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Serum BNP levels are associated with malignant pericardial effusion

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ABSTRACT

Introduction: The development of malignant pericardial effusion indicates a poor prognosis and is the leading cause of cardiac tamponade. The objectives of the study were to examine the levels of BNP in traumatic, malignant and non-malignant pericardial effusion etiologies, and to assess the value of serum and pericardial fluid BNP levels in the prognosis of malignant pericardial effusion.

Methods: A of 56 patients with clinical and echocardiographic diagnosis of pre-tamponade or tamponade who required pericardiocentesis were included in the study. BNP levels were assessed in the serum and within the pericardial fluid. The diagnostic value of BNP levels in discriminating between malignant and non- malignant etiology of pericardial effusion was examined using a receiver-operating characteristic (ROC).

Results: Pericardial fluid BNP levels were similar across all etiology groups. In patients with malignant etiology, the amount of pericardial fluid was high and their serum BNP levels were relatively low. BNP levels were strong predictors of malignant pericardial effusion, and the cut-off point of BNP ≤ 250 pg/ml demonstrated the highest sensitivity (90.0%) for malignant etiology.

Conclusions: Low serum BNP levels were significantly associated with malignancy in patients undergoing pericardiocentesis for pericardial effusions. Serum BNP levels <250 pg/ml may trigger more extensive diagnostic testing for malignant pericardial effusion in patients with small pericardial effusion who are not considered for pericardiocentesis due to small effusion, in whom the etiology is unclear.

1. Introduction

Etiologies of pericardial effusion include cancer, connective tissue diseases, metabolic causes, aortic diseases, infections, pericardial injury and trauma [1–3]. This condition can lead to acute complications such as cardiac tamponade, a life-threatening emergency or can lead to chronic complications such as constrictive pericarditis [4].

In patients with pericardial effusions, B-type natriuretic peptide (BNP), a cardiac neurohormone and a member of natriuretic peptide (NP) family which is secreted from the cardiac ventricles in response to stretch [5], was reported to be a useful marker to assess disease severity [6] and disease progression [7]. However, conflicting reports exist regarding the association between serum BNP levels and pericardial fluid accumulations. Several studies have reported that BNP levels in pericardial fluid accumulation were elevated [8,9]. In contrast, other studies have documented that in large pericardial effusion [10] or cardiac tamponade [11], plasma BNP levels were relatively suppressed, while after pericardiocentesis, plasma BNP levels increased markedly. These observations were suggested to reflect the physically compressed and decompressed cardiac chambers respectively. Another study reported no change in plasma BNP levels after pericardiocentesis [12]. These studies have included patients with different etiologies, including malignant and non-malignant pericardial effusion, and therefore have possibly conflicting results.

Malignant pericardial effusion is a common and serious manifestation [13] reported in >10% to 40% of cases [3,14]. The development of malignant pericardial effusion indicates a poor prognosis and is the leading cause of cardiac tamponade [14,15]. Therefore, early diagnosis of malignant pericardial effusion is important in order to provide timely treatment. This condition poses a complex challenge to the clinicians who need to determine the cause of pericardial effusion and to develop strategies for the relief of symptoms and for prevention of recurrences [16]. To date, to the best of our knowledge, no study has assessed whether serum or pericardial fluid BNP levels can predict malignant pericardial effusion etiology. Therefore, the objectives of the study were to examine and compare the levels of BNP in different groups of etiologies, including traumatic, malignant and non-malignant pericardial effusion, and to assess the value of serum and pericardial fluid BNP levels in the prognosis of malignant pericardial effusion.

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Table 1
Patients' characteristics, pericardial fluid biomarkers and echocardiography variables in the traumatic, malignancy, and non-malignant etiology groups.

