Levels of NT-proBNP in patients with cancer

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Abstract. At present, it is well known that natriuretic peptides may be produced by cancer cells. Stimulation of N-terminal pro B-type natriuretic peptide (NT-proBNP) synthesis may be a reaction to activity of several proinflammatory cytokines. NT-proBNP is also a marker of myocardial damage during cardiotoxic chemotherapy by anthracyclines. The present study aimed to analyze the association between NT-proBNP and patient/disease characteristics in patients without cardiac symptoms. The present clinical study included 112 patients with cancer who were undergoing anticancer therapy between December 2017 and December 2021. From each patient, peripheral blood was obtained for detection of NT-proBNP before any therapy, after therapy and 1 year after the first sample. NT-proBNP was examined using an immunochemical method. The mean ± SEM value of NT-pro-BNP in the first, second and third sample was 561.0±75.1, 1,565.4±461.1 and 1,940.7±581.1 ng/l. A total of 15 (13.4%), 27 (24.1%) and 25 (30.1%) patients had elevated levels of NT-pro-BNP in the first, second and third sample above the normal value adjusted to age. It was observed that NT-proBNP was increased in older patients and in patients with progressive metastatic disease with poor prognosis. Patients with non-elevated NT-proBNP in the second and third sample had significantly improved OS compared with patients with elevated NT-proBNP [hazard ratio (HR), 0.47; 95% CI, 0.26-0.85; P=0.002 for the second sample; and HR, 0.29; 95% CI, 0.14-0.60; P=0.0000007, for the third sample]. The baseline NT-proBNP value was not prognostic for OS (HR, 0.98; 95% CI, 0.50-1.92; P=0.96). The present results suggest that the level of NT-proBNP was associated with the extent of oncologic disease. Higher levels were associated with progression of metastatic disease and shorter overall survival.

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Introduction

In cancer patients there are many mechanisms contributing to damage of cardiovascular system: breakdown of coagulation, anemia, exhaustion of organism, release of cardio-depressive factors such as cytokines, malignant pericarditis, direct interaction of tumor and heart or vascular system and anticancer therapy (1).

Natriuretic factors are peptic substances produced by atrial and ventricular myocardium. Primary stimulus to synthesis of this factor is intramural pressure of atriums by increasing of venous return during intravascular hypovolemia (2). Cardiac natriuretic peptides ANP (atrial natriuretic peptide), BNP (B type natriuretic peptide) and C-type natriuretic peptide (CNP) are known because of their compensation effects-systemic arterial vasodilatation, natriuresis, diuresis, inhibition of system renin-angiotensin-aldosteron and neuromodulation (3). BNP is secreted in a form of pro-hormone (pre-pro-BNP) (2). After stimulation of myocardial cells it is split into two fragments-BNP (biological active peptid) and inactive N-terminal fragment NT-proBNP. Concentration of BNP and NT-proBNP are equal in the healthy population. The measurement of NT-proBNP is considered advantageous compared to BNP due to longer biological halftime and higher biochemical stability. This is the reason, why NT-proBNP is biomarker examined in normal conditions (4). NT-proBNP is used mainly for diagnosis of heart failure. In addition, it may predict the development of heart failure and death in patients with cardiovascular disease. However, NT-proBNP could have predictive power beyond cardiovascular risk (5). These biomarkers are not exclusively produced by the heart but are produced by several organs in response or in association with cardiovascular diseases (6).

However, the interpretation of elevated NT-proBNP levels remains difficult because of several confounding factors, such coronary disease, advanced age, renal insufficiency, respiratory diseases such as pulmonary hypertension leading to right ventricular dysfunction, thromboembolic disease, atrial fibrillation, cirrhosis, sepsis, or dysthyroid status could be responsible for elevation of NT-proBNP (7).

