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Thieme

Serum NT-pro-BNP Levels Predict Cardiovascular Events in Acromegaly Patients

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ABSTRACT

Background   Acromegaly is associated with an increased risk of fatal and non-fatal cardiovascular (CV) events. Controlling acromegaly decreases, but does not normalize this risk. Brain natriuretic peptide (BNP) assessment is used in the general population for the diagnosis of heart failure and to predict ischemic recurrences and mortality. This is a retrospective, longitudinal, monocenter study that evaluates the role of serum N-terminal fragment of BNP (NT-pro-BNP) for predicting CV events in acromegaly patients.

Methods   Serum NT-pro-BNP levels were measured in 76 patients with acromegaly (23 males, 57.7 ± 1.5 years), and compared with other predictors of CV events. NT-pro-BNP cut-off value discriminating the occurrence of CV events was determined by ROC analysis. CV events were recorded during a follow-up of 78.6 ± 6.4 months.

Results   CV events occurred in 9.2 % of patients. Mean log(NT-pro-BNP) concentration was higher in patients who experienced CV events than in those who did not (p < 0.01) and in patients who died due to CV events than in those who died due to other causes (p < 0.01). Based on the ROC curve, a cut-off value of 91.55 pg/mL could predict CV events (OR 19.06). Log(NT-pro-BNP) was lower in surgically treated patients by surgery (p < 0.05), and in those cured by neurosurgery (p < 0.02).

Conclusions   High NT-pro-BNP value is an independent middle-term predictor of fatal or non-fatal CV events in patients with acromegaly. According to this parameter, surgically treated patients show lower CV risk than those managed with medical therapy, especially if the disease is cured.

BNP	Brain natriuretic peptide
NT-pro-BNP	N-terminal fragment of BNP
CV	Cardiovascular
OSAS	Obstructive sleep apnoea syndrome
c-MR	Cardiac magnetic resonance
CT	Computed tomography
AS	Agatston score
FS	Framingham score
LVM	Left ventricular mass
EF	Ejection fraction
SSa	Somatostatin analogs
PEGV	Pegvisomant
ULN	Upper limit of normality
SE	Standard error
ROC	Receiver operating characteristic
AUROC	Area under the ROC curve
NPV	Negative predictive value
PPV	Positive predictive value
DA	Diagnostic accuracy
EAT	Epicardial adipose tissue
GHD	Growth hormone deficiency

Background

Acromegaly is a rare endocrine disorder, due to excess of growth hormone (GH) and insulin-like growth factor (IGF)-1 caused in most cases by pituitary tumors [1]. In addition to the typical outward manifestations, hormone hypersecretion indirectly increases morbidity and mortality, especially in individuals suffering from cardiovascular (CV) disorders and cancer [2]. The availability of enhanced diagnostic tools and new medical therapies have significantly lowered the CV risk in patients with acromegaly than in the past, at least when serum IGF-1 concentration is normalized [3]. However, especially in patients with comorbidities such as diabetes mellitus, hypertension, or obstructive sleep apnoea syndrome (OSAS), the burden of CV disease remains markedly increased, regardless of acromegaly control [4].

In this respect, the ability to identify acromegaly patients at risk for CV complications by both invasive and non-invasive approaches has improved over the years [5]. At present, bidimensional cardiac ultrasonography (c-US) is regarded as the gold standard for investigating cardiomyopathy in patients with acromegaly [6], as well as in the general population, and it should be performed at the time of disease diagnosis, and annually over the follow-up period. Although cardiac magnetic resonance (c-MR) proved to be more sensitive than c-US in diagnosing acromegaly cardiomyopathy [7], it is an expensive and not widely available technique [8]. In addition, the Agatston score (AS) is a semi-automated tool based on the calculation of the extent of coronary artery calcifications detected by unenhanced low-dose computed tomography (CT) scan [9], which demonstrates a good correlation with contrast-enhanced CT coronary angiography [10], despite its inability to detect soft non-calcified plaques. Instead, Framingham Score (FS), a

gender-specific algorithm based on patient's age, lipid profile, smoking habits, and occurrence of hypertension, is used to predict the long-term (10 years) risk of hard coronary heart disease and cerebrovascular events in the general population [11]. Both FS and AS have been shown to be suitable markers for evaluating middle term (5 years) risk of CV events in patients with acromegaly [5, 6].