	Traumatic etiology (n = 10)	Malignant etiology (n = 20)	Non-malignant etiology (n = 26)	P-value
Patients' characteristics				
Age (yr)	71.6 ± 10.3	62.2 ± 17.1	62.2 ± 19.9	0.24
Admission HR (beat/min)	74.88 ± 15.5	89.0 ± 21.0	86.6 ± 25.1	0.248
Aspirin % (n)	40.0% (n = 4)	40.0% (n = 8)	34.6% (n = 9)	–
Plavix % (n)	0.0% (n = 0)	5.0% (n = 1)	11.5% (n = 3)	–
Ticagrelor % (n)	30.0% (n = 3)	0.0% (n = 0)	0.0% (n = 0)	–
Fluid biomarkers				
BNP (pg/ml)	2180.4 ± 1576.2	2107.6 ± 1343.7	2353.6 ± 1636.6	0.85
PH	7.36 ± 0.05	7.42 ± 0.06	7.34 ± 0.14	0.07
PMN (μL/1000)	84.2 ± 3.2	44.2 ± 20.8	46.3 ± 24.0[b]	0.03[a], 0.04[c]
RBC (10e6/μL)	1,663,667 ± 2,291,401.3	176,000.0 ± 224,566.2	25,666.67 ± 22,052.9	0.20
LDH (U/l)	658.8 ± 758.6	871.6 ± 562.7	1171.3 ± 1223.5	0.35
Glucose (mg/dl)	112.5 ± 39.2	126.4 ± 42.8	106.8 ± 49.7	0.36
Protein (g/dl)	5.2 ± 1.31	5.1 ± 1.3	4.8 ± 1.4	0.76
Albumin (g/dl)	3.0 ± 0.8	2.6 ± 0.8	2.3 ± 0.6	0.12
Echocardiography variables				
LVEF (%)	58.1 ± 7.6	60.1 ± 8.2	60.1 ± 9.4	0.80
LVEDD (mm)	49.4 ± 7.4	50.2 ± 5.7	49.5 ± 4.8	0.90
LVESD (mm)	33.8 ± 5.6	34.6 ± 4.9	33.4 ± 4.8	0.74
LADs (mm)	40.4 ± 7.0	39.7 ± 6.6	41.0 ± 5.6	0.78
TRPG (mm Hg)	25.9 ± 6.7	25.5 ± 7.5	28.4 ± 11.2	0.53
IVC (mm)	10.5 ± 6.4	11.0 ± 5.2	12.5 ± 5.3	0.52
RVSP (mm Hg)	36.4 ± 7.2	36.5 ± 8.7	41.1 ± 12.8	0.26

HR, heart rate; oxygen saturation; NOAC, BNP, B-type natriuretic peptide; WBC, white blood cells; PMN, polymorphonuclear leukocytes; RBC, red blood cell count; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LADs, left atrial systolic diameter; TRPG, tricuspid regurgitation pressure gradient; IVC, inferior vena cava collapse, RVSP, right ventricular systolic pressure.
[a] Significant differences between malignant and traumatic etiology groups.
[b] Significant differences between malignant and non-malignant etiology groups.
[c] Significant differences between traumatic and non-malignant etiology groups.

2. Methods

2.1. Patients

A total of a consecutive, unselected cohort of 56 patients with clinical and echocardiographic diagnosis of pre-tamponade or tamponade who required pericardiocentesis were recruited successively between February 2014 and December 2017. The study complied with the ethical guidelines of the Declaration of Helsinki and the study was reviewed and approved by the Poriya Medical Center's Ethical Review Board. Eligible patients were recruited from the cardiovascular department of Poriya Medical Center. Patients' medical history records were obtained and clinical assessments were performed. Diagnosis of pre-tamponade/tamponade was determined by clinical and echocardiographic assessment and the patients were grouped based on etiology into the following groups: traumatic (interventional procedures), malignant, and non-malignant etiologies (pericarditis, cardiotomy, and renal failure). The traumatic etiology in our cohort included the following interventional procedures: percutaneous coronary intervention, pacemaker/implantable cardioverter defibrillator implantation, and arrhythmia ablation.