At present, it is well known that natriuretic peptides may be produced by cancer cells, as well (8). In this regard, small cell lung cancer may secrete both pro-atrial natriuretic peptide and BNP. Also, BNP is expressed both in normal adrenal glands and in adrenal tumors, suggesting that natriuretic peptides may have other roles unrelated to the cardiovascular system (9). There are many studies which described the relationship

between an NT-proBNP, and the presence of inflammation with elevation C-reactive protein and IL-6 cytokine. These studies confirmed a significant correlation between IL-6, CRP and NT-proBNP (9,10).

A study of Sachico Bando showed a significant positive correlation between the NT-proBNP and the CRP levels in cancer patients, which suggested that the plasma BNP levels may have been elevated due to cancer related inflammation. In addition, the plasma BNP levels are increased in advanced stages of cancer, which might be accompanied by systemic inflammation. Furthermore, the plasma BNP levels tended to decrease after radical surgery in patients with solid cancers. Similarly, plasma BNP levels were shown to decrease after chemotherapy in patients with hematological cancers (3). BNP has been shown to be upregulated at the transcriptional and translational levels by proinflammatory cytokines in cardiac myocytes. Proinflammatory signals are postulated to stimulate members of the mitogen-activated protein kinase (MAPK) family and c-Jun kinase, as well as other intracellular signaling cascades, which leads to the upregulation of the BNP gene expression (3). ProBNP synthesis may be stimulated by several pro-inflammatory cytokines including tumor necrosis factor-alfa and several interleukins (11). However, the specific cause of elevation of natriuretic peptide plasma levels seen in cancer has not been elucidated. In recent years, it has been demonstrated that natriuretic peptides, or compounds with similar activity, decrease the number of several cancer cells *in vitro* through a reduction of DNA synthesis and inhibition of C-Fos and c-Jun proto-oncogenes, inhibit lung metastases and skin carcinogenesis in animal models, and diminish the expression of vascular endothelial growth factor and that of its receptor VEGFR2, thus having the potential to control vasculogenesis (12). A study by Tuňón *et al* (13) has shown the opposite effects of natriuretic peptides on carcinogenesis depending on their concentrations. In this paper, atrial natriuretic peptide enhanced proliferation of human gastric cells in vitro at low concentrations but inhibited their proliferation through cyclic guanosine 3-5-monophosphate-dependent pathways when it was present at high concentration (13). Then, given that most data suggest an anticancer effect of natriuretic peptides, the possibility exists that their production by cancer cells represents a negative feedback mechanism to control the tumor growth (5). In this case the NT-proBNP elevation would only be a response to the existence of malignancies. Nevertheless, the fact that natriuretic peptides are related with mechanism of cancer which are common to multiple malignancies would agree with these findings (14). Elevated levels of cardiovascular peptides including BNP/NT-proBNP was reported in patients with renal cell cancer in a study by Kamai *et al* (8). This study reported that higher preoperative serum levels of BNP, NT-proBNP and vascular endothelial growth factor (VEGF), were associated with worse performance status, local invasion, distant metastasis and shorter overall survival. Moreover, serum levels of BNP and NT-proBNP decreased significantly after tumor resection. This decrease might be associated with alleviation of stress on the heart (8). Serum measurement of NT-proBNP level in patient undergoing chemotherapy with anthracyclines is useful for both, acute and late toxicity. Measurement of Troponin I and Troponin T is useful for acute toxicity during the chemotherapy, but not for late toxicity 12 months after chemotherapy, when Troponin T and I is in normal range (15). A study by Mladosievicova *et al* (16) documented that higher level of NT-proBNP detected in childhood leukemia survivors after low anthracycline cumulative doses might reflect an initial stage of anthracycline cardiotoxicity before the development of echocardiographic abnormalities. NT-pro-BNP is one of the best available biochemical markers of late anthracycline cardiotoxicity (16). Study of Pudil *et al* (6) reports that cardiac biomarkers including cardiac troponins and natriuretic peptides are the most promising clinical tool for both baseline assessment and marker of early cardiac injury or strain which may predict subsequent changes in LVEF and development of HF in different cardiotoxic cancer therapies including anthracyclines, HER-2 antibodies (trastuzumab), VEGF TKIs and ICIs. Given the fulminant nature of ICI-related myocarditis, early detection is essential for the best possible treatment. Elevated troponin was found in 94% of all cases of ICI-related myocarditis, the diagnostic value of NT-proBNP was lower with 66% sensitivity (17).

