Limitations of N-Terminal Pro-B-Type Natriuretic Peptide in the Diagnosis of Heart Disease among Cancer Patients Who Present with Cardiac or Pulmonary Symptoms

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Key Words

Natriuretic peptides · Cancer · Heart disease · Sensitivity and specificity

Abstract

Objectives: Recognizing heart disease is relevant to oncologists because cancer patients are at an increased risk of cardiac mortality due to shared risk factors and the adverse effects of cancer therapy. This study assessed the extent to which the measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) aids in the diagnosis of heart disease in addition to a history of coronary artery disease and the presence of atrial fibrillation (composite test). The NT-proBNP cutoff value was 100 pg/ml. **Methods:** A series of 583 consecutive cancer patients (68.4 ± 11.0 years) who were referred because of cardiac or pulmonary symptoms prospectively underwent a diagnostic work-up. Heart disease was diagnosed if at least one of the following conditions was present: (a) history of coronary artery disease, (b) atrial fibrillation, (c) impaired left ventricular systolic function, (d) significant valvular disease, (e) pulmonary hypertension, or (f) left ventricular hypertrophy. **Results:** Except for (a), all 6 con-

ditions were associated with NT-proBNP >100 pg/ml. The sensitivity/specificity values of the composite test were 0.92/0.50 for any heart disease. Several extracardiac covariates were associated with NT-proBNP >100 pg/ml, which contributed to the low test specificity. **Conclusions:** The low specificity of NT-proBNP limits its value for the diagnosis of heart disease in cancer patients.

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Introduction

Heart disease is relevant to oncologists because cardiovascular risk factors also increase an individual's cancer risk and because cancer therapies may be detrimental to the heart [1–4]. Diagnostic and therapeutic advances have improved the life spans of cancer patients; therefore, heart disease has become a major cause of mortality. Today, a woman with early-stage breast cancer is less likely to die of cancer than to die of heart disease [5]. Recognizing heart disease in cancer patients is often difficult because dyspnea, exercise intolerance, and fatigue are common in both conditions.

Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) is increased not only in systolic heart failure but also in the settings of valvular disease, atrial fibrillation, pulmonary hypertension, and left ventricular hypertrophy [6–8]. Therefore, NT-proBNP is promising as a marker of a wide range of heart diseases that allows oncologists to either exclude heart disease or appropriately select patients for an in-depth evaluation by a cardiologist. Although widely incorporated in oncology studies, the role of NT-proBNP in both diagnosing and monitoring heart disease in cancer patients remains unclear [9–11].

The current study aimed to assess the extent to which the addition of the NT-proBNP level to a history of coronary artery disease and the presence of atrial fibrillation aids in the diagnosis of heart disease in cancer patients with symptoms suggestive of heart or lung disease.

Patients and Methods

Patients

This prospective single-center study included 586 consecutive patients with a history of previous or active malignant disease who were referred from primary care, oncology, or radio-oncology to the cardiology or pulmonology service of an academic teaching hospital between May 2007 and October 2014 for dyspnea, cough, chest pain, pulse irregularities, or exercise intolerance. All but 8 patients were outpatients, and none were confined to bed. We excluded 3 cases because of incomplete data, leaving 583 patients available for analysis. Data from a subgroup of the study cohort have been published in a previous paper [12]. This study was approved by the Ethics Committee of the Baden-Württemberg State Chamber of Physicians, and informed consent was obtained.

Diagnostic Procedures

The patients underwent an examination to identify heart and lung disease that included their medical history, electrocardiography, echocardiography, and pulmonary function testing, as previously described [12]. Further studies were done when indicated.

Heart disease was diagnosed based on the presence of at least one of the following cardiac conditions: (a) a history of coronary artery disease (defined as either angiographically proven coronary artery disease or a hospital diagnosis of myocardial infarction); (b) atrial fibrillation; (c) impaired left ventricular systolic function (an ejection fraction <50% as determined using the biplane-modified Simpson's rule); (d) significant valvular heart disease [at least mild aortic stenosis (mean pressure gradient ≥ 20 mm Hg), moderate aortic regurgitation, moderate mitral regurgitation, or mild mitral stenosis]; (e) pulmonary hypertension (peak systolic pressure gradient across the tricuspid valve ≥ 35 mm Hg), or (f) left ventricular hypertrophy (end-diastolic septal wall thickness ≥ 12 mm). Minor echocardiographic findings (mild aortic regurgitation, mild mitral regurgitation, and a systolic pressure gradient across the tricuspid valve of 30–34 mm Hg) were also recorded. These findings were considered clinically insignificant when designing the study.