Brain natriuretic peptide (BNP) is a hormone produced by ventricular cardiomyocytes and released into the circulation in response to volumetric or pressure ventricular wall overload [12]. Elevated levels of the N-terminal fragment of its pro-hormone (NT-pro-BNP) are used to differentiate cardiac from pulmonary causes of acute heart failure [13], assess the severity of chronic heart failure [14, 15], and predict ischemic recurrences and short- or long-term CV mortality [16, 17]. Studies exploring the role of NT-pro-BNP as a predictor of CV events in acromegaly patients have yielded conflicting results. One study concluded that NT-pro-BNP is not a reliable indicator of cardiac dysfunction in acromegaly patients, because no correlation between c-US parameters and this biochemical marker could be demonstrated [18]. By contrast, Andreassen et al. found an inverse association of circulating levels of both BNP and NT-pro-BNP with ventricular ejection fraction (EF), and positive association with left ventricular mass (LVM) evaluated by c-MR, thus suggesting that B-type natriuretic peptides are markers of cardiac dysfunction [19]. Recently, Eichner et al. demonstrated a significant relationship between IGF-1 and changes in NT-pro-BNP levels but no associations with LVM index, suggesting a different effect of acromegaly on CV parameters [20]. Although most of the studies support the role of NT-pro-BNP in the prediction of major CV and cerebrovascular events for the general population, its predictive role in patients with acromegaly is poorly documented.

The aim of our study was to evaluate the role of serum NT-pro-BNP levels to predict the middle-term risk of cardiovascular events in acromegaly patients and compare it with demographic and clinical characteristics and other surrogate markers of cardiovascular function.

Methods

This was a retrospective longitudinal single-institution study including 76 subjects (23 men and 53 women; mean age at the time of diagnosis of acromegaly was 47.3 ± 1.5 years; mean age at the time of evaluation was 57.7 ± 1.5 years) referred to our Endocrine Unit from 2000 to 2012. Acromegaly was diagnosed in all cases in accordance with the guidelines in use at the time of diagnosis.

Pituitary macroadenoma was demonstrated in 49/76 (64.5 %) cases and microadenoma in the remaining 27 (35.5 %) cases. All treatments undertaken by patients are mentioned in ▶ **Fig. 1**. Among medically treated patients, 47 received first-generation somatostatin analogs (SSa), 10 received pegvisomant (PEGV), and 12, both SSa and PEGV.

Serum GH and IGF-1 levels were measured by immunoradiometric assay, using commercial kits (Immulite 1000 Immunoassay System, Siemens). The sensitivity threshold values for GH and IGF-I values were 0.04 and 6 ng/mL, respectively. The intra- or the inter-assay coefficients of variation, for each assay, were < 5 % and < 10 %, respectively. The range of normality for serum IGF-I levels was calculated in 485 healthy subjects. Serum IGF-I normal values for subjects aged
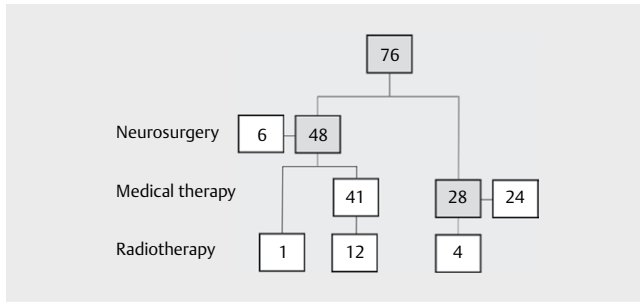
► **Fig. 1** Therapies performed by patients during the follow-up. Among the 76 patients, 48 underwent surgery (alone, n = 6; followed by radiotherapy, n = 1; medical therapy, n = 29, or by both medical therapy and radiotherapy, n = 12), while 28 patients underwent first-line medical treatment (alone, n = 24, or followed by radiotherapy, n = 4).

