EXTRA Dementia and Geriatric Cognitive Disorders

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Original Research Article

The Use of N-Terminal Pro-Brain Natriuretic Peptide to Evaluate Vascular Disease in Elderly Patients with Mental Illness

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Key Words
Cognition · Cystatin C · Homocysteine · N-terminal pro-brain natriuretic peptide · Psychogeriatric patients · Vascular disease

Abstract
Background: Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) is regarded as a sensitive marker of cardiovascular disease. Vascular disease plays an important role in cognitive impairment. ***Method:*** In 447 elderly patients with mental illness, serum NT-proBNP level and the presence or absence of vascular disease according to the medical record were used to categorize patients in different subgroups of vascular disease. ***Results and Conclusion:*** Patients with vascular disease and elevated serum NT-proBNP level had a lower cognition level, shorter survival time, lower renal function and a higher percentage of pathological brain imaging than patients with vascular disease and normal NT-proBNP level. Thus, elevated serum NT-proBNP level might be helpful to detect patients who have a more severe cardiovascular disease.

Introduction

With an ageing population, the prevalence of dementia will continue to rise in the coming decades, placing a high burden on social and economic resources. Since effective treatments are lacking, prevention of dementia deserves high priority [1, 2]. In recent years, a re-

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lationship has been found between vascular disease and cognitive impairment in elderly patients with mental illness [2]. Therefore, it is important to identify modifiable vascular risk factors, which could be used in preventing or delaying the onset of dementia [2]. Evidence has emerged that proper control of vascular disorders and maintenance of active lifestyle may prevent or delay the onset and progression of dementia [2, 3].

N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) have an established role in identifying patients with heart failure, but these markers are also increased in myocardial ischaemia/coronary artery disease [4–6]. In previous studies in elderly patients with mental illness [7, 8], we observed an increased frequency of pathological values of serum NT-proBNP in patients with vascular disease compared to patients without vascular disease. We concluded that the serum NT-proBNP level might be useful to identify patients in need of control and treatment of vascular risk factors and also provided prognostic information.

Since many clinical and epidemiological studies published during the last 3 decades show that even mild hyperhomocysteinaemia is associated with vascular disease [9–12], we investigated elderly patients with mental disease with regard to plasma homocysteine (tHcy) and the presence of vascular disease [13–15]. Briefly, our findings showed that patients with mental illness and any forms of vascular disease had significantly higher plasma tHcy concentrations than patients without vascular disease, and that elevated plasma tHcy in mental illness was mainly associated with the presence of vascular disease and not related to the specific psychogeriatric diagnosis.

In the present study, we investigated NT-proBNP levels in different forms of vascular disease in elderly patients with mental illness. Furthermore, since serum NT-proBNP level has been associated with an increased risk of both cardiac [4–6] and noncardiac [16] vascular diseases and might detect subclinical vascular disease, we have used serum NT-proBNP level and the presence or absence of vascular disease according to the medical records to categorize patients in four groups. Group I consisted of patients with vascular disease and an elevated level of serum NT-proBNP, whereas patients in Group II also showed the presence of vascular disease but with a normal level of serum NT-proBNP. Patients in Group III had no clinically overt vascular disease but an elevated level of serum NT-proBNP, and patients in Group IV showed no vascular disease and had a normal level of serum NT-proBNP. In order to study the possible use of serum NT-proBNP to evaluate vascular disease in elderly patients with mental illness, we investigated the distribution of different diagnoses, survival time, cognition (Mini-Mental State Examination, MMSE, score), brain imaging (computed tomography, CT, scan), renal function, and plasma tHcy in these four groups.