Serum NT-proBNP was measured by enzyme-linked immunosorbent assay (Roche Diagnostics, Mannheim, Germany). The lower limit of detection of C-reactive protein (CRP) was 0.71 mg/l. A value of 0.35 mg/l was assigned to the 46 patients with undetectable CRP levels. The estimated glomerular filtration rate (eGFR) was calculated [13].

The basic test consisted of the history and an electrocardiogram (ECG). A positive test result was defined as (1) a history of coronary artery disease or (2) the presence of atrial fibrillation. The composite test included both the basic test and the measurement of NT-proBNP. A positive test result was defined as a positive basic test or an NT-proBNP level that exceeded the predefined cutoff value of 100 pg/ml [6].

Data Analysis

Univariate logistic regression analysis was used to evaluate associations, given as an odds ratio (OR) and 95% confidence interval (CI), of the cardiac conditions (a–f) and the presence of ≥ 1 minor echocardiographic finding with an NT-proBNP value >100 pg/ml as the binary dependent variable. Patients exhibiting none of the cardiac conditions (a–f), and no minor echocardiographic findings formed the reference group. These associations were adjusted for sex, age, BMI, the ln-transformed CRP level [ln(CRP)], the hemoglobin (Hb) level, and eGFR. The presence of ≥ 1 minor echocardiographic finding was entered into the model only if none of the cardiac conditions (a–f) was present. The presence of both atrial fibrillation and significant valvular heart disease perfectly predicted the outcome of NT-proBNP >100 pg/ml. The penalized likelihood method was used to account for the subsequent problem of complete separation [14, 15]. Multiple linear regression was used to evaluate the effects of the cardiac conditions (a–f), the presence of ≥ 1 minor echocardiographic finding, and the above-mentioned extracardiac covariates on the logarithmically transformed NT-proBNP values [ln(NT-proBNP)] as a continuous variable.

Given the exploratory nature of this study, the test results should not be interpreted as confirmatory, and no adjustment for multiple testing was made. A p value <0.05 was considered significant. The analyses were performed using SAS, version 9.2 (SAS Institute, Chicago, Ill., USA).

Results

The demographic and clinical characteristics of the study group are presented in table 1. There were 655 malignancies in the 583 patients. Of the 72 patients with multiple tumors, 61 had different tumors. The most frequent entities were the following: lung (n = 148), breast (n = 139), prostate (n = 70), as well as colorectal cancers (n = 50) and lymphomas (n = 83). A total of 345 patients (59.2%) had neither radiotherapy of the chest nor chemotherapy. Among the remaining 238 patients, 125 (52.5%) had already survived more than 5 years after receiving their first cancer diagnosis. The median time interval (interquartile range) between the date of the first cancer diagnosis and referral was 43 (7–111) months.

Table 1. Demographic and clinical characteristics

	All patients (n = 583)	Radiotherapy		Chemotherapy	
		before 1995 (n = 23)	from 1995 onwards (n = 74)	anthracyclin- based (n = 79)	no anthracyclines (n = 114)
Male/female	311/272	8/15	22/52	16/63	54/60
Age, years	68.4±11.0	68.5±11.3	65.4±11.6	62.0±14.1	66.4±11.0
Active malignant disease	222 (38.1)	3 (13.0)	22 (29.7)	21 (26.6)	48 (42.1)
Heart disease, %	43.4	73.9	43.2	40.5	37.7
History of coronary disease	51/583 (8.8)	7/23 (30.4)	9/74 (12.2)	5/79 (6.3)	7/114 (6.1)
Atrial fibrillation	91/583 (15.6)	5/23 (21.7)	0/74 (0.0)	12/79 (15.2)	17/114 (14.9)
Impaired left ventricular function	35/583 (6.0)	2/23 (8.7)	5/74 (6.8)	7/79 (8.9)	3/114 (2.6)
Valvular disease	46/583 (7.9)	8/23 (34.8)	5/74 (6.8)	6/79 (7.6)	5/114 (4.4)
Pulmonary hypertension	90/583 (15.4)	8/23 (34.8)	10/74 (13.5)	11/79 (13.9)	18/114 (15.8)
Left ventricular hypertrophy	90/583 (15.4)	7/23 (30.4)	10/74 (13.5)	11/79 (13.9)	10/114 (8.8)
Arterial hypertension	358/583 (61.4)	13/23 (56.5)	38/74 (51.4)	34/79 (43.0)	61/114 (53.5)
Diabetes	90/583 (15.4)	4/23 (17.4)	7/74 (9.5)	8/79 (10.1)	19/114 (16.7)
BMI	27.7±5.4	26.6±4.9	27.3±6.5	27.8±6.4	27.2±5.2
CRP, mg/l	4.30 [1.70–11.50]	4.60 [1.80–19.40]	3.90 [2.00–9.30]	3.20 [1.10–9.20]	4.95 [1.80–17.40]
Hb, g/dl	13.5±1.7	13.5±1.7	13.4±1.6	13.4±1.6	13.2±2.0
eGFR, ml/min/1.73 m ²	82 [67–96]	81 [67–86]	88 [68–97]	88 [70–99]	82 [70–97]
NT-proBNP, pg/ml	178 [76–499]	635 [301–1526]	194 [79–389]	178 [108–899]	157 [68–381]

