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Association Between Baseline Hemodynamic Indices, Cardiotoxicity Risk and Survival in Women with Breast Cancer

Charles-Edouard Decorads, MD^a; Aurélien Lambert, MD^b; Véronique Roch, MSc^a; Laetitia Imbert, PhD^{a,c}; Mathieu Perrin, MD^a; Marine Claudin, MD^a; Matthieu Doyen, MD^c; Quentin Citerne, PharmD^a; Zohra Lamiral, MSc^d; Didier Peiffert, MD, PhD;^e Catherine Henneon, MD^b and Pierre-Yves Marie, MD, PhD^{a,f}.

^a Université de Lorraine, Department of Nuclear Medicine and Nancyclotep Imaging Platform, CHRU Nancy, F-54000, Nancy, France.

^b Institut de cancérologie de Lorraine, Department of Medical Oncology, F-54500, Vandœuvre-lès-Nancy, France.

^c Université de Lorraine, INSERM, UMR1254, 54000, Nancy, France.

^d Université de Lorraine, CHRU-Nancy, INSERM, CIC 1433, Nancy, France.

^e Institut de cancérologie de Lorraine, Department of Radiation Oncology, F-54500, Vandœuvre-lès-Nancy, France

^f Université de Lorraine, INSERM, UMR 1116, 54000, Nancy, France.

Address for correspondence: Pierre-Yves Marie, Médecine Nucléaire, Hôpital de Brabois, CHRU-Nancy, Allée du Morvan, 54500 Vandoeuvre-lès-Nancy, France.

Tel: (+33) 3 83 15 39 09; Fax: (+33) 3 83 15 44 78; E-mail: py.marie@chru-nancy.fr

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Abstract

Background: The outcome of breast cancer (BrCa) women monitored by low-dose equilibrium radionuclide angiography (ERNA) remains challenging to predict. This study aims to determine whether heart rate (HR) to blood pressure (BP) ratio-based indexes, previously confirmed to predict outcomes of various diseases, also predict BrCa therapy-related cardiotoxicity and survival.

Methods: Predictors of cardiotoxicity and survival were determined among pre-therapy variables, including shock index (SI=HR/systolic BP) and age-adjusted SI (ASI), in a female BrCa cohort with normal baseline ERNA-left ventricular ejection fraction (LVEF).

Results: We included 274 women with a median age of 54.8 (interquartile range: 45.5-65.4) years, 271 treated with anthracyclines, and 96 with trastuzumab. During a median follow-up of 25.9 (18.6-33.5) months, 31 women developed cardiotoxicity (LVEF < 50% and \geq 10% drop from baseline), and 25 died.

Baseline ASI was a multivariate predictor ($p < 0.001$) of (i) cardiotoxicity, in association with trastuzumab treatment ($p = 0.010$), and LV end-diastolic volume ($p = 0.001$) and (ii) survival, in association with metastasis ($p < 0.001$) and estimated glomerular filtration rate ($p = 0.008$).

Cardiotoxicity poorly impacted survival ($p = 0.064$). The 36-month cardiotoxicity and mortality rates were markedly higher for patients in the upper half of baseline ASI values (ASI > 30 years.min⁻¹.mmHg⁻¹, 16.5% and 20.7%, respectively) than in the lower half (7.6% and 4.5%, respectively, both $p < 0.05$).

Conclusions: In BrCa women with normal baseline ERNA-LVEF, HR/BP ratio-based indexes unmask hemodynamic profiles associated with increased cardiotoxicity risk and decreased survival, highlighting the need for a comprehensive assessment of cardiac- and vascular-related risks in BrCa women monitored by ERNA.

Keywords: equilibrium radionuclide angiography; breast cancer; cardiotoxicity; hemodynamics; shock index.

Condensed abstract.

In a cohort of 274 women breast cancer women who were monitored by equilibrium radionuclide angiography for potentially cardiotoxic drugs (anthracyclines or trastuzumab) and who had no history of cardiac disease and a normal left ventricular ejection fraction before treatment, baseline indexes based on heart-rate/blood pressure ratios unmask hemodynamic profiles strongly associated with an increased risk of cardiotoxicity and subsequently decreased survival. Although further validations in other cohorts are needed, these findings highlight the need for a more comprehensive assessment of the cardiac- and vascular-related risk in breast cancer women monitored by equilibrium radionuclide angiography.