2.2. Serum and pericardial BNP levels

Blood samples were obtained prior to pericardiocentesis procedure for assessment of serum BNP levels. Pericardial fluid was collected for BNP analysis during pericardiocentesis procedure. Serum and pericardial fluid samples were collected in chilled tubes containing ethylendiaminetetraacetic acid (EDTA). The samples were centrifuged at 2056*g* for 15 min at 4 °C and the plasma was stored at −80 °C until analysis. Quantitative assessment of serum and fluid BNP were measured using a BNP chemiluminescent microparticle immunoassay, and samples were analyzed on an Abbott ARCHITECT analyser (Abbott Diagnostics Division, Malvern, PA, USA).

2.3. Echocardiography assessment

A standard two-dimensional and Doppler A transthoracic echocardiogram (TTE) assessment was performed, using one of 3 commercially available systems (Vivid 7, E9 and I, GE Medical systems, Milwaukee, WI). Presence of small to large pericardial effusion with evidence right ventricular collapse was considered as tamponade. Presence of a moderate to large pericardial effusion with evidence of respiratory ventricular interdependence (by MMODE or mitral inflow early diastolic velocities), right atrial collapse, enlarged and non-collapsing inferior vena cava was considered as pre-tamponade [17].

2.4. Statistical analysis

Data were statistically analyzed with SPSS 14.0 software (SPSS Inc., Chicago, Illinois, USA) and the MedCalc 7.2.1.0 package (MedCalc Software, Mariakerke, Belgium). Differences among traumatic, malignant, and non-malignant etiology groups were compered. Clinical, echocardiographic, serum and fluid data were compared, using analysis of variance (ANOVA) with post-hoc Scheffé tests to examine the differences among the groups. For data sets that were not normally distributed, the Kruskal-Wallis analysis followed by the Mann-Whitney test with Bonferroni correction was performed to assess the differences. The differences between the levels of BNP in patients with inferior vena cava (IVC) ≤10 and IVC >10 were compared, using

Fig. 1. Panel a. Serum BNP levels in traumatic, malignant and non-malignant etiology groups; Panel b. Pericardial fluid BNP levels in traumatic, malignant and non-malignant etiology groups. Panel c. Pericardial fluid amount in traumatic, malignant and non-malignant etiology groups. Box plots showing median levels of BNP measured in the three groups of patients. The top and bottom borders of the box mark the 75th and 25th percentiles, respectively; whiskers mark the 90th and 10th percentiles. A circle represents extreme outliers beyond the 90th and 10th percentiles; horizontal line indicates the median.