Figures in parentheses are percentages. Data are the mean ± SD, or median value, with interquartile ranges in brackets. Active malignant disease: residual tumor or time interval between surgery/end of chemotherapy/radiotherapy and referral <3 months. Chemotherapy without anthracyclines: alkylating agents (n = 70), antimetabolites (n = 45), microtubule targeting agents (n = 41), and molecular targeting agents (n = 9).

Active malignant disease (see table 1 for definition) was present in 38.1% of the study group. Patients with this condition had higher ($p < 0.01$, Wilcoxon rank-sum test) CRP levels [8.65 (3.40–27.50) mg/l] than those not having active disease [2.85 (1.40–6.65) mg/l].

Table 1 lists the distribution of the cardiac conditions (a–f) in the entire study group as well as in those patients who had received pre-1995 radiotherapy of the chest (n = 23), radiotherapy from 1995 onwards (n = 74), anthracycline-based chemotherapy (n = 79), or chemotherapy without anthracyclines (n = 114). Patients with heart disease commonly presented with more than one cardiac finding. The frequency of heart disease stratified by age is depicted in figure 1. Pulmonary disease was present in 62.4% of patients, either alone (35.9%) or in combination with heart disease (26.6%).

Except for ‘history of coronary artery disease’ (OR 2.5; $p = 0.06$), all of the 6 cardiac conditions (a–f) were significantly associated with an increased odds of NT-proBNP >100 pg/ml in the fully adjusted model, and the ORs were as follows: atrial fibrillation (90.2, 95% CI 5.6

Fig. 1. The relative frequency of heart disease among the study population stratified by age. The black portion of each bar represents the frequency of patients with impaired left ventricular systolic function.

Fig. 2. The density functions of NT-proBNP for patients with and without heart disease. The NT-proBNP values are plotted on a logarithmic scale. **a** All patients: $n = 583$. Patients without heart disease: $n = 330$. Patients with heart disease: $n = 253$. **b** Patients with-

out heart disease ($n = 63$) and both of the following conditions: CRP above the median value (>4.30 mg/l) and BMI below the median value (<27.0). Patients with heart disease ($n = 56$) and both CRP below the median value and BMI above the median value.

to $>1,000$), valvular heart disease (20.8, 95% CI 1.1–405.3), pulmonary hypertension (7.6, 95% CI 2.7–21.9), impaired left ventricular systolic function (4.3, 95% CI 1.2–15.8), and left ventricular hypertrophy (3.0, 95% CI 1.4–6.5). Minor echocardiographic findings were also associated with an increased odds of NT-proBNP >100 pg/ml (2.0, 95% CI 1.2–3.4). The following extracardiac covariates were related with an increased odds of NT-proBNP >100 pg/ml: female sex, higher $\ln(\text{CRP})$, lower BMI, and older age.