Abbreviations

ASI: age-adjusted shock index

BP: blood pressure

BrCa: breast cancer

eGFR: estimated glomerular filtration rate

ERNA: equilibrium radionuclide angiography

HR: heart rate

LVEF: left ventricular ejection fraction

MSI: modified shock index

SI: shock index

SIC: shock index-C

Introduction

Breast cancer (BrCa) survival rates have significantly improved over the past few decades.

However, this progress has been accompanied by an increase in cardiovascular risk and cardiotoxicity specifically associated with anthracycline and trastuzumab treatments.

Predicting cardiotoxicity and its subsequent impact on prognosis remains difficult in BrCa women treated with anthracycline, trastuzumab, or both, especially in those exhibiting normal cardiac function before treatment.¹⁻³

Cardiotoxicity is commonly defined as a decrease in the left ventricular ejection fraction (LVEF) of at least 10% during therapy to a value below the 50-53% range, depending on the cardiac imaging method used, echocardiography or equilibrium radionuclide angiography (ERNA).¹⁻⁴ Unfortunately, decreases in LVEF and intrinsic LV contractility may be masked by several factors, such as sympathetic system activation⁵⁻⁷ and variations in cardiac load and blood pressure (BP).⁷⁻⁹

High heart rate (HR)-to-BP ratios, reflecting poor hemodynamic conditions and considered alone or combined with age or creatinine clearance, are strong predictors of outcome in patients with advanced cancer,^{10,11} severe cardiac,¹²⁻¹⁵ or infectious diseases.¹⁶ This prediction seems independent of that provided by LVEF in cardiac disease patients.¹³⁻¹⁵ The question arises whether these HR/BP-based indexes may unmask a cardiocirculatory vulnerability that leads to an increase in cardiotoxicity risk and a worse prognosis in BrCa women with a normal pre-therapy LVEF at ERNA.

This study aims to determine whether therapy-related cardiotoxicity and subsequent survival can be predicted by HR/BP-based indexes in BrCa women monitored with low-dose ERNA and who had no history of cardiac disease and a normal ERNA-LVEF before treatment.

Methods

Study design

This retrospective study included consecutive BrCa women who were scheduled to receive anthracyclines, trastuzumab, or both, had no history of significant cardiovascular disease, and were part of a low-dose ERNA-based LVEF monitoring program.³ The pre-therapy ERNA was recorded between January 2019 and June 2021, with at least one follow-up ERNA recorded before February 2023.

The cancer treatments, administered in a French regional oncology center (Institut de Cancérologie de Lorraine), typically included anthracycline followed by one year of trastuzumab for cancers overexpressing the erb-b2 receptor tyrosine kinase 2 (formerly HER2) receptor.

Based on estimated risk,⁴ the time interval between serial LVEF measurements during the treatment period was usually three months. A subsequent 5-year medical consultation follow-up was conducted.

All patients were informed that their medical data may be used for research purposes, and the local Ethics Committee approved the study.

ERNA recording and analysis

As previously described in detail in the Journal of Nuclear Cardiology,⁴ LVEFs were obtained from low-dose ERNAs recorded with a high-sensitivity semiconductor camera (D-SPECT camera, Spectrum Dynamics, Haifa, Israel). Briefly, red blood cells were labeled *in vivo* by the intravenous injection of 250 to 650 MBq of [^{99m}Tc]NaTcO₄ as a proportion of body weight (Figure 1) 20-30 minutes after injecting approximately 6 mg of stannous

pyrophosphate. These low radiotracer doses were previously shown to be associated with a mean effective dose of only 2.3 mSv per ERNA investigation.⁴

Five to 15 minutes after the injection, patients were set in a semi-reclining prone position with ECG leads placed on their backs (Figure 1). Projections were recorded during a 10-minute period with a 'region-centric' acquisition, maximizing the counts arising from a heart area previously defined on a short pre-scan.^{4,17}

