mmHg]	8.1 ± 1.8	5.8 ± 1.5	7.2 ± 1.9	**0.019*#§**
Night-time DBP ARV [mmHg]	6.2 ± 1.6	3.6 ± 1.0	5.3 ± 1.1	**0.008*#§**
Daytime SBP VIM	12.9 ± 2.7	9.4 ± 1.8	9.9 ± 2.1	**<0.001*#**
Daytime DBP VIM	9.6 ± 1.5	6.6 ± 1.3	7.3 ± 1.3	**<0.001*#**
Night-time SBP VIM	11.8 ± 2.9	7.3 ± 1.9	9.6 ± 2.3	**<0.001*#§**
Night-time DBP VIM	9.1 ± 1.8	4.8 ± 1.3	7.7 ± 1.5	**0.003*#§**

The bold is expressing when p value is < 0.05 (and so when statistically significant)

ARV average real variability, *CoV* coefficient of variation, *DBP* Diastolic blood pressure, *SBP* Systolic blood pressure, *SD* standard deviation, *VIM* variability independent of the mean, *wSD* weighted standard deviation

* for $p < 0.05$ between Clusters 1 and 2; # for $p < 0.05$ between Clusters 1 and 3; § for $p < 0.05$ between Clusters 2 and 3

proteasome inhibitors. The potential opportunity to include BPV in the predictive factors in this category of patients provides an easily obtainable measure, accessible even in peripheral centers.

Clustering analysis identified individuals with a higher rate of CTR-CVT during follow-up, who had higher BPV levels, but no difference in other conventional CV risk determinants. This suggests a higher sensibility of BPV in stratifying subjects at higher risk of developing CTR-CVT.

The present study provides highly sensitive BPV cut-off values, thus allowing them to be used as screening tests to identify those patients deserving of closer follow-up and a more aggressive management of BP values and other CV risk factors.

Translational outlook

Further studies should determine the predictive value of BPV for CTR-CVT in other categories of individuals and cancer therapies, respectively. Furthermore, future investigations should address the effect on disease-free survival and overall survival of a personalized management oriented by BPV.

Data availability

Research data are available on request.

Compliance with ethical standards

Conflict of interest Alberto Milan received honoraria for advisory board from Amgen. Sara Bringhen received honoraria from Bristol-Myers Squibb, Celgene, Amgen, and Janssen; advisory boards for Amgen, Karyopharm, Janssen, and Celgene; consultancy fees from Takeda and Janssen. Francesca Gay received honoraria from Amgen, Janseen, Celgene, BMS, Takeda, and Abbvie; advisory boards for Amgen, Janseen, Celgene, BMS, Takeda, and Abbvie; advisory adaptive for Roche Oncopeptides. The other authors declare no conflict of interest. The other authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, and/or interpretation of data; in the writing of the manuscript and/or in the decision to publish the results.

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