The multiple regression models yielded similar results. Based on the standardized regression coefficient (β), atrial fibrillation had the greatest impact on $\ln(\text{NT-proBNP})$ in the fully adjusted model ($\beta = 0.386$), followed by (2) pulmonary hypertension ($\beta = 0.178$), (3) valvular heart disease ($\beta = 0.165$), (4) impaired left ventricular systolic function ($\beta = 0.136$), (5) coronary artery disease ($\beta = 0.071$; $p = 0.02$), and (6) left ventricular hypertrophy ($\beta = 0.002$; $p = 0.93$). Minor echocardiographic findings ($\beta = 0.029$; $p = 0.35$) were not correlated with increased NT-proBNP. The following extracardiac covariates were associated with higher NT-proBNP: higher $\ln(\text{CRP})$ ($\beta = 0.157$), lower BMI ($\beta = 0.149$), lower eGFR ($\beta = 0.145$), older age ($\beta = 0.103$), and female sex ($\beta = 0.067$; $p = 0.03$). The multiple linear regression models suggested that an increase in $\ln(\text{CRP})$ from the median value of the lowest

quartile $\ln(1.1$ mg/l) to the median value of the highest quartile $\ln(26.20$ mg/l) increased the $\ln(\text{NT-proBNP})$ level 0.61 times as much as ‘impaired left ventricular systolic function’. Moving from the median values of the highest quartiles to the median values of the lowest quartiles for BMI (33.6 vs. 21.9) and eGFR (109 vs. 54 ml/min/1.73 m^2) increased $\ln(\text{NT-proBNP})$ 0.46 and 0.57 times as much as ‘impaired left ventricular function’, respectively. This factor rose to 2.01 when these changes in CRP, BMI, and eGFR occurred at the same time.

Overall, 88.5% of patients with any type of heart disease and 91.4% of patients with impaired left ventricular systolic function exhibited NT-proBNP >100 pg/ml. Figure 2 depicts the estimated density function of NT-proBNP for patients with and without heart disease.

The characteristics of the composite test are presented in table 2. More inclusive definitions of heart disease increased its positive predictive value from 0.32 to 0.58. The negative predictive value decreased to 0.89.

Discussion

The results of this study show that the measurement of serum NT-proBNP, in addition to a history of coronary artery disease or the presence of atrial fibrillation, helps

Table 2. Test characteristics of NT-proBNP for the diagnosis of heart disease in addition to patient history and ECG

Cardiac condition	Basic test prevalence	Composite test	
		sensitivity/ specificity	positive/negative predictive value
History of coronary disease or atrial fibrillation	1.00	1.00/0.40	0.32/1.00
History of coronary disease or atrial fibrillation or (1) impaired left ventricular systolic function	0.89	0.98/0.41	0.35/0.98
History of coronary disease or atrial fibrillation or (1) impaired left ventricular systolic function or (2) significant valvular disease	0.76	0.98/0.44	0.41/0.98
History of coronary disease or atrial fibrillation or (1) impaired left ventricular systolic function or (2) significant valvular disease or (3) pulmonary hypertension	0.59	0.97/0.48	0.52/0.96
History of coronary disease or atrial fibrillation or (1) impaired left ventricular systolic function or (2) significant valvular disease or (3) pulmonary hypertension or (4) left ventricular hypertrophy	0.50	0.92/0.50	0.58/0.89
History of coronary disease or atrial fibrillation or (1) impaired left ventricular systolic function or (2) significant valvular disease or (3) pulmonary hypertension or (4) left ventricular hypertrophy or (5) ≥ 1 minor echocardiographic finding	0.33	0.83/0.59	0.79/0.65

Prevalence: proportion of patients with a history of coronary artery disease or an ECG diagnosis of atrial fibrillation among the cohorts listed in the first column of the table. Positive composite test: (a) a history of coronary artery disease or an ECG diagnosis of atrial fibrillation, or (b) an NT-proBNP level >100 pg/ml.

to recognize heart disease in cancer patients if a fixed cut-off value of 100 pg/ml is used. In this setting, NT-proBNP will identify a specific cardiac condition only if that condition is associated with the binary outcome of NT-proBNP >100 pg/ml. The finding that NT-proBNP, evaluated both as a binary and continuous variable, is elevated not only in patients with impaired left ventricular systolic function but also in other types of heart disease is consistent with the results of previous studies.