Tomographic images were reconstructed using the following parameters: 16-interval frames, 4 iterations, 32 subsets, Kernel and Gaussian filters of respectively 0.125 and 5 mm, and a 128 x 128 matrix, resulting in a voxel size of 4.92 x 4.92 x 4.92 mm³.^{4,17}

The LVEF was computed using the count-based method of the Quantitative Blood Pool software (Cedars-Sinai Medical Center) and with manual displacements of LV limits if obvious errors in the automatic contouring process were apparent.^{4,17} The final LVEF values were obtained in percentages after correcting for the relative underestimation of end-systolic volume according to a calibration procedure based on count/volume correlations.^{4,17} The LV end-diastolic volume (EDV) was considered to be that provided by the contour-detection method of the QBS software. The end-systolic volume (ESV) was computed as $EDV \times (1 - LVEF / 100)$. These LV volumes were indexed to the patient's body surface area.

Effective doses were calculated by applying a ratio of 7.09×10^{-3} mSv/MBq of injected Tc-99m,¹⁸ according to the activity measured in the syringe before injection, with a dedicated dose calibrator.

Cardiotoxicity was defined as a $\geq 10\%$ drop from baseline LVEF to an LVEF value $< 50\%$.¹⁻⁴

Cine-loops of the ERNA images from the graphical abstract are available in a supplemental movie file.

Hemodynamic parameters

Systolic, diastolic and mean brachial BP, and HR were measured before each ERNA recording with an automatic sphygmomanometer. These measurements were used to compute the shock index ($SI = HR / \text{systolic BP}$),¹⁰⁻¹⁶ modified shock index ($MSI = HR / \text{mean BP}$),¹³ age-adjusted SI ($ASI = \text{Age} \times SI$),¹³ and shock index-C ($SIC = SI \times 100 - \text{clearance rate}$).¹⁴ The clearance rate was estimated as: $(140 - \text{age}) / \text{serum creatinine} \times 0.85$.¹⁴

Statistical analysis

Quantitative variables were expressed as medians with interquartile ranges (IQR), and qualitative variables as percentages. Time-to-event outcomes were compared using the log-rank test and Cox proportional hazards models with hazard ratios reported with their 95% confidence intervals [CI]. Cox proportionality assumptions were checked. Log linearity was assessed using a Restricted Cubic Splines analysis with two continuous variables dichotomized according to the shape of the spline curve (LVEF and diastolic BP). Only variables associated with a P value < 0.10 in the univariate Cox analysis were considered in the multivariate Cox analysis, and P thresholds of 0.05 and 0.10 were used to respectively enter or remove variables in the stepwise ascending Cox multivariate analysis. Several qualitative variables, which occurred too infrequently to allow accurate evaluation (< 15% of patients), were regrouped in the Cox analysis (cardiovascular risk factors, potentially cardioprotective treatments). Event rates were also estimated and compared using the Kaplan-Meier method and log-rank tests.

Results

Among the 310 BrCa women initially included, 36 were subsequently excluded because of an abnormal pre-therapy LVEF or a missing pre-therapy or follow-up ERNA.

As detailed in Table 1, at the time of the pre-therapy ERNA, the median age was 54.8 (IQR: 45.5-65.4) years; 29 (11%) women had metastases, 45 (16%) had cardiovascular risk factors, such as hypertension (n=20), diabetes (=16) and dyslipidemia (n=26); 47 (17%) patients were treated with beta-blockers (n=23) or angiotensin-converting enzyme inhibitors (n=30); and HR/BP ratios could be determined in 261 (95%) women.

A total of 271 (99%) women received anthracyclines and 96 (35%) trastuzumab. During a median follow-up of 25.9 (18.6-33.5) months from the baseline ERNA, 31 (11%) women were diagnosed with cardiotoxicity at a median interval of 5.0 (3.0-6.8) months from baseline, and 25 (9%) died at a three times more extended time interval from baseline, namely: 15.2 (7.2-25.6) months. None of these deaths were considered to have a direct cardiac cause.