Patients and Methods

Study Population

The present study population consisted of 447 patients consecutively enrolled [187 males and 265 females, with a median age of 75 years (10–90th percentiles, 55–87)] who were referred to the Psychogeriatric Department at the Lund University Hospital for diagnostic assessments and treatment. Patients on any kind of ongoing vitamin substitution were excluded from the study. The diagnosis was based on psychiatric, neurological, somatic, and laboratory investigations, psychometric testing, measurements of regional cerebral blood flow, electroencephalography, and CT scan [13]. MMSE was performed in all patients [17]. The patients were classified into two groups on the basis of brain imaging findings: one group with normal findings (n = 217) and a second group with pathological findings (n = 177),

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showing white matter lesions and/or cerebral infarction. The majority of the patients were living in their own homes, alone or with relatives. Dementia was diagnosed in 211 patients, 77 patients were diagnosed with Alzheimer's disease (AD), 89 patients with vascular dementia (VaD), and 45 patients with other types of dementia (mainly mixed VaD and AD). In total, 236 patients were diagnosed with mental diseases without dementia (non-dementia), 51 patients with depression, 6 patients with confusional states, 24 patients with other psychiatric disorders (mainly psychosis), and 122 patients with mild cognitive impairment (MCI) [18]. In addition, 33 patients presented with subjective symptoms of cognitive impairment but normal psychometric tests. They had normal CT and were apparently healthy in other respects. These patients were treated as a separate group of patients called subjective cognitive impairment. The diagnosis of the psychogeriatric diseases was based on the DSM-IV criteria [19]. Furthermore, patients with VaD fulfilled the NINDS-AIREN criteria [20] for VaD, and patients with AD were diagnosed in accordance with the NINCDS-ADRDA criteria [21]. Survival time was determined as months at the end of the study (6 years) or months until death. The study was approved by the ethics committee of the University of Lund. Informed consent to participate was given by all subjects (or by relatives, if the patients were unable to communicate).

The patients (n = 447) were divided into different groups according to the presence of a diagnosis and/or symptoms indicating vascular disease in their medical records. One group (n = 277) consisted of patients with any form of vascular disease and included diagnoses/symptoms such as VaD, cerebral infarction, transient ischaemic attacks, myocardial infarction, angina pectoris, peripheral vascular disease, atrial fibrillation, and hypertension. A subgroup of these patients (n = 104) consisted of patients with manifest occlusive arteriosclerotic vascular disease (called manifest vascular disease) and included diagnoses/symptoms such as cerebral infarction, transient ischaemic attacks, myocardial infarction, angina pectoris, or occlusive peripheral vascular disease. In 99 patients, hypertension was observed as the vascular disease. Cerebral infarction or transient ischaemic attacks were observed in 64 patients, myocardial infarction or angina pectoris in 40 patients, atrial fibrillation was diagnosed in 37 patients, and heart failure without any other vascular disease was diagnosed in 12 patients. In 170 patients, there was no indication of any vascular disease.

Analyses

Blood samples for tHcy determination were collected in evacuated tubes containing EDTA at about 8 a.m. after an overnight fast and centrifuged within 15 min at 3,000 *g* for 5 min. The plasma was stored at –20°C until analysis. Total plasma tHcy was measured with high-performance liquid chromatography after reduction of disulphide bonds with dithiothreitol and deproteinization with sulphosalicylic acid [22].

Serum cystatin C measurements were performed by a polystyrene-enhanced turbidimetric method (DakoCytomation, Copenhagen, Denmark). The upper reference limits for serum cystatin C are 1.15 mg/l for subjects below 50 years of age and 1.44 mg/l for subjects above 50 years of age.

The serum level of NT-proBNP was determined using an immunoassay (Modular Analytics E170; Roche Diagnostics, Mannheim, Germany). The upper reference limit is 300 ng/l.

Statistics

The results are presented as medians and 10–90th percentiles. The Mann-Whitney U test was used at the 5% level of significance to evaluate the study. The χ^2 test was used for comparison of percentages of pathological CT findings.