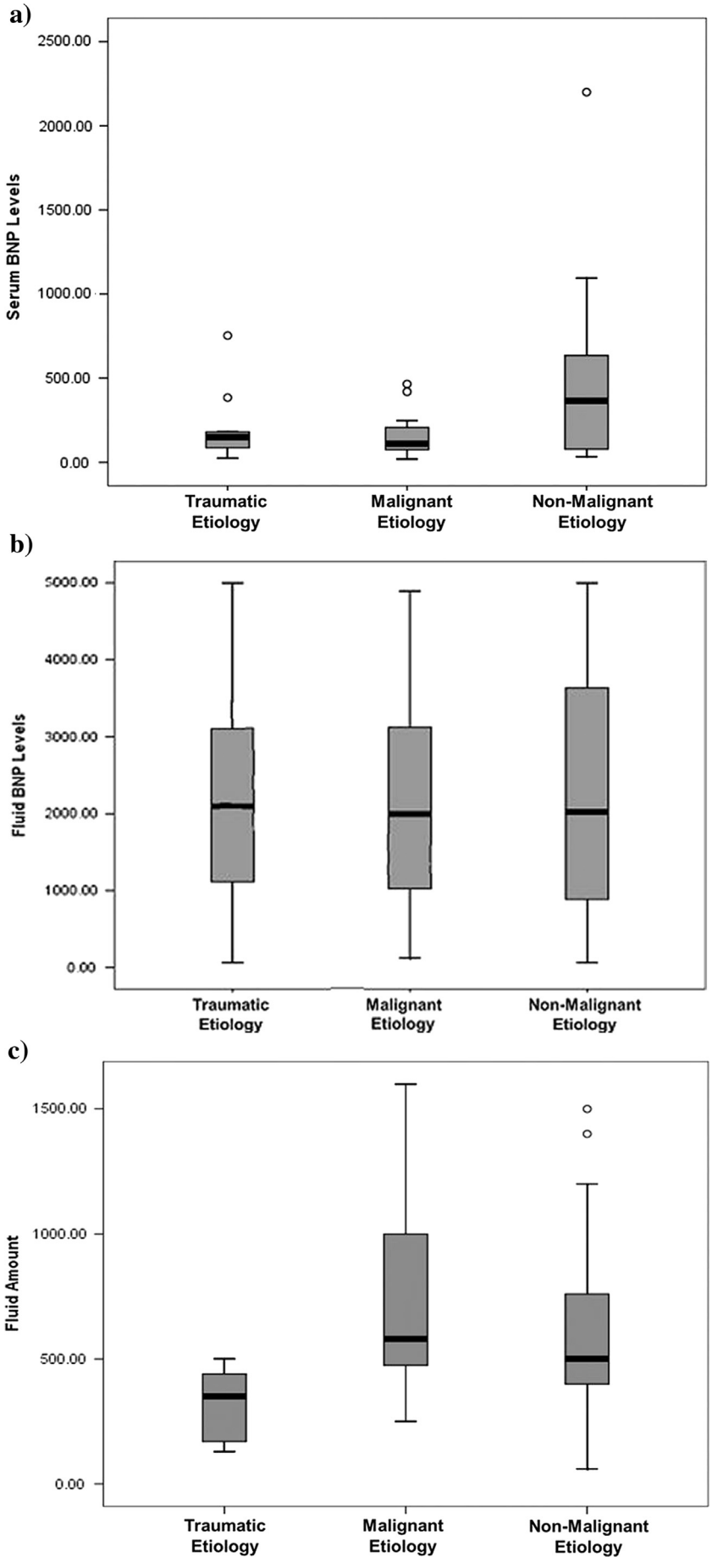
a)
Serum BNP Levels
2500.00
2000.00
1500.00
1000.00
500.00
0.00
Traumatic Etiology
Malignant Etiology
Non-Malignant Etiology
b)
Fluid BNP Levels
5000.00
4000.00
3000.00
2000.00
1000.00
0.00
Traumatic Etiology
Malignant Etiology
Non-Malignant Etiology
c)
Fluid Amount
1500.00
1000.00
500.00
0.00
Traumatic Etiology
Malignant Etiology
Non-Malignant Etiology

Table 2
Multiple logistic-regression analysis of factors used in a predication model of patients with and without pericardial effusion with malignant etiologies.

Predicator	P-value	Odds ratio	(95% CI)
Fluid amount	0.07	1.002	1.000–1.004
IVC	0.37	1.890	0.462–7.728
Serum BNP	0.01*	0.995	0.991–0.999

The odds ratio reflects the odds for patients with pericardial effusion with malignant etiologies. The odds ratio for age represents the exponent for each year of age in the logistic equation. CI denotes confidence interval. IVC, inferior vena cava collapse, BP, blood pressure; BNP, B-type natriuretic peptide.
* $p \leq 0.001$.

the Mann-Whitney test. The Spearman's rank correlation coefficient was performed to assess the relationships between serum and fluid BNP levels and LV dimensions and functions.

In the malignant, and non-malignant etiology groups, in order to determine a combination of the independent variables to predict malignant etiology of pericardial effusion, we used multiple logistic regressions. The predictors included in the model were IVC (≤10 or >10), fluid amount, and BNP levels. We evaluated the contribution of the independent variables to predict malignant and non- malignant etiology of pericardial effusion. The diagnostic value of BNP levels in discriminating between malignant and non-malignant etiology of non-traumatic pericardial effusion was examined by computing sensitivity and specificity, calculating the Youden index to extract the optimal BNP cut-off level and plotting a receiver-operating characteristic (ROC) and area under the curve (AUC) to assess its diagnostic performances. A p-value of <0.05 was considered significant. A p-value of <0.05 was considered significant.