As detailed in Table 2, the main univariate baseline Cox predictors of cardiotoxicity were the four HR/BP-based variables ($p \leq 0.002$) and trastuzumab treatment ($p = 0.005$), which outperformed the prediction provided by all other baseline variables. The multivariate baseline predictors of cardiotoxicity were: ASI (hazard ratio per 10 bpm/mmHg.year increments [95% CI]: 2.23 [1.56-3.20], $p < 0.001$), trastuzumab treatment (2.38 [1.16-4.88], $p = 0.010$) and LV end-diastolic volume (per 10 mL/m² increments): 1.32 [1.11-1.56], $p = 0.001$).

Cardiotoxicity was slightly predictive of death (2.33 [0.93-5.83], $p = 0.064$). The multivariate baseline predictors of death were ASI (2.54 [1.68-3.83], $p < 0.001$), metastasis (10.9 [4.8-24.9], $p < 0.001$), and estimated glomerular filtration rate (1.29 [1.07-1.55], $p = 0.008$) (Table 2).

The median ASI of 29.94 was rounded up to 30 years.min⁻¹.mmHg⁻¹, to distinguish an upper half of 129 patients with ASI > 30 years.min⁻¹.mmHg⁻¹ and a lower half of 132 patients. At 36 months, both cardiotoxicity and mortality rates were markedly higher in patients in the upper half of ASI values (16.5% [10.0%-23.0%] and 20.7% [10.9%-30.6%], respectively) than in the lower half (7.6% [3.1%-12.1%] and 4.5% [0.0%-9.0%], respectively, both $p < 0.05$) (see Figure 2 and graphical abstract).

Discussion

Our study demonstrates that HR/BP-based indexes are potent predictors of cardiotoxicity and increased mortality in BrCa women monitored with low-dose ERNA and who had no history of cardiac disease and a normal ERNA-LVEF before treatment. The predictive value of HR/BP is enhanced when adjusted for age (ASI) and when considering other known risk factors such as (i) metastatic stage and kidney function for survival,¹⁹ and (ii) trastuzumab treatment for cardiotoxicity,^{1,2} with cardiotoxicity being additionally influenced by the baseline LV end-diastolic volume measured with the 3D ERNA technique. Interestingly, our findings also indicate that overall survival was only marginally impacted by prior cardiotoxicity. Since all deaths within the cohort were due to non-cardiac events, this marginal impact could be due to indirect factors such as the fact that more severe cancers are likely to require more extensive cardiotoxic treatments.

The correlation between HR/BP-based indexes and survival has been previously reported in advanced cancer patients,^{10,11} presumably because it reflects more generalized adverse effects on circulatory system function (e.g., autonomic dysfunction, inflammation, chemotherapy, hypovolemia, cachexia...).¹¹ The respective roles of cancer severity, frailty, and exercise

deconditioning could lead to different therapeutic measures, but their evaluation would require further dedicated studies.

Nevertheless, the association between HR/BP-based indexes and the risk of cardiotoxicity is a novel observation brought forward in our study.

Although all included women had a normal (> 50%) baseline ERNA-LVEF, a deterioration in the cardiovascular system was presumably unmasked in some of them by high ASI values, determined with the formula $HR / SBP \times age$, and to a smaller extent by high end-diastolic volumes. More precisely, this deterioration might involve (i) sympathetic overstimulation of contractility,⁵ with this overstimulation suggested by the particularly high resting HR achieved in women with elevated ASI (88 bpm in the upper quartile, on average), (ii) a low LV afterload, considering that a lower BP would have helped maintain the LVEF of diseased hearts within the normal range, similarly to what is observed in sepsis patients,⁶ and (iii) an increase in end-diastolic volume, with this increase being also known to enhance the LVEF and stroke volume of diseased hearts (Frank-Starling mechanism).⁷

Age, the third variable included in the ASI formula, is an additional cardiotoxicity risk factor consistent with further age-related cardiovascular deterioration.

Finally, it is important to remember that a > 50% LVEF is not synonymous with normal contractility. LVEF and LV stroke volumes also depend on preload conditions (end-diastolic volume), post-load conditions (blood pressure, systemic vascular resistance),⁷⁻⁹ and the degree of contractile stimulation by neuroendocrine factors (sympathetic activation).⁵⁻⁷

Limitations. While our study provides valuable insights, it is important to note that our findings need to be validated in independent, larger, multicentric cohorts. Furthermore, the tangible clinical benefits of monitoring HR/BP in association with ERNA parameters need to be evaluated in specifically designed prospective studies.