Among the 6 cardiac conditions studied, atrial fibrillation exerted the greatest impact on NT-proBNP. This strong relationship is of little clinical value because most oncologists consider the patient's resting ECG before ordering additional tests. Cancer patients who exhibit symptoms suggestive of heart disease and atrial fibrillation and whose cardiac status has not yet been fully determined should be referred to cardiology for evaluation; laboratory tests play no role in the detection of atrial fibrillation. The same applies to patients with documented

coronary artery disease. Therefore, the lack of effect of a history of coronary artery disease on the odds for NT-proBNP >100 pg/ml is not a limitation to its value as a diagnostic test. The measurement of NT-proBNP should not be used as a test in its own right but as an adjunct to the patient history and the ECG.

Although the diagnostic value of the left ventricular ejection fraction is limited, many cardio-oncology studies revolve around this parameter [16–18]. Therefore, we rearranged the order of the cardiac conditions (a–f) derived from univariate logistic regression or multiple linear regression. We placed the item 'impaired left ventricular function' above 'valvular disease' and 'pulmonary hypertension' when calculating the characteristics of the composite test presented in table 2. This order is not intended to grade the severity of heart disease. For instance, left ventricular hypertrophy should not be dismissed as a minor condition. Recognizing left ventricular hypertrophy is relevant to oncologists because arterial hypertension is

Table 3. Impact of extracardiac determinants on the characteristics of the composite test for the diagnosis of any type of heart disease

All patients (n = 583)	Sensitivity 0.92	Specificity 0.50
Following the sequential exclusion of patients with:		
a CRP level (>11.50 mg/l) in the highest quartile (n = 439)	0.89	0.52
a BMI (<24.1) in the lowest quartile (n = 342)	0.88	0.60
female sex (n = 190)	0.84	0.62
age (>75.7 years) in the highest quartile (n = 139)	0.78	0.69

The numbers in parentheses denote the numbers of patients who remained in the study group following the sequential exclusion of patients based on CRP levels, BMI, sex, and age. Positive test result: (a) a history of coronary artery disease or an ECG diagnosis of atrial fibrillation, or (b) an NT-proBNP level >100 pg/ml.

highly prevalent among cancer patients and is associated with increased cardiovascular risk [19–22]. In this study, the presence of left ventricular hypertrophy was associated with NT-proBNP >100 pg/ml.

Heart disease was so uncommon among cancer patients younger than 45 years of age that the measurement of NT-proBNP would hardly ever be useful for this group, as illustrated in figure 1. By contrast, heart disease was highly prevalent among patients who had undergone pre-1995 radiotherapy of the chest. The measurement of NT-proBNP will not significantly alter the high pretest probability of the disease; and a direct move from clinical judgment to an in-depth evaluation by cardiology is mandatory in this cohort. The prevalence of heart disease was 43.1% among patients older than 45 who had not undergone pre-1995 radiotherapy. Diagnostic tests are most valuable in patients with this intermediate probability of disease. A sensitivity of at least 0.90 entails an acceptably low risk of overlooking heart disease, which is fundamental to a test for heart disease in cancer patients. Table 2 shows that NT-proBNP performs well in terms of sensitivity at a cutoff value of 100 pg/ml. Because NT-proBNP is a global marker of heart disease, the specificity will be low for only one type of disease. This low specificity does not limit its value for oncologists, who are not concerned with identifying specific conditions. In particular, oncologists should not focus on left ventricular systolic function when assessing the cardiotoxicities of various cancer therapies. Impaired left ventricular systolic function secondary to cancer treatment is a rare finding, even following either anthracycline-based chemotherapy or pre-1995 radiotherapy of the chest, as shown in table 1. Cardiotoxicity often manifests in other ways [23–26]. In the current study, the specificity of the composite test did not

exceed 0.50, even following the inclusion of the whole array of heart diseases. Therefore, measuring NT-proBNP falls short of the demands for specificity that a test for heart disease should satisfy.