In clinical practice NT-proBNP is useful in diagnosis of cardiovascular diseases, however, the false positivity in cancer patients is mostly unknown. Our study aimed to correlate NT-proBNP with patients/disease characteristics and patient's outcome in patients without cardiac symptoms.

Our primary mission was to examine the relationship between levels of NT-proBNP and the status of cancer disease. Specific aims are correlation of levels NT-proBNP with gravity of tumor, correlation of levels NT-proBNP with life expectancy, with clinicopathological variables.

Materials and methods

Patients. This clinical study included consecutive cancer patients that undergo treatment at the Department of Oncology of St. Jacob Hospital in Bardejov, between December 2017 and December 2021. Eligible were patients with solid tumor older than 18 years old, ECOG performance status 0,1 or 2, without symptoms of acute cardiac failure, acute respiratory failure, that were able to undergo an outpatient treatment and follow up. Eligible patients were all patients regardless of the status of their disease, including non-metastatic patients, metastatic patients with who were undergoing cancer therapy and achieved disease control (complete and partial remission and/or stable disease) or metastatic patients with disease progression.

All patients were thoroughly evaluated with complete medical history, physical examination, and laboratory and disease assessment. The study was approved by local ethic committee and all patients signed informed consent.

NT-pro-BNP measurement. From each patient we obtained peripheral blood for detection NT-proBNP before therapy, after the end of therapy and 1 year after the first sample. These samples were evaluated in a biochemical laboratory of St. Jacob Hospital by immunochemical method using ELESCYS proBNP reagent, with a COBAS e 411 ROCHE machine.

Level of NT-proBNP is age dependent. The cut-off value for cardiac failure exclusion is <450 ng/l when patients are under the age of 50, <900 ng/l for patients 50-75 years old and <1,800 for patients older than 75 years (18).

Statistical analysis. The patients' characteristics were summarized and tabulated using the median (range) for continuous variables and frequency (percentage) for categorical variables. For analysis of associations between categorical variables, Fisher's exact test was used. A Kruskal-Wallis test with Dunn's post hoc test was used for univariate analyses of associations between clinical characteristics and continuous variables. Patients were divided into two group dichotomized based NT-pro-BNP cut-off level adjusted to age (see above) ('low' vs. 'high'). Overall survival was calculated from the date of initial pro-BNP measurement to the date of death or last follow-up. Univariate Kaplan-Meier statistical approach was used to assess outcome of survival data in conjunction with pro-BNP status in certain populations among our studied group and long-rank test was used to compare survival between groups. All p values presented were two-sided, and associations were considered significant if the p value is less or equal to 0.05. Statistical analyses were performed using NCSS 2007 software (Hintze J., 2007, Kaysville, Utah, USA).

Results

Patients' characteristics. The study population consisted of 112 cancer patients. Sixty-three percent of patients were older than 65 years. Most patients were metastatic (83.0%). The most common diagnoses were gastrointestinal malignancies (49.1%), breast cancer (19.6%), lung cancer (16.1%), genitourinary cancer (9.8%) and gynecological cancer (5.4%). We monitored serum tumor markers specific for each diagnosis, when suitable marker was available. Patients' characteristics are summarized in Table I.

Table I. Patient characteristics.