A greater than two-fold increase in the risks of cardiotoxicity and death was observed in approximately half of the cohort with baseline ASI values higher than $30 \text{ years} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$. These risks appear even more precisely defined when considering ASI as a continuous variable. However, further efforts are needed to better define ASI thresholds and high-risk groups. Future studies analyzing the changes in hemodynamic parameters during treatment could be informative in this setting.

Conclusion. In BrCa women monitored with low-dose ERNA and who had no history of cardiac disease and a normal ERNA-LVEF before treatment, indexes based on pre-therapy HR/BP ratios unmask hemodynamic profiles strongly associated with an increased risk of cardiotoxicity and subsequently decreased survival. Although further validations in other cohorts are needed, these findings underpin the need for a more comprehensive assessment of cardiac- and vascular-related risks in the BrCa women monitored with ERNA. This would allow to better adapt monitoring and treatments to the individual patient.

New Knowledge Gain: In breast cancer women monitored with ERNA for potentially cardiotoxic treatments, heart rate/blood pressure ratio-based indexes unmask hemodynamic profiles associated with subsequent increased cardiotoxicity risk and decreased survival.

Clinical implications: Special attention could be paid to the baseline heart rate-to-blood pressure ratios of breast cancer women monitored by low-dose equilibrium radionuclide angiography for potentially cardiotoxic treatments.

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Independent data access and analysis. All authors had full access to all the data in the study. Pierre-Yves Marie, the corresponding author, takes responsibility for the integrity of the study and the data analysis.

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Figures legends

Figure 1: Prescribed [^{99m}Tc]-Tc(O $_4$)⁻ doses as a proportion of body weight (left panel) and a representative image of patient position during the SPECT recording (right panel).

Bod weight	Prescribed doses
≤ 60kg	250 MBq
61 to 70 kg	300 MBq
71 to 80 kg	350 MBq
81 to 90 kg	400 MBq
91 to 100 kg	460 MBq
101 to 110 kg	520 MBq
111 to 120 kg	590 MBq
121 to 250 kg	650 MBq



Figure 2: Kaplan–Meier curves for cardiotoxicity (left panel) and all-cause mortality (right panel) rates over the 36-month follow-up period in BrCa women with ASI baseline values $> 30 \text{ years}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$, compared to women with baseline ASI values $\leq 30 \text{ years}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$. The actual number of event-free patients at each of the 6-month follow-up intervals is given below the x-axis.