21–35, 36–50, and 51–75 years were 115–358, 94–284, and 64–238 ng/mL, respectively. Serum IGF-1 levels were expressed in ng/mL and as the upper limit of normality (xULN). According to the most recent consensus statement on acromegaly, the disease was considered adequately controlled when IGF-1 levels were ≤ 1.0 xULN and random GH < 1.0 ng/mL. For patients treated with PEGV, the disease was considered controlled only on the basis of IGF-1 values [21].

Serum NT-pro-BNP level was measured by chemiluminescent enzyme immunoassay (Immulite 2000 system, Siemens). The sensitivity threshold of the NT-pro-BNP assay was 5.0 pg/mL. The intra- or the inter-assay coefficients of variation were < 2 % and < 5 %, respectively. Skilled technical personnel performed all assays according to the manufacturers' recommendations. The normal reference range of NT-pro-BNP was < 110 pg/mL.

Furthermore, FS was calculated in all patients to estimate the 10-year CV risk, using an interactive tool (https://framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/) based on a specific algorithm which integrates the following parameters: sex, age, systolic blood pressure, hypertension treatment, smoking habit, diabetes, HDL, and total cholesterol values [11].

Patients were followed up for 78.6 ± 6.4 months. During this period, they underwent conventional clinical, instrumental and biochemical evaluation, to monitor response to specific treatments, acromegaly complications, and cardiometabolic profile [22]. Patients gave their informed consent to the procedures and to the study, which was approved by the local ethical committee of our university hospital.

Statistical analysis

Numerical data are expressed as mean ± standard error (SE) and categorical variables as numbers and percentages. Since examined variables were not normally distributed (Kolmogorov Smirnov test), the non-parametric approach was used. NT-pro-BNP values were log-transformed [log(NT-pro-BNP)] and compared by Mann Whitney test in patients with versus those without CV events (both fatal and non-fatal), and in dead versus alive patients.

To determine the optimal NT-pro-BNP cut-off value, and to discriminate the presence/absence of CV events in the entire cohort of patients, a Receiver Operating Characteristic (ROC) curve was realized, and the area under the curve (AUROC) was calculated along with the relative 95 % Confidence Interval (95 % CI) and significance. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and diagnostic accuracy (DA) were evaluated for the cut-off individuated through the ROC analysis.

Logistic univariate regression models were estimated to assess the possible dependence of CV events on some potential explicative variables [clinical features, including gender, age, age at diagnosis, tumor dimension, therapies, duration of active disease (calculated from the presumed onset of symptoms), BMI, presence of OSAS, arterial hypertension, systolic and diastolic blood pressure values, smoking habit; biochemical parameters, including serum GH and IGF-1 levels, IGF-1 xULN values, serum NT-pro-BNP levels; type 2 diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, and overall deaths]. Variables with p-value < 0.05 at univariate analysis were then subjected to multivariate analysis and included in the model to identify independent predictive factors of CV events.

Logistic univariate regression models were also estimated to assess the possible dependence of NT-pro-BNP on clinical (patients' age and BMI) and echocardiography parameters (interventricular septum, end-diastolic diameter, ejection fraction, left ventricular mass, and E/A ratio).

Finally, Kaplan-Meier curves were realized to quantify the survival time until the occurrence of any CV event, both in the entire group of patients and after stratification for gender and the NT-pro-BNP cut-off was identified by ROC curve analysis. The curves related to different groups were then compared using the Log rank test.

Statistical analyses were performed using SPSS 20.0 for the Window package. A p-value < 0.05 was considered to be statistically significant.

Results

Clinical characteristics

The demographic and clinical characteristics of patients enrolled in this study are mentioned in ► **Table 1**.

At baseline, 47/76 (61.8 %) patients showed disease control; of these, 40/47 (85.1 %) were under medical therapy, six patients (12.8 %) had surgery alone, and one patient (2.1 %) had surgery as well as radiosurgery. Serum GH levels and IGF-1 x ULN values were lower in patients with controlled disease than those in the other patients (GH: 0.5 ± 0.05 vs 2.3 ± 0.4 ng/mL, p < 0.02; IGF-1: 0.7 ± 0.02 vs 1.6 ± 0.2 xULN, p < 0.005) (► **Table 2**).