3. Results

All patients had a confirmed diagnosis of pericardial effusion, including traumatic etiologies. In the malignant etiology group, 8 had hematologic, 6 lung, 1 pancreas, 1 renal, and 4 mediastinal mass. In traumatic etiology group, 2 patients underwent ablation, 4 pacemaker implantation, and 4 percutaneous coronary intervention. Patients' characteristics, pericardial fluid biomarkers and echocardiography variables are presented in Table 1. Patients' characteristics did not significantly differ among the group. There were no differences in the biomarkers in the blood serum or in pericardial fluid and echocardiography assessment variables among the groups, except for polymorphonuclear leukocytes (PMN).

Serum BNP (pg/ml) levels were significantly lower in the malignant group compared with the non-malignant etiology group, (110.3 [IQR, 73.8–208.4] vs 366.3 [IQR, 78.1–656.5]) $p = 0.03$), Fig. 1a. The levels of Serum BNP (pg/ml) did not significantly differ between malignant and traumatic groups (110.3 [IQR, 73.8–208.4] vs. 150.2 [IQR 75.2–282.3], respectively). Levels of fluid BNP (pg/ml) were not significantly different among groups, with 2094.0 (IQR, 1056.8–3520.3) in the traumatic group, 1993.2 (IQR, 902.3–3253.0) in the malignancy group, and 2019.8 (IQR, 854.1–3675) in the non-malignant group (Fig. 1b). Pericardial fluid amount (ml) was significantly lower in the traumatic group (350.0 ml [IQR, 170.0–455.0]), than in both the malignant (580.0 ml [IQR, 462.5–1000]) and non-malignant etiology (500.0 ml [IQR, 395.0–765.0]) groups (Fig. 1c). The amount of pericardial fluid was not significantly different between the malignant and non-malignant etiology groups. The amount of pericardial fluid (ml) was not significantly correlated with serum and fluid BNP levels.

Fluid pericardial BNP or serum BNP levels were not correlated with LV dimensions and function, while BNP levels in the serum were negatively moderately correlated with EF ($r = -0.43$, $p = 0.001$), but not with left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD). Results of a multivariable logistic regression indicated that there are no significant associations between fluid amount and IVC (Table 2). Low serum BNP levels predict malignant pericardial effusion, when controlling for fluid amount, and IVC. A cutoff of BNP ≤ 250 pg/ml was found to have the highest sensitivity (90.0%) and specificity (53%) with an AUC = 0.67, $p < 0.03$ for malignant etiology in non-traumatic pericardial effusion (Fig. 2).

4. Discussion

The major findings of our study are that serum BNP levels predict malignant pericardial effusion, and the cut-off point of BNP ≤ 250 pg/ml demonstrated the highest sensitivity (90.0%) for malignant etiology. This observation is important because the first challenge for clinicians in the management of pericardial effusion is to try to establish an etiologic