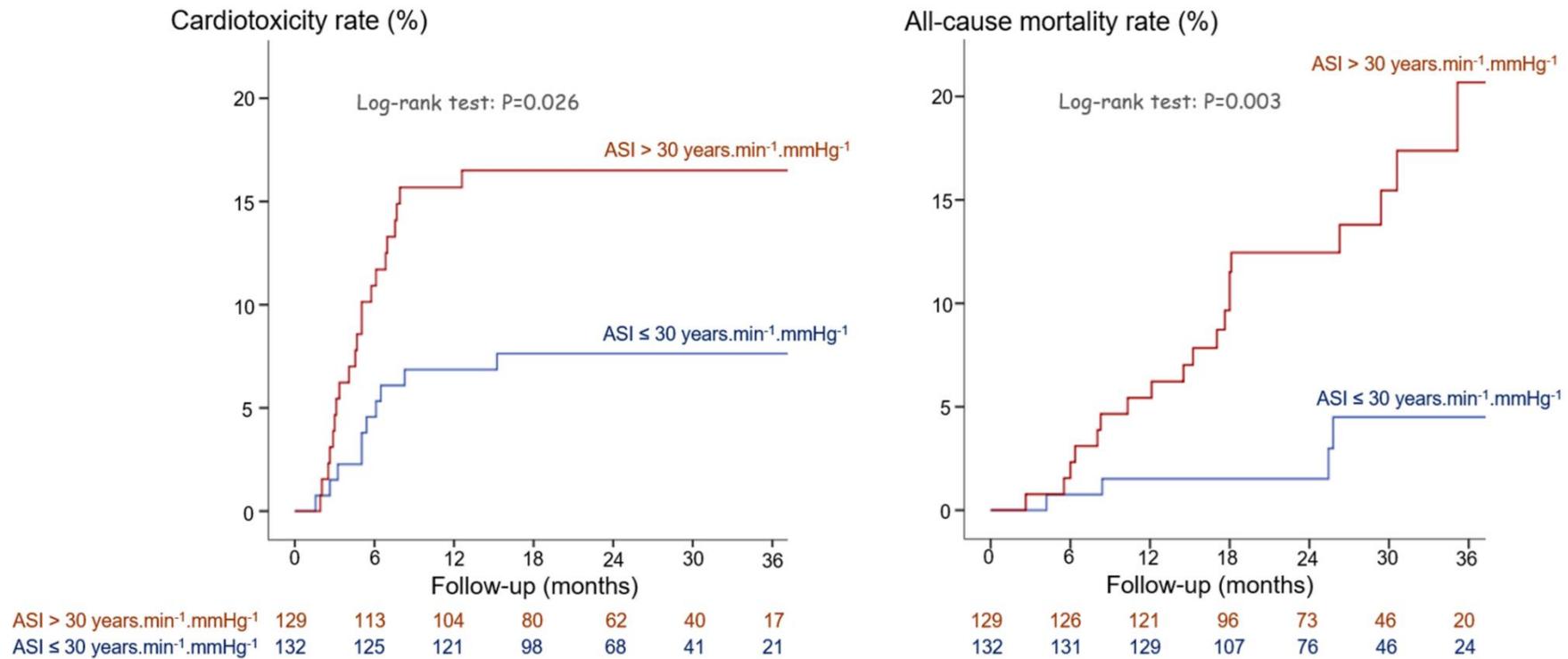


Table 1: Baseline data collected at the time of the baseline pre-therapy ERNA.

Age (years)	54.8 (45.5-65.4)
Body mass index (kg/m ²)	25.4 (22.3-29.3)
≥ 1 cardiovascular risk factor	45 (16%)
- diabetes	16 (6%)
- dyslipidemia	26 (10%)
- hypertension	20 (7%)
Beta-blockers	23 (8.4%)
ACEI	30 (11%)
eGFR (ml/min/1.73 m ²)	88.4 (77.6-99.4)
Oncology	
ERBB2 positivity	92 (33%)
Hormone receptor positivity	173 (63%)
TNBC	67 (24%)
Metastasis	29 (11%)
Prior breast surgery	241 (87%)
Prior radiotherapy	49 (18%)
Trastuzumab	96 (35%)
Anthracycline	272 (99%)
ERNA	
LVEF (%)	65.0 (59.0-71.0)
Indexed EDV (mL/m ²)	65 (54-77)
Indexed ESV (mL/m ²)	23 (16-29)
Hemodynamics	
Heart rate (min ⁻¹)	78.0 (71.8-86.0)
Systolic BP (mmHg)	139.0 (124.5-155.0)
Diastolic BP (mmHg)	76.0 (70.0-80.0)
Mean BP (mmHg)	96.7 (88.0-105.2)
SI (min ⁻¹ .mmHg ⁻¹)	0.577 (0.489-0.653)
MSI (min ⁻¹ .mmHg ⁻¹)	0.816 (0.729-0.915)

SIC ($\text{min}^{-1} \cdot \text{mmHg}^{-1} \cdot \text{ml/min}$)	-28.6 (-36.4; -19.2)
ASI ($\text{years} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$)	29.94 (24.63-36.35)

ACEI = angiotensin-converting enzyme inhibitor; ASI = age-adjusted shock index; EDV = end-diastolic volume; ESV = end-systolic volume; eGFR = estimated glomerular filtration rate by 2009 Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI); ERBB2 = erb-b2 receptor tyrosine kinase 2 (formerly HER2); BP = blood pressure; MSI = modified shock index; LVEF = left ventricular ejection fraction, SI = shock index; SIC = shock index-C; TNBC = triple-negative breast cancer.

Table 2: Hazard ratios (HRs) with 95% confidence intervals [95% CI] and P values for the Cox univariate and multivariate baseline prediction of cardiotoxicity and death.