Six patients were lost to follow-up due to death (three, CV diseases; one malignancy; two, other causes), and the other four experienced non-fatal CV events. Overall, the prevalence of CV events in patients was 9.2 %, with no differences between patients with uncontrolled and controlled acromegaly (2/29 vs 5/47, p NS). The mean age of patients who experienced CV events was not significantly different from that of the other ones (62.3 ± 3.6 vs 57.1 ± 1.6 years, p NS).

Cardiovascular risk evaluation

Mean FS was not significantly different between patients with active acromegaly compared to those with controlled disease

▶ **Table 1** Demographic, clinical, biochemical, and radiological characteristics of all patients with acromegaly at baseline evaluation.

Patients (no.)	76
Male/Female (no.)	23/53
Age (years)	57.7 ± 1.5
BMI (Kg/m^2)	29.2 ± 0.5
Current or past smokers (no.)	29
Age at diagnosis (years)	47.3 ± 1.5
Estimated duration of active acromegaly (years)	7.4 ± 0.8
Pituitary tumour dimension (macro/microadenoma) (no)	49/27
Controlled/active acromegaly at baseline (no.)	47/29
Medical therapy (no.)	69
Radiotherapy (no.)	17
Neurosurgery (no.)	48
GH (ng/mL)	2.2 ± 0.3
IGF-1 (ng/mL)	160.3 ± 9.3
IGF-1 xULN	0.7 ± 0.04
NT-pro-BNP (pg/mL)	216.14 ± 99.4
log(NT-pro-BNP)	1.6 ± 0.06
Arterial hypertension (no.)	48
Type 2 diabetes mellitus (no.)	21
Dyslipidemia (no.)	26
OSAS (no.)	17

BNP: brain natriuretic peptide; BMI: basal metabolic index; GH: growth hormone; OSAS: obstructive sleep apnea syndrome; FS: Framingham score; IGF-1: insulin-like growth factor-1; ULN: upper limit of normality
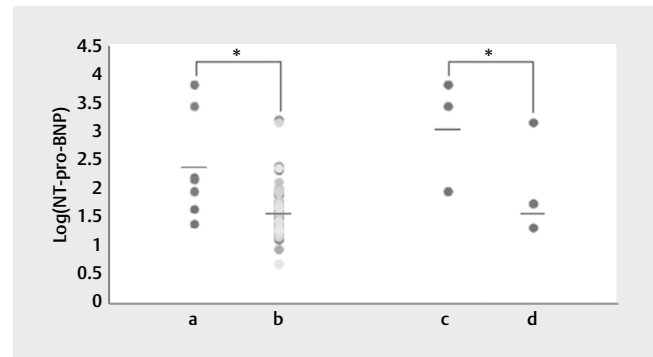
▶ **Table 2** Clinical and biochemical parameters of patients with controlled and active acromegaly. The number of patients with fatal or non-fatal cardiovascular (CV) events, occurring during the follow-up, is also mentioned in this table.

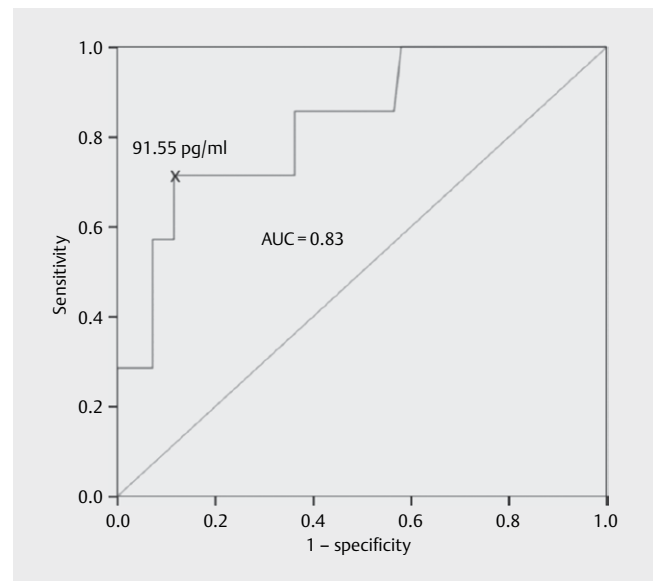|	Patients with controlled acromegaly	Patients with active acromegaly	p-value
Patients (no.)	47	29	
GH (ng/mL) *	0.5 ± 0.05	2.3 ± 0.4	**<0.01**
IGF-1 xULN	0.7 ± 0.02	1.6 ± 0.2	**<0.01**
NT-pro-BNP (pg/mL)	115.7 ± 48.9	1072.2 ± 823.9	NS
log(NT-pro-BNP)	1.5 ± 0.06	1.8 ± 0.1	NS
Framingham score	11.02 ± 0.8	12.5 ± 1.08	NS
Patients with CV events (no.)	5	2	NS