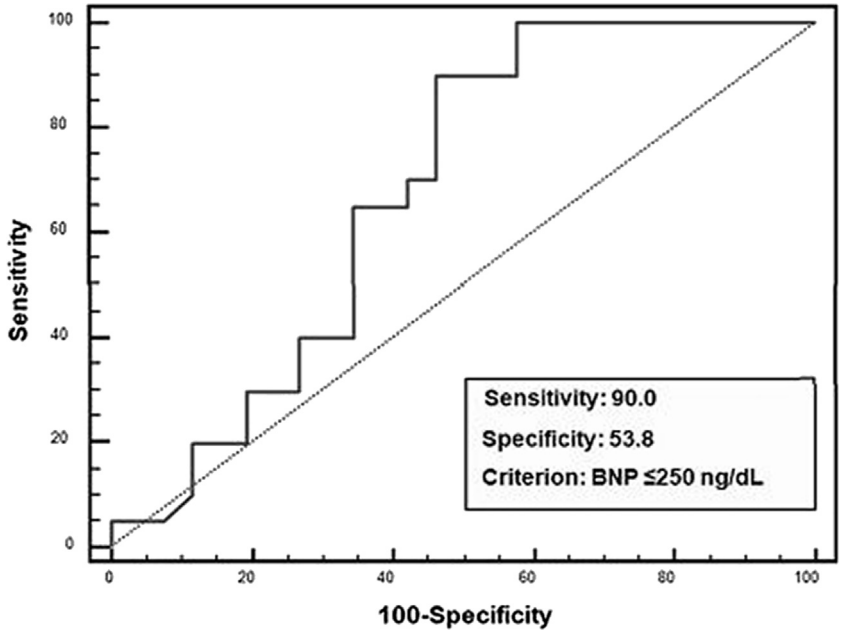

Fig. 2. ROC curves for BNP, differentiating between Malignant and Non-Malignant pericardial effusion.

diagnosis [18]. Moreover, while acute traumatic pericardial effusion induced by interventional procedures [1,2] are obvious with known underlying cause, chronic pericardial effusion with malignant and non-malignant etiologies are much more challenging to diagnose. This is due to the fact that chronic pericardial effusion has a wide variety of etiologies [3], making it more difficult to diagnose. Therefore, a serum test is informative and simple to perform, and can potentially complement diagnostic imaging and increase diagnostic accuracy in a short time period.

In the traumatic group, serum BNP levels were low and the amount of fluid was relatively low. In fact, in wounds or iatrogenic perforations, pericardial fluid accumulates quickly and is accompanied by marked evolution, with only small amounts of blood, which is responsible for a quick rise in intra-pericardial pressure and overt cardiac tamponade, which can occur within minutes [3]. On the contrary, in chronic conditions, pericardial fluid accumulates slowly, allowing the collection of a large effusion over days or weeks before the significant increase in pericardial pressure is responsible for symptoms [19]. Similarly, we found that the 2 chronic groups, malignant and non-malignant pericardial effusion etiologies, had a significantly higher amount of pericardial fluid compared to the traumatic group.

Our study findings did not support the traditional theory that BNP production is suppressed by the constraining effects of the pericardial fluid and reduced ventricular stretching [10]. The traditional explanation for the association between low serum BNP levels in patients with pericardial effusion is based on the hemodynamic mechanism, in which NP surge is related to the physical stretch of the relevant cardiac chambers [20], whereas the opposite effect occurs in pericardial effusion with compression, and therefore, lower BNP levels are expected. However, in our study, fluid BNP levels were not significantly different among the different etiology groups, whereas serum BNP levels were significantly low in the traumatic and malignancy groups compared to the non-malignancy group. It is also important to note that in traumatic pericardial group, because of a percutaneous procedure complication, blood enters the pericardium and therefore BNP levels of the fluid are expected to be similar to the levels in the plasma. In addition, in the traumatic pericardial effusion, low serum BNP levels are expected as a result of the rapid inward compression of the cardiac chambers, with even small accumulation of fluid. In contrast, in the malignancy group, the amount of pericardial fluid was high, whereas serum BNP levels were relatively low, and in the non-malignancy group, both the amount of fluid and serum BNP were high. Thus, the hemodynamic explanation may not be the sole mechanism for the low BNP levels in pericardial effusion. Furthermore, the amount of pericardial fluid was not significantly associated with the levels of BNP in the serum or in the pericardial fluid and IVC diameter in patients with confirmed pericardial effusion. These findings suggest that the mechanisms responsible for low BNP levels in the serum are not related to reduced physical pressure exerted by the accumulation of fluid in the pericardium, but are probably related to systemic factors.

The mechanisms for discrepancy between fluid and blood BNP levels are not clear. An explanation for the low systemic serum BNP levels in the malignant etiology group may be related to systemic degradation of BNP. Neprilysin, the enzyme responsible for the degradation of many substances, including BNP, was shown to be over-expressed in cancer patients [21,22], and as such may potentially explain the relation between malignant pericardial effusions and systemic low BNP serum levels [23]. It is also possible that most of the BNP that is produced remains within the pericardium and therefore its level in the serum does not reflect those measured in the pericardial fluid. On the other hand, the increased serum BNP in the non-malignant group may be related to inflammation. Studies have shown that inflammation increases plasma BNP levels [24,25] without left ventricular abnormalities [25]. Future studies should address the mechanisms for the differences in BNP levels in different etiologies.