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Table 1. Age, serum NT-proBNP, plasma tHcy, and serum cystatin C in different groups of patients with and without vascular disease

	n	Age years	Serum NT-proBNP ng/l	Plasma tHcy μmol/l	Serum cystatin C mg/l
No vascular disease	170	68 (48–82)	115 (27–368)	11.6 (7.7–19)	0.85 (0.65–1.12)
Vascular disease	277	78 (62–88)**	298 (67–2,333)***	15.1 (9.3–23.6)***	1.04 (0.74–1.44)***
No MVD	150	77 (61–88)***	324 (61–2,318)***	14.7 (9.1–23)***	1.06 (0.73–1.55)***
MVD	104	80 (66–88)***	290 (86–2,500)***	15.3 (9.6–23.6)***	1.04 (0.76–1.41)***
CI or TIA	64	79 (69–88)***	273 (75–1,731)***	15.6 (10–23.3)***	1.02 (0.79–1.39)***
Atrial fibrillation	37	81 (66–90)***	1,004 (109–2,985)***	17.6 (11.1–28.0)***	1.14 (0.79–1.84)***
Hypertension	99	75 (60–89)***	250 (56–1,299)***	13.7 (8.7–23)*	0.99 (0.7–1.34)**
MI or angina	40	80 (57–88)***	331 (102–6,074)***	14.9 (8.8–26.9)**	1.08 (0.72–1.41)**
Heart failure	12	74 (58–85)	311 (79–2,942)**	14.2 (10.3–20.9)*	1.02 (0.83–1.63)*

Values represent medians (10–90th percentiles). MVD = Manifest occlusive vascular arteriosclerotic disease; CI = cerebral infarction; TIA = transitory ischaemic attack; MI = myocardial infarction; angina = angina pectoris.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Patients with different forms of vascular disease are compared to patients without vascular disease.

Table 2. Age, serum NT-proBNP, plasma tHcy, and serum cystatin C in patients without vascular disease but elevated NT-proBNP level and in patients with vascular disease but normal level of serum NT-proBNP

	n	Age years	Serum NT-proBNP ng/l	Plasma tHcy μmol/l	Serum cystatin C mg/l
No VD but elevated NT-proBNP	23	78 (68–90)	549 (305–2,400)	14.5 (10.6–30.8)	1.1 (0.83–1.4)
VD but normal NT-proBNP	140	74 (58–84)**	135 (44–271)***	13.1 (8.8–20)*	0.92 (0.72–1.3)**

Values represent medians (10–90th percentiles). VD = Vascular disease.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Patients without vascular disease but elevated NT-proBNP are compared to patients with vascular disease but normal level of serum NT-proBNP.

Results

Different Forms of Vascular Disease

Levels of serum NT-proBNP, plasma tHcy, and serum cystatin C were elevated in all groups of patients with different forms of vascular disease compared to patients without vascular disease (table 1). Furthermore, correction for the age difference between patients with and without vascular disease did not change the significant elevations of serum NT-proBNP, plasma tHcy, and serum cystatin C (data not shown). Notably, the levels of serum NT-proBNP were particularly increased in patients with atrial fibrillation. Patients with hypertension exhibited similar serum NT-proBNP level than the other groups of patients with vascular disease.

Patients without vascular disease according to their medical records but with an elevated level of NT-proBNP showed elevated levels of plasma tHcy and serum cystatin C compared to patients with vascular disease but a normal level of serum NT-proBNP (table 2).

Subgroups of Vascular Disease

All patients were divided into four groups depending on their level of NT-proBNP and the presence or absence of vascular disease according to their medical records (table 3).

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Table 3. Age, serum NT-proBNP, plasma tHcy, serum cystatin C, MMSE score, and survival time in patients with different vascular diseases

	n	Age years	Serum NT-proBNP, ng/l	Plasma tHcy μmol/l	Serum cystatin C mg/l	MMSE score	Survival time months	Pathological CT, %
Group I	137	81 (71–90)***, a	841 (346–3,914)***, a	16.0 (11.1–26.4)***, a	1.1 (0.83–1.58)***, a	21 (13–27)***, a	38 (6–56)***, a	71***, b
Group II	140	74 (58–84)***	135 (44–271)***	13.1 (8.8–20)**	0.92 (0.72–1.3)***	26 (17–29)**	46 (17–61)*	60***
Group III	23	76 (68–90)***	549 (304–2,400)***	14.5 (10.6–30.8)***	1.1 (0.82–1.4)***	26 (16–29)	37 (4–53)***	35
Group IV	147	65 (47–80)	98 (23–225)	11.0 (7.6–18.2)	0.83 (0.65–1.03)	27 (20–30)	49 (31–62)	28