BNP: brain natriuretic peptide; CV: cardiovascular: IGF-1: insulin-like growth factor-1; ULN: upper limit of normality * Excluding patients treated with Pegvisomant

▶ **Fig. 2** Log(NT-pro-BNP) values in each patient who experienced cardiovascular (CV) events **a** versus the other patients **b**, and in each patient who died for CV events **c**, versus the patients who died due to other causes **d**; mean log(NT-pro-BNP) values are expressed for each group of patients (_). * p<0.01.

▶ **Fig. 3** ROC curve represents the sensitivity (71.4%) and specificity (88.4%) of serum NT-pro-BNP cut-off value = 91.55 pg/mL to predict cardiovascular events in acromegaly patients. AUC = 0.83 with confidence interval 0.67-0.99.

(12.5 ± 1.08 vs 11.02 ± 0.8, p NS) (▶ **Table 2**), or between patients who experienced CV events and those who did not (13.7 ± 1.5 vs 11.3 ± 0.7, p NS).

Overall, the mean log(NT-pro-BNP) value was higher, although not significantly, in patients with uncontrolled acromegaly than in other patients (1.8 ± 0.1 vs 1.5 ± 0.06, p = 0.06) (▶ **Table 2**). However, the value was significantly lower in patients treated by surgery alone or followed by medical therapy, than in the patients managed only with medical treatment (1.4 ± 0.09 vs 1.8 ± 0.1, p<0.02; 1.5 ± 0.07 vs 1.8 ± 0.1, p<0.05), and in patients cured by neurosurgery than in those still active thereafter (1.4 ± 0.04 vs 1.6 ± 0.07, p<0.02). However, when we excluded patients treated by surgery from the analysis, log(NT-pro-BNP) values were higher in patients with active disease than in those with controlled acromegaly. No difference was observed among patients treated with different drugs.

Mean log(NT-pro-BNP) concentration was significantly higher in patients who experienced CV events than in other patients (2.4 ± 0.9 vs 1.6 ± 0.4, p<0.01) and in patients who died due to CV events than in those who died due to other causes (3.08 ± 0.9 vs 1.6 ± 0.4, p<0.01) (▶ **Fig. 2**).

▶ **Table 3** Characteristics of patients enrolled in this study. Patients were categorized on the basis of NT-pro-BNP cut-off value detected by ROC curve.

NT-pro-BNP values (pg/mL)	<91.55	>91.55	p
Patients (no).	63	13	
M/F	18/45	5/8	NS
Age (years)	55.2 ± 1.6	69.9 ± 1.6	<0.02
BMI (Kg/m²)	29.7 ± 0.6	28.9 ± 1.3	NS
Age at diagnosis (years)	44.7 ± 1.6	60.5 ± 2.3	<0.02
Estimated duration of active disease (years)	7.8 ± 0.9	10.9 ± 2.2	= 0.05
Pituitary tumour (macro/microadenomas)	43/20	7/6	NS
GH (ng/mL)	2.1 ± 0.4	2.6 ± 0.8	NS
IGF-1 (ng/mL)	160.1 ± 10.3	142.4 ± 12.6	NS
IGF-1 xULN	0.7 ± 0.04	0.8 ± 0.07	NS
Patients with controlled/active disease (no.)	40/23	7/6	NS
Medical therapies (SSa/Peg/SSa + Peg)	56 (37/8/11)	13 (10/2/1)	NS
Radiotherapy (no.)	14	3	NS
Neurosurgery (no.)	43	5	<0.05
NT-pro-BNP (pg/mL)	33.5 ± 2.6	618.9 ± 256.5	<0.05
log(NT-pro-BNP)	1.4 ± 0.03	2.4 ± 0.1	<0.02
Hypertension (no.)	37	11	NS
Diabetes mellitus type 2 (no.)	19	2	NS
Dyslipidemia (no.)	23	3	NS
OSAS (no.)	15	2	NS
Smokers and ex-smokers (no.)	25	4	NS
Total deaths (no.)	2	4	<0.001
Fatal cardiovascular events (no.)	0	3	<0.001
Non-fatal cardiovascular events (no.)	2	2	= 0.07