Variable	No. (%)
Age	
Age <65 years	41 (36.6)
Age ≥65 years	71 (63.4)
Status of disease	
Present primary tumor without metastases	19 (17.0)
Metastatic disease with disease control (complete or partial remission or stable disease)	28 (25.0)
Metastatic disease with disease progression	65 (58.0)
Chemotherapy	
Chemotherapy-naive patients	68 (60.7)
Pretreated patients	43 (38.4)
Type of cancer	
Gastrointestinal cancer	55 (49.1)
Genitourinary cancer	11 (9.8)
Gynecological cancer	6 (5.4)
Lung cancer	18 (16.1)
Breast cancer	22 (19.6)

Association between NT-proBNP and patients/disease characteristics and patients outcome. Mean ± standard error of mean (SEM) value of NT-pro-BNP in the first, second and third sample was 561.0±75.1, 1,565.4±461.1 and 1,940.7±581.1 ng/l. Differences were statistically significant between all the samples (P<0.001). Fifteen (13.4%), 27 (24.1%) and 25 (30.1%) patients had elevated level of NT-pro-BNP in the first, second and third sample above the normal value adjusted to age (see cut-off value in Methods section).

There was a significant elevation of NT-proBNP in all samples in patients older than 65 years (Tables II-IV). Moreover, in the second and third sample the NT-proBNP level was significantly elevated in patients with progressive metastatic disease compared to stationary, or nonmetastatic disease. Within the distinct diagnoses, all three samples showed the highest NT-proBNP level in genitourinary cancers, however, the difference was not statistically significant. In second sample, pro-BNP was also associated with serum tumor marker level, while in the third sample it was associated with previous therapy. There were 25 patients with left and 8 patients with right sided colon cancer, however, there was no difference in any of NT-proBNP based on tumor location. Mean ± SEM value of NT-pro-BNP in the first, second and third sample for left vs. right-sided colon cancer was: 789±238.8 vs. 807.0 vs. 413.6, P=0.76, 971.1±242.1 vs. 929.4±419.3, P=0.95, 1,312.3±406.0 vs. 848.7±907.8, P=0.88.

In median follow-up of 20.2 months (range 1.3-67.1 months) 72 (64.3%) of patients died. Patients with non-elevated NT-proBNP above cut-off value in the second and third sample had significantly better OS compared to patients with elevated NT-proBNP (HR=0.47, 95% CI 0.26-0.85, P=0.002 for second sample and HR=0.29, 95% CI 0.14-0.60, P=0.0000007 for third sample, respectively). Baseline NT-proBNP value was not prognostic for OS (HR=0.98, 95% CI 0.50-1.92, P=0.96) (Figs. 1-3).

Discussion

Our findings show that in all samples the NT-proBNP was elevated in older people. In the second and the third sample, NT-proBNP was significantly elevated in patients with progressive metastatic disease compared to nonmetastatic and stationary metastatic disease. In the second sample there was a significant elevation of specific serum tumor marker along with NT-proBNP. In the third sample there was significant elevation of NT-proBNP in chemotherapy naive patients compare to chemotherapy pretreated patients.

Finding of Kamai *et al* (8) in patients with renal cell carcinoma (RCC) suggested that the preoperative serum levels of cardiovascular hormones (BNP, NT-proBNP) might be related to progression of renal cell carcinoma and a worse prognosis. The author based this interpretation on the fact that the serum levels of NT-proBNP declined after the nephrectomy. Authors reported that higher preoperative serum levels of BNP, NT-proBNP and vascular endothelial growth factor (VEGF), as well as elevated HIF-2 alpha expression in the primary tumor, were associated with worse performance status, local invasion, distant metastasis and shorter overall survival. Possible reason for lower BNP after nephrectomy may be an indirect production of these hormones by cancer cells (8). It can be comparable with our study, where patient with progressive metastatic disease have got significantly

Table II. Association between NT-proBNP-1 and patient characteristics.