We demonstrated that although pericardial BNP levels were similar across all etiology groups, the serum BNP levels were low in the malignant etiology group. However, previous studies have reported that pericardial BNP levels are more sensitive and accurate indicators of left ventricular dysfunction than plasma BNP levels [26,27]. Furthermore, we observed that in patients with pericardial effusion, only serum BNP levels were negatively correlated with LV functions, but not with dimensions, whereas fluid BNP levels were not significantly associated with either ventricular functions or dimensions. In contrast, a previous study found that plasma and pericardial fluid BNP levels are significantly associated with left ventricular end-diastolic index (LVEDVI) as well as systolic volume index (LVESVI) [26]. Future studies should investigate the mechanisms responsible for the differences between fluid and serum BNP levels in malignant and non-malignant etiology and their relationship to the severity of pericardial effusion.

Previous studies reported conflicting findings regarding serum BNP levels in patients with pericardial effusion, with some studies reporting an increase [8,9], whereas others reported a decrease [10,11]. The differences in BNP levels were probably due to different pericardial effusion etiologies. These studies included heterogeneous patient populations with different pericardial effusion etiologies, including bacterial/tuberculosis, pulmonary adenocarcinoma, hypothyroidism, rheumatologic condition, uremic, rheumatoid arthritis, autoimmune diseases, sclerodermy - CREST syndrome, viral/idiopathy, infectious as well as itraogenic causes (such as post-cardiac surgery or interventional cardiology procedures) [8–11]. In our study, we grouped patients based on similar etiologies, traumatic, malignant, and non-malignant pericardial effusion. In fact, different types of malignant diseases have been reported to be implicated with pericardial effusion [11]. However, it is not completely clear what types of malignancy are associated with changes in BNP levels in patients with pericardial effusion. Our hypothesis-generating study warranted further investigation of the differences in BNP levels in patients with different types of malignancies in a larger cohort.

Another major limitation of the study is that we did not include subgroups of different interventional procedures, including ablation, pacemaker placement, and percutaneous coronary interventions, which may lead to iatrogenic pericardial effusion. Future studies should further investigate whether different interventional procedures, such as surgical and interventional cardiology procedures, differently affect BNP levels. Our study was conducted in a single center with a small sample size, and therefore future multicenter studies with larger cohorts should examine the usefulness of a serum BNP test in the diagnosis of pericardial effusion. In addition, we did not examine the diagnostic value of NT-proBNP, which has a longer half-life than BNP and higher plasma concentration [28]. NT-proBNP levels were found to be equally useful in the diagnosis of chronic heart failure as BNP [29], and perhaps may be relevant for the diagnosis of pericardial effusion with malignant etiology. Moreover, in this study, we did not measure the levels of serum or fluid atrial natriuretic peptide (ANP), which is produced by the atria in response to stretch. However, BNP has been shown to be a more sensitive biomarker in congestive heart failure than ANP [30]. Future studies should investigate whether NT-proBNP and ANP may be used in the diagnosis of malignant pericardial effusion.

In conclusion, we found that although fluid BNP levels were similar across all etiology groups, in patients with malignant etiology, the amount of pericardial fluid was highest and their serum BNP levels were relatively low. In addition, low serum BNP levels were significantly associated with malignancy in patients undergoing pericardiocentesis for pericardial effusions. Based on our results, serum BNP levels <250 pg/ml may trigger more extensive diagnostic testing for malignant pericardial effusion due to its high sensitivity. This could be especially relevant for patients with small pericardial effusion without hemodynamic compromised, who are not considered for pericardial drainage due to small effusion, in whom the etiology is unclear. Future research investigation should be conducted in patients with malignant pericardial effusion, especially in patient who may not need drainage.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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