BNP: brain natriuretic peptide; BMI: basal metabolic index; GH: growth hormone; OSAS: obstructive sleep apnea syndrome; FS: Framingham score; IGF-1: insulin-like growth factor-1; ULN: upper limit of normality; SSa: somatostatin analogues; Peg: Pegvisomant

▶ **Table. 4** Linear univariate regression analysis: clinical and biochemical characteristics of patients with acromegaly according to cardiovascular events

	OR (confidence interval)	p-value
Gender	7.083 (1.261 – 39.780)	0.026
Age	1.048 (0.976 – 1.124)	0.195
BMI	0.171 (0.832 – 1.159)	0.473
Age at diagnosis	1.026 (0.965 – 1.091)	0.411
Years of active disease	1.049 (0.955 – 1.153)	0.313
Tumor dimension	0.375 (0.077 – 1.818)	0.223
Systolic blood pressure	1.019 (0.974 – 1.066)	0.412
Diastolic blood pressure	1.067 (0.974 – 1.170)	0.164
Arterial hypertension	4.610 (0.537 – 39.608)	0.164
Type 2 diabetes mellitus	0.408 (0.046 – 3.612)	0.421
Hypercholesterolemia	1.602 (0.330 – 7.781)	0.559
Hypertriglyceridemia	8.800 (1.183 – 65.475)	0.034
OSAS	2.154 (0.246 – 18.844)	0.488
Smoking habit	2.347 (0.486 – 11.340)	0.289
GH *	0.909 (0.646 – 1.280)	0.584
IGF-1 ng/mL	1.001 (0.992 – 1.010)	0.825
IGF-1 xULN	1.823 (0.338 – 9.827)	0.485
Acromegaly control	0.787 (0.084 – 7.403)	0.834
Neurosurgery	0.200 (0.036 – 1.111)	0.066
Radiotherapy	2.946 (0.590 – 14.708)	0.188
Somatostatin analogues	0.339 (0.068 – 1.694)	0.188
Pegvisomant	3.778 (0.770 – 18.534)	0.101
Framingham score	1.092 (0.927 – 1.285)	0.293
FS 10-year risk	1.194 (1.044 – 1.367)	0.010
NT-pro-BNP (pg/mL)	1.001 (1.000 – 1.003)	0.044
log(NT-pro-BNP)	6.396 (1.874 – 21.826)	0.003
NT-pro-BNP#	19.062 (3.158 – 115.071)	0.001
NT-pro-BNP§	11.810 (2.182 – 63.916)	0.004

BNP: brain natriuretic peptide; BMI: basal metabolic index; OSAS: obstructive sleep apnea syndrome; FS: Framingham score; IGF-1: insulin-like growth factor-1; ULN: upper limit of normality; * Excluding patients treated with Pegvisomant; # increased/normal values according to the cut-off detected by ROC curve; § increased/normal values according to the local reference normal range calculated in the general population

Based on the ROC curve analysis, the best cut-off value of serum NT-pro-BNP levels predicting CV events in acromegaly patients was 91.55 pg/mL, with a sensitivity of 0.714, specificity of 0.884, PPV of 0.385, NPV of 0.968, and DA of 0.868 (▶ **Fig. 3**). Patients with serum NT-pro-BNP values >91.55 pg/mL showed significantly higher mean age, estimated duration of active disease, than the others in addition to more number of deaths. Among seven patients who experienced CV events, five showed serum NT-pro-BNP levels >91.55 pg/mL (OR 19.06), and in three cases the CV event was fatal (▶ **Table 3**).