Variable	NT-proBNP-1						
	No.	Mean, ng/l	SE, ng/l	P-value[a]	Normal, n (%)	Elevated, n (%)	P-value[b]
All patients	112	561.0	75.1	NA	97 (86.6)	15 (13.4)	NA
Age							
<65 years	41	213.6	117.5	<0.01	39 (95.1)	2 (4.9)	0.05
≥65 years	71	761.5	89.3		58 (81.7)	13 (18.3)	
Status of disease							
Present primary tumor without metastases	19	547.0	183.8	0.33	18 (94.7)	1 (5.3)	0.52
Metastatic disease with disease control	28	528.7	151.4		24 (85.7)	4 (14.3)	
Progressive metastatic disease	65	578.9	99.4		55 (84.6)	10 (15.4)	
Chemotherapy							
Chemotherapy-naïve patients	68	619.3	96.7	0.22	56 (82.4)	12 (17.6)	0.16
Pretreated patients	43	480.7	121.6		40 (93.0)	3 (7.0)	
Type of cancer							
Gastrointestinal cancer	55	602.3	106.9	0.13	46 (83.6)	9 (16.4)	0.22
Genitourinary cancer	11	805.2	239.1		8 (72.7)	3 (27.3)	
Gynecological cancer	6	830.3	323.8		5 (83.3)	1 (16.7)	
Lung cancer	18	515.9	186.9		16 (88.9)	2 (11.1)	
Breast cancer	22	298.8	169.1		22 (100.0)	0 (0.0)	
Serum tumor marker							
Normal range	53	522.7	113.2	0.53	47 (88.7)	6 (11.3)	0.95
<1.5-fold	13	743.9	228.7		11 (84.6)	2 (15.4)	
1.5-10-fold	19	627.7	189.1		16 (84.2)	3 (15.8)	
>10-fold	15	455.0	212.9		13 (86.7)	2 (13.3)	

[a]Kruskal-Wallis test with Dunn's post hoc test. [b]Fisher's exact test. NA, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide.

higher levels of NT-proBNP after therapy, and one year after diagnosis. Antineoplastic therapy with anthracyclines is often complicated by the development of cardiotoxicity leading to heart failure (19). In some instances, it is detected too late with echocardiography, when significant myocardial damage has already occurred (20). Serum measurement of NT-proBNP level in patient treated with anthracyclines is useful for both, acute and late toxicity (15). In our study, we had 22 patients with breast cancer of whom 16 were treated with chemotherapy. In our study, there was significant elevation of NT-proBNP in metastatic patients after therapy and one year after diagnosis. However, the elevation in several patients with breast cancer was not significant. There were no patients with acute cardiac failure in association with chemotherapy. The association between the NT-proBNP and malignant disease confirms a study by Papazisis *et al* (21) who assessed a group of patients with metastatic renal cell carcinoma treated with sunitinib (a tyrosine kinase inhibitor). Patients who obtained a clinical benefit 15 days after treatment had significantly lower NT proBNP compared to patients without any clinical benefit (a three-fold increase in patients with progressive disease compared to stable NT-proBNP levels in patients with clinical benefit, P<0,0001). Median progression free survival was 12.0 months in patients with less than 1.5-fold increase (n=22) and 3.9 months in patients with more than 1.5-fold increases in plasma NT-proBNP (n=13) (Long-rank test, P=0.001) (21). Similar in our study patients with good clinical benefit from therapy with stable metastatic disease had significantly lower levels of NT-proBNP after treatment and one year after the diagnosis, too. The elevation of NT-proBNP and CA-125 were markers of shorter survival in patients with breast cancer treated with trastuzumab. A study by Rossner *et al* (22) divided 28 patients with HER-2 positive breast cancer to two group. Group with NT-proBNP levels <155 pg/ml (n=16, age 57±13 years) vs. group B with NT-proBNP >155 pg/ml (n=12, age 62±9 years) levels before and after trastuzumab therapy. Obtained results have shown NT-proBNP of 65±36 pg/ml vs. 66±33 pg/ml in group A vs. 520±443 pg/ml vs. 498±411 pg/ml in group B. Elevated levels of NT-proBNP, CA-125 and CA15-3 indicated a higher median three-month-mortality in trastuzumab-treated patients on long term immunotherapy (22). In our study, there was significant elevation of cancer-specific tumor marker in the second sample of NT-proBNP (after therapy). This is in line with findings of study by Rossner *et al* (22). Similar results like antecedent and our study had two studies in primary and metastatic brain tumor patients. These studies reported that greater NT-proBNP concentration was associated with greater

Table III. Association between NT-proBNP-2 and patient characteristics.