The following factors contributed to the low specificity. First, the presence of minor echocardiographic findings was associated with NT-proBNP >100 pg/ml. Including minor echocardiographic findings in the criteria for diagnosing heart disease would increase specificity at the expense of sensitivity, as shown in table 2. Second, some cancer therapies may increase the odds for NT-proBNP >100 pg/ml on the grounds of minor myocardial injuries, which are not accounted for by the 6 cardiac conditions (a–f). In line with this assumption is our finding that anthracycline-treated patients have higher adjusted values for ln(NT-proBNP) compared to a control group with no previous chemotherapy but no increased odds of heart disease [12]. Third, systemic inflammation and low body weight are common among cancer patients. Both of these conditions were associated with NT-proBNP >100 pg/ml. The sequential exclusion of patients exhibiting values for CRP in the highest and BMI in the lowest quartiles steadily increased the specificity from 0.50 to 0.60, as demonstrated in table 3. The limitations of a fixed NT-proBNP cutoff value also become clear by separately analyzing the 48 patients who were assigned to the highest quartile for CRP (>11.50 mg/l) and the lowest quartile for BMI (<24.1). NT-proBNP exceeded 100 pg/ml in 13 out of the 20 patients without heart disease. Thus, NT-proBNP would be only 35% specific for heart disease and diagnostically useless in this group. An unexpected finding was that anemia was not related to NT-proBNP levels above this threshold. Age- and sex-specific cutoff values for NT-proBNP were established to distinguish be-

tween cardiac and pulmonary dyspnea in the general population [27]. The additional application of CRP- and BMI-specific cutoff values to individual cancer patients would make the use of NT-proBNP rather unwieldy.

An interesting question is how many of the diagnostically false-positive test results were physiologically true positive in patients with systemic inflammation. The principal trigger of proBNP release is myocardial wall stress. The increased cardiac output demands observed in the setting of systemic inflammation places excess stress on the heart, which may be reflected in increased NT-proBNP, even in the absence of structural heart disease. We have previously demonstrated in patients with chronic dyspnea that CRP levels in the highest quartile (>5.80 mg/l, median value 10.90 mg/l) are associated with increased NT-proBNP [28]. The grade of systemic inflammation was higher in the current study, as 40.9% of the whole study group and 61.3% of the patients with active disease had CRP >5.80 mg/l. Ongoing cardiac stress in a proinflammatory environment may be the main reason why NT-proBNP performs less well in terms of specificity as a test for structural heart disease in patients with cancer than in groups with less systemic inflammation if a cutoff value of 100 pg/ml is used [6].

Medical decision making usually focuses on cutoff values, but NT-proBNP is a continuous variable, and the probability of heart disease increases with rising NT-proBNP. High values of NT-proBNP might thus help the oncologist to rule in heart disease. However, the density distribution curves of NT-proBNP presented in figure 2 show a large area of overlap between patients with and without heart disease. Figure 2 also illustrates the impact of the extracardiac determinants on the density distribution curves of NT-proBNP. The curve of the patients without heart disease and both CRP above the median value and BMI below the median value nearly superimposes the curve of the patients with heart disease in whom CRP was below the median and BMI was above the median.

These considerations are relevant to the utility of serial NT-proBNP measurements before and after anticancer therapy in the detection of cardiotoxicity. Chemotherapy may cause systemic inflammation, weight loss, and a deterioration in renal function, all of which are associated with increased NT-proBNP. The linear regression models carry two implications. First, caution should be exercised when interpreting a rise in NT-proBNP as evidence of cardiotoxicity in the presence of systemic inflammation, weight loss, or impaired renal function following chemotherapy; second, diagnostically false-positive

test results are common when oncologists use a rise in NT-proBNP as a criterion for referring a postchemotherapy patient with newly developed systemic inflammation, deterioration in renal function, or weight loss to a cardiologist.

This single-center study has limitations. First, the prevalence of coronary artery disease was underestimated because the diagnosis was only based on patient history. A definitive diagnosis of this condition requires confirmation via coronary angiography, but this study could not have been completed were invasive techniques utilized in all patients. Exercise testing could not be routinely performed to detect myocardial ischemia because many of the patients were either unable to exercise or had to discontinue exercising due to fatigue or lung-related dyspnea, which would further decrease the limited sensitivity of ergometry. Second, we did not include parameters related to diastolic left ventricular function in the analysis because tissue Doppler imaging was not available to us before 2008. The assessment of transmitral flow curves via Doppler echocardiography should not be used to diagnose diastolic dysfunction [29]. This limitation contributed to the low test specificity. Many of our patients with left ventricular hypertrophy, atrial fibrillation, pulmonary hypertension, or valvular heart disease probably had left ventricular diastolic dysfunction; therefore, not all patients with that condition were overlooked.

Natriuretic peptides are valuable in both the diagnosis and management of heart failure, and they have the ability to identify, among patients with dyspnea, those with cardiac dyspnea. Because of its low specificity, however, we do not recommend the use of NT-proBNP for identifying or monitoring heart disease in patients with either a history of cancer or active cancer.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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