Logistic univariate regression analysis showed a significantly positive association of CV events with male gender (OR 7.1; 95 % C.I. 1.26 - 39.78; p = 0.026), hypertriglyceridemia (OR 8.8; 95 % C.I. 1.18 - 65.47; p = 0.034) and, as a continuous variable, with 10-years risk score at FS (OR 1.2, 95 % C.I. 1.04 - 1.36; p = 0.010), log(NT-pro-BNP) values (OR 6.4; 95 % C.I. 1.87 - 21.82; p = 0.003), NT-pro-BNP above 1 x ULN (OR 11.8, 95 % C.I. 2.18 - 63.91; p = 0.004), and above the cut-off detected by ROC curve (OR 19.06; 95 % C.I. 3.15 - 115.07; p = 0.001) (▶ **Table 4**). Nevertheless, in the multivariate regression analysis, only the last two variables were observed to be independently associated with CV events (OR 10.3, p < 0.033, and OR 20.7, p 0.009, respectively).

Logistic univariate regression analysis also showed a positive correlation of NT-pro-BNP with age (OR 0.02; 95 % C.I. 0.010 - 0.028; p < 0.01) but not with BMI (OR 0.01; 95 % C.I. -0.025 - 0.027, p NS). No echocardiography parameters correlated with NT-pro-BNP values (p NS).

The Kaplan Meier curves demonstrated that the "event-free-survival" was significantly shorter in men than in women (p < 0.02), and in patients with serum NT-pro-BNP values > 91.55 pg/mL than in the other patients (p < 0.001).

Discussion

In this study, we found the occurrence of a CV event in 9.2 % of our patient cohort with acromegaly, with a mortality rate of 43 %, during a mean follow-up of 6.5 years. The CV events were not associated either with disease activity, or with increased FS score, but the risk of developing a CV event was 19 times greater in patients with serum NT-pro-BNP levels above 91.55 pg/mL, based on the ROC curve analysis. Accordingly, patients who experienced CV events showed NT-pro-BNP concentrations significantly higher than the other patients. In addition, the univariate regression analysis showed a positive dependence of CV events also on the male gender, hypertriglyceridemia and, to a less extent, on increased FS, the multivariate analysis confirmed a significant dependence only on serum NT-pro-BNP levels above 1 x ULN or above the cut-off value demonstrated by the ROC curve analysis.

Particularly, although the identified cut-off value was within the normal reference range it was calculated for the general population, regardless of their predictive role for CV risk, and was based on ROC curve analysis in correlation with CV outcome.

In a previous study, we demonstrated that the combined evaluation of FS and AS could predict an increased risk for CV events in 41 % of our acromegaly patients and that coronary calcifications could be detected in half of these patients [5]. More recently, Aulinas et al. proposed the use of the combined evaluation of epicardial adipose tissue (EAT) index and serum cystatin levels, as a surrogate marker of coronary and CV risk in acromegaly patients [23]. It is noteworthy, however, that the evaluation of NT-pro-BNP concentration is less expensive and widely available than AS and EAT, which are assessed by cardiac CT. Indeed, measurement of serum BNP or the more specific NT-pro-BNP value is currently used to evaluate cardiac dysfunction, and to predict mortality risk for CV events in the general population [12–17, 24].

Recently, Eichner et al. investigated the relationship between serum IGF-1 levels and NT-pro-BNP concentrations in the general population and found a sex-specific association between these parameters [20]. Indeed, higher IGF-1 levels and IGF-1/IGFBP-3 ratio were associated were higher NT-pro-BNP values in women, while a U-shaped relation of baseline IGF-1, IGFBP-3, and IGF-1/IGFBP-3 ratio with increased NT-pro-BNP levels was observed in men. Data on BNP or NT-pro-BNP concentrations, and their role in the evaluation of cardiovascular status, are scanty and conflicting in patients with abnormalities in the GH/IGF-1 axis. In a study published by Arikan et al. in 2010, serum NT-pro-BNP values were found to be slightly higher in naïve acromegaly patients than in controls [18]. However, other studies did not confirm this finding. A few studies observed similar NT-pro-BNP levels among patients with active or controlled acromegaly and healthy subjects [25, 26], or an inverse correlation between serum IGF-1 and BNP levels in acromegaly patients evaluated after pituitary surgery, and with normal left ventricular systolic function and dimensions [27]. Other studies demonstrated an increase in serum NT-pro-BNP levels during somato-statin analogs therapy, probably indicating an initial impairment of cardiac function [19, 28]. Conversely, Potter et al. found no significant changes in NT-pro-BNP levels during medical treatment [25]. Nevertheless, the differences among the findings of these studies are probably related to the small dimension of the casuistries, and/or to the non-homogeneous status of cardiac function and morphology of the patients. On the other hand, several studies demonstrated a significant increase of NT-pro-BNP levels in patients with GHD, together with a significant decrease during GH replacement, associated with the improvement of CV performances [28–30].