Variable	NT-proBNP-2						
	No.	Mean, ng/l	SE, ng/l	P-value[a]	Normal, n (%)	Elevated, n (%)	P-value[b]
All patients	112	1565.4	461.1	NA	85 (75.9)	27 (24.1)	NA
Age							
<65 years	41	1014.1	762.7	0.01	31 (75.6)	10 (24.4)	>0.99
≥65 years	71	1883.8	579.6		54 (76.1)	17 (23.9)	
Status of disease							
Present primary tumor without metastases	19	446.0	1106.4	0.01	18 (94.7)	1 (5.3)	0.01
Metastatic disease with disease control	28	385.7	911.4		27 (96.4)	1 (3.6)	
Progressive metastatic disease	65	2400.8	598.2		40 (61.5)	25 (38.5)	
Chemotherapy							
Chemotherapy-naive patients	68	1786.3	596.1	0.33	53 (77.9)	15 (22.1)	0.50
Pretreated patients	43	1247.8	749.6		31 (72.1)	12 (27.9)	
Type of cancer							
Gastrointestinal cancer	55	1180.4	643.4	0.27	42 (76.4)	13 (23.6)	0.31
Genitourinary cancer	11	4994.2	1438.7		7 (63.6)	4 (36.4)	
Gynecological cancer	6	4227.8	1948.0		3 (50.0)	3 (50.0)	
Lung cancer	18	875.9	1124.7		16 (88.9)	2 (11.1)	
Breast cancer	22	651.6	1017.3		17 (77.3)	5 (22.7)	
Serum tumor marker							
Normal range	55	1260.7	692.3	0.03	47 (85.5)	8 (14.5)	0.26
<1.5-fold	11	1133.7	1548.0		7 (63.6)	4 (36.4)	
1.5-10-fold	18	2411.2	1210.2		12 (66.6)	6 (33.3)	
>10-fold	19	2151.4	1177.9		14 (73.7)	5 (26.3)	>0.99

[a]Kruskal-Wallis test with Dunn's post hoc test. [b]Fisher's exact test. NA, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide.

mass effect and extent of perifocal brain edema. Elevated NT-proBNP concentration before surgery was associated with inferior outcomes at the hospital discharge and with inferior prognosis of brain tumor patients (23). Therefore, NT-proBNP can be considered for perioperative risk stratification, prognostication and evaluation of cognitive/mental health status in brain tumor patients. A study by Bunevicius conducted in 245 patients undergoing craniotomy for brain tumor (mostly meningioma 36% and high-grade glioma 20%) ascertained that greater NT-proBNP concentrations were associated with greater 5-year mortality risk (HR 1.845, 95%, CI, (1.166-2.920), P=0.009) controlling for patients age, gender, history of cardiovascular disease, histological diagnosis and adjuvant therapy. In summary, greater preoperative NT-proBNP concentration is associated with worse health status, unfavorable discharge outcome and shorter survival of brain tumor patients (24). Next study by authors Pavo *et al* (10) from 2015 demonstrated that NT-proBNP is systematically elevated in cancer patients and that it is likewise associated with long-term mortality independently of age, gender, tumour entity, tumor stage and manifest cardiac disease at the first clinical presentation. This study confirmed a significant correlation between the pro-inflammatory cytokine IL-6 and inflammatory marker CRP and the hormone NT-proBNP. Whether the effect on