	Cardiotoxicity						Death					
	Univariate			Multivariate			Univariate			Multivariate		
	n	HR [95% CI]	P value	n	HR [95% CI]	P value	n	HR [95% CI]	P value	n	HR [95% CI]	P value
Age (per 10-year inc.)	274	1.18 [0.91-1.55]	0.22				274	1.25 [0.93-1.70]	0.14			
Body mass index (per 10 kg/m ² inc.)	274	0.73 [0.39-1.35]	0.31				274	1.90 [1.03-3.51]	0.04			
≥ 1 cardiovascular risk factor	274	1.48 [0.64-3.42]	0.36				274	1.35 [0.51-3.61]	0.55			
Beta-blockers or ACEIs	274	1.69 [0.76-3.77]	0.20				274	2.25 [0.97-5.21]	0.059			
eGFR (per 10 ml/min/1.73 m ² inc.)	272	1.08 [0.88-1.33]	0.46				272	1.28 [1.03-1.60]	0.029	259	1.29 [1.07-1.55]	0.008
ERBB2 positivity	274	2.58 [1.28-5.19]	0.008				274	0.34 [0.12-0.99]	0.049			
Hormone receptor positivity	274	0.85 [0.42-1.71]	0.64				274	0.64 [0.29-1.39]	0.26			
TNBC	274	0.71 [0.29-1.71]	0.44				274	1.54 [0.66-3.56]	0.32			
Metastasis	274	0.63 [0.15-2.63]	0.53				274	15.2 [6.8-33.9]	<.0001	259	10.9 [4.8-24.9]	<.0001
Prior breast surgery	274	4.14 [0.57-30.4]	0.16				274	0.14 [0.06-0.31]	<.0001			
Prior radiotherapy	274	1.09 [0.45-2.64]	0.86				274	1.01 [0.38-2.70]	0.99			
Trastuzumab	274	2.77 [1.37-5.62]	0.005	261	2.56 [1.25- 5.27]	0.010	274	0.54 [0.22-1.36]	0.19			
LVEF (%)	274	---	---				274	0.99 [0.94-1.05]	0.81			
> 65%	274	0.53 [0.26-1.10]	0.09				274	---				

Indexed EDV (per 10 mL/m ² inc.)	273	1.14 [0.99-1.31]	0.079	261	1.32 [1.11-1.56]	0.001	273	0.96 [0.93- 0.98]	0.0006			
Indexed ESV (per 10 mL/m ² inc.)	273	1.25 [0.94-1.66]	0.124				273	0.94 [0.90- 0.99]	0.029			
Heart rate (per 10 bpm inc.)	274	1.37 [1.07- 1.76]	0.014				274	1.64 [1.33-2.04]	<0.0001			
Systolic BP (per 10 mmHg inc.)	261	0.83 [0.69- 1.00]	0.045				261	0.97 [0.80-1.17]	0.76			
Diastolic BP (mmHg)		---	---					1.00 [0.97- 1.04]	0.78			
> 80 mmHg	261	0.34 [0.10-1.12]	0.077				261	---	---			
Mean BP (mmHg)	261	0.97 [0.94-1.00]	0.039				261	1.00 [0.97- 1.03]	0.99			
SI (per 0.1 min ⁻¹ .mmHg ⁻¹ inc.)	261	1.44 [1.18-1.74]	0.0003				261	1.49 [1.22- 1.81]	<0.0001			
MSI (per 0.1 min ⁻¹ .mmHg ⁻¹ inc.)	261	1.38 [1.16-1.63]	0.0002				261	1.38 [1.17- 1.64]	0.0002			
SIC (per 10 min ⁻¹ .mmHg ⁻¹ -ml/min inc.)	261	1.41 [1.17-1.71]	0.0004				261	1.41 [1.16- 1.73]	0.0007			
ASI (per 10 year.min ⁻¹ .mmHg ⁻¹ inc.)	261	2.22 [1.55-3.17]	<.0001	261	2.60 [1.81-3.71]	<.0001	261	2.34 [1.57-3.49]	<.0001	259	2.54 [1.68-3.83]	<.0001

Inc.: increment. The other abbreviations are defined in Table 1.