In our study, serum NT-pro-BNP levels did not correlate with IGF-1 levels or acromegaly control, based on criteria proposed by the most recent guidelines [21]. Nevertheless, if the definition of disease control was based only on IGF-1 normalization, the rate of controlled patients reached up to 88 %, and NT-pro-BNP levels correlated with disease control.

IGF-1 levels could be lower in the cohort with NT-pro-BNP over 91.55 pg/mL just because of the physiological reduction of IGF-1 levels with age and were found to be higher in these patients as compared to those with NT-pro-BNP lower than the identified cut-off. Indeed, IGF-1 x ULN values were similar between the two groups. On the other hand, the role of the age of the patients could be less relevant than the estimated duration of active disease, which was significantly higher in patients with NT-pro-BNP over 91.55 pg/mL in terms of impact on CV outcome.

With regard to the impact of disease management, we found lower NT-pro-BNP concentrations in patients who underwent pituitary surgery, irrespective of disease control achievement. Our data are in agreement with studies showing a reduced CV risk in acromegaly patients treated by surgery. In fact, some authors reported an increase in CV risk in patients effectively treated with SSa, but not in those cured by surgery [31]. This finding could be explained on the basis of worsened glucose tolerance during SSa treatment, irrespective of disease control, demonstrated by some studies [25, 32]. However, it is in contrast with the study by Ito et al. who showed an inverse relationship between IGF-1 and NT-pro-BNP in operated patients, and by Verhelst et al. who did not find any difference in NT-pro-BNP values between patients cured by surgery or those with a controlled disease by medical therapies [26, 27]. On the other hand, Colao et al. showed a similar improvement in the ventricular hypertrophy 12 months after SSa or surgical first-line treatment, but a more pronounced improvement of systolic function in SSa-treated patients [33]. Some discrepancies among different studies could be because of the evaluation of a small number of patients by most researchers. In addition, the patients with higher CV risk were possibly treated more conservatively, with first-line SSa, rather than being proposed for neurosurgery.

Our study has some limitations, including its retrospective nature, and the small number of CV events. Nevertheless, we evaluated a wide and homogeneous group of patients, who were followed up at the same center for at least 12 months.

Conclusions

In conclusion, this study suggests that a high NT-pro-BNP value is an independent middle-term predictor of fatal or non-fatal CV

events in patients with acromegaly. Based on this parameter, surgically treated patients show lower CV risk than those managed with medical therapy, especially if the disease is cured. The assessment of NT-pro-BNP concentration is easily feasible and can integrate other surrogate markers such as AS and FS, or imaging investigation such as c-US or c-MR, for improving the evaluation of survival expectancy. The role of NT-pro-BNP in the longitudinal evaluation of the CV risk assessment in acromegaly patients deserves further investigation.

Declarations

Ethics approval and consent to participate Patients gave their informed consent to the procedures and to the study, which was approved by the local ethical committee of the university hospital "Gaetano Martino" of Messina (protocol n. 560 of January 13, 2020).

Availability of data and materials All data generated or analyzed during this study are included in this published article and its supplementary information files

Author contributions

MR, SC, MM, FF, FS, and GG analyzed and interpreted patient data, GDB performed CV examinations, LG performed biochemical analysis, AA performed the statistical analysis and interpreted related results, MR, MM, and SC were the major contributors in writing the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no competing interests

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