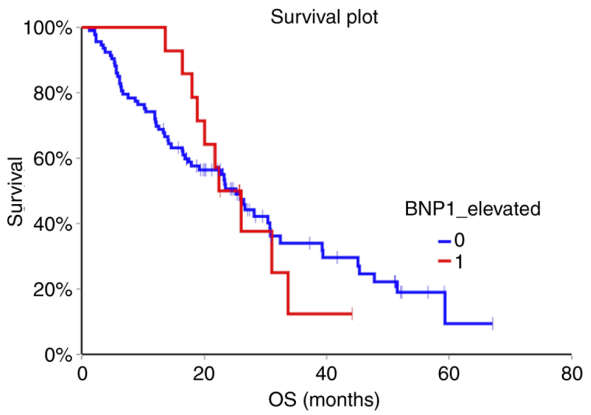

Figure 1. Kaplan-Meier estimates of probabilities of OS according to serum NT-proBNP level (N=112). Patients with non-elevated NT-proBNP in the baseline sample had non-significantly different OS compared with patients with elevated NT-proBNP (hazard ratio, 0.98; 95% CI, 0.50-1.92; P=0.96). NT-proBNP, N-terminal pro B-type natriuretic peptide; OS, overall survival; 0, non-elevated NT-proBNP; 1, elevated NT-proBNP.

mortality is primarily due to a determinant local influence on the tumour microenvironment or it is induced by systemic cardiovascular dysregulation cannot be determined (10). In our

Table IV. Association between NT-proBNP-3 and patient characteristics.

Variable	NT-proBNP-3						
	No.	Mean, ng/l	SE, ng/l	P-value[a]	Normal, n (%)	Elevated, n (%)	P-value[b]
All patients	83	1940.7	581.1	NA	58 (69.9)	25 (30.1)	NA
Age							
<65 years	28	726.5	992.8	0.01	20 (71.4)	8 (28.6)	>0.99
≥65 years	55	2558.8	708.4		38 (69.1)	17 (30.9)	
Status of disease							
Present primary tumor without metastases	15	515.3	1321.5	0.01	14 (3.3)	1 (6.7)	0.01
Metastatic disease with disease control	28	392.1	967.2		26 (2.9)	2 (7.1)	
Progressive metastatic disease	40	3559.3	809.2		18 (45.0)	22 (55.0)	
Chemotherapy							
Chemotherapy-naive patients	54	2486.1	717.5	0.05	35 (64.8)	19 (35.2)	0.21
Pretreated patients	29	925.2	979.1		23 (79.3)	6 (20.7)	
Type of cancer							
Gastrointestinal cancer	41	1218.6	809.0	0.09	32 (78.0)	9 (22.0)	0.03
Genitourinary cancer	11	5486.3	1561.9		6 (4.5)	5 (45.5)	
Gynecological cancer	5	2204.2	2316.6		3 (0.0)	2 (40.0)	
Lung cancer	11	2985.4	1561.9		4 (6.4)	7 (63.6)	
Breast cancer	15	460.4	1337.5		13 (86.7)	2 (13.3)	
Serum tumor marker							
Normal range	38	1897.7	902.7	0.81	30 (78.9)	8 (21.1).0)	0.12
<1.5-fold	8	561.0	1967.3		6 (75.0)	2 (25.0	
1.5-10-fold	12	1446.1	1606.3		6 (50.0)	6 (50.0)	
>10-fold	9	1663.9	1854.8		5 (55.6)	4 (44.4)	

[a]Kruskal-Wallis test with Dunn's post hoc test. . [b]Fisher's exact test. NA, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide.

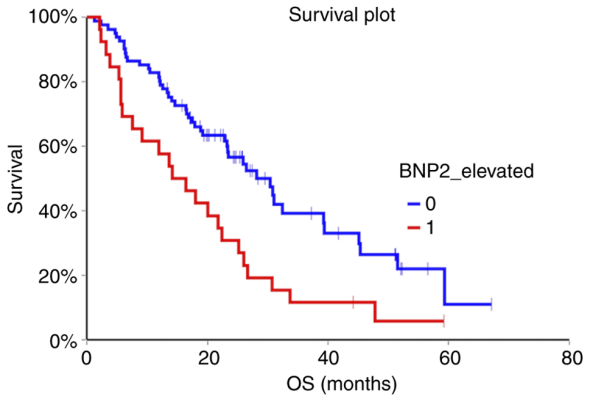

Figure 2. Kaplan-Meier estimates of probabilities of OS according to serum NT-proBNP level (N=112). Patients with non-elevated NT-proBNP in the second sample had significantly improved OS compared with patients with elevated NT-proBNP (hazard ratio, 0.47; 95% CI, 0.26-0.85; P=0.002). NT-proBNP, N-terminal pro B-type natriuretic peptide; OS, overall survival; 0, non-elevated NT-proBNP; 1, elevated NT-proBNP.

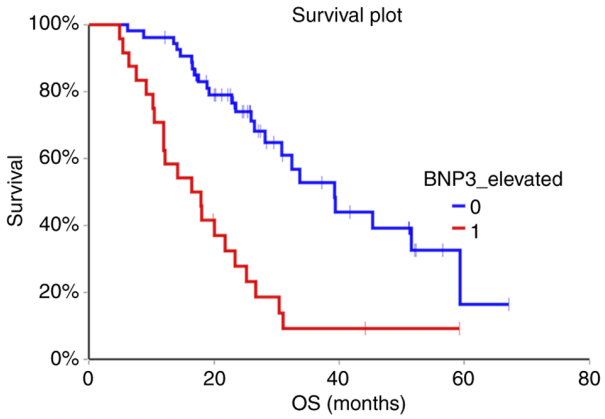

Figure 3. Kaplan-Meier estimates of probabilities of OS according to serum NT-proBNP level (N=112). Patients with non-elevated NT-proBNP in the third sample had significantly improved OS compared with patients with elevated NT-proBNP (hazard ratio, 0.29; 95% CI, 0.14-0.60; P=0.0000007). NT-proBNP, N-terminal pro B-type natriuretic peptide; OS, overall survival; 0, non-elevated NT-proBNP; 1, elevated NT-proBNP.

study in accord to the study by Pavo, there was a significant association between CRP and NT-proBNP from the second sample (P-value 0.003) and between CRP and NT-proBNP (P-value 0.0002) from the third sample.

This study has several limitations, including a relative limited samples size, patients and cancer types of heterogeneity and this study doesn't stratify patients according to their

clinical and/or molecular subtypes. Moreover, there are other factors that potentially affect NT-proBNP level including obesity, anemia and/or ongoing volume therapy. On the other hand, these data represent pro-BNP measurement in consecutive patients treated in oncology department in regional hospital in and study results could help better elucidate clinical utility of NT-proBNP in cancer patients.

In conclusion we have observed that NT-proBNP was significantly increased in older patients, in patients with progressive metastatic disease with poor prognosis, especially in genitourinary malignancies and lung cancer. The levels of NT-proBNP were increased in genitourinary and gastrointestinal cancer compared to other diagnoses, however, not statistically significant. Our detections and mentioned clinical studies suggest that level of NT-proBNP shows the extent of oncologic disease. Higher levels are associated with progression of metastatic disease in cancer patients and with shorter overall survival. These findings suggest that subclinical dysfunction of cardiovascular system is common and has prognostic significance in cancer patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JCJr, JCSr, MC and MM were involved in data collection, analysis, manuscript writing, and study conception and design. JCJr and MM confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethic committee of Hospital of St. Jacob in Bardejov, Slovakia. All participants provided written informed consent.

Patient consent for publication

All study participants provided written informed consent for the publication of data.

Competing interests

The authors declare that they have no competing interests.

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