Values represent medians (10–90th percentiles).
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Patients in Groups I–III are compared to patients in Group IV.
[a] $p < 0.001$; [b] $p < 0.05$. Patients in Group I are compared to patients in Group II.

Table 4. The main diagnoses (VaD, AD, MCI, and depression) subdivided according to different forms (Groups I–IV) of vascular diseases

	n	Age years	Serum NT-proBNP ng/l	Plasma tHcy μmol/l	Serum cystatin C mg/l	MMSE score	Survival time months	Pathological CT, %
VaD, Group I	58	83 (73–91)	882 (371–3,889)	16.4 (10.7–309)	1.12 (0.81–1.56)	19 (11–25)	25 (4–54)	90
VaD, Group II	31	80 (68–86)*	144 (57–285)***	16.0 (9.3–29.6)	1.0 (0.79–1.49)	21 (11–28)	36 (12–59)*	90
AD, Group I	17	81 (76–92)**	601 (305–7,929)***	16.9 (11.7–23.6)	1.12 (0.92–1.64)***	18 (11–25)	37 (5–61)	41
AD, Group II	16	77 (68–86)	178 (75–272)	14.0 (7.9–22.8)	0.96 (0.74–1.38)	21 (10–29)	40 (7–62)	44
AD, Group III	11	81 (69–94)	493 (303–2,125)***	15.5 (10.4–42)	1.07 (0.8–1.48)*	26 (15–29)	33 (1–58)	18
AD, Group IV	33	77 (63–85)	136 (48–245)	15.0 (9.3–19.4	0.91 (0.68–1.07)	22 (11–27)	41 (29–59)	18
MCI, Group I	26	78 (62–88)***	633 (318–4,394)***	16.0 (10–23.2)***	1.13 (0.73–1.59)***	26 (19–29)**	44 (13–58)*	54**
MCI, Group II	45	68 (57–79)**	122 (39–276)*	12.9 (9.3–16.6)**	0.86 (0.69–1.18)**	27 (21–30)	50 (35–61)	56***
MCI, Group IV	48	61 (47–77)	85 (23–179)	10.1 (7–15.9)	0.74 (0.62–0.92)	28 (24–30)	52 (32–64	25
Depression, Group I	9	81 (72–90)***	609 (321–13,978)***	17.9 (9.7–36.2)**	1.08 (0.66–2.65)**	26 (17–29)*	39 (9–62)	56
Depression, Group II	15	63 (55–86)	109 (27–264)	10.7 (8.3–17.3)	0.89 (0.71–1.56	29 (24–30)	41 (19–59)	40
Depression, Group IV	25	65 (47–78)	89 (11–272)	10.1 (7.1–16.6)	0.85 (0.64–1.09)	29 (22–30)	42 (23–54)	32

Values represent medians (10–90th percentiles).
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Patients in Groups I–III are compared to patients in Group IV.

Group I consisted of patients with vascular disease and an elevated level of serum NT-proBNP, whereas patients in Group II also showed the presence of vascular disease but with a normal level of serum NT-proBNP. Patients in Group III had no clinically overt vascular disease but an elevated level of serum NT-proBNP, and patients in Group IV showed no vascular disease and had a normal level of serum NT-proBNP. In Groups I–III, the levels of serum NT-proBNP, plasma tHcy, and serum cystatin C were elevated, and the survival time was lower than in Group IV. The MMSE score was lower and the frequencies of pathological CT findings were higher in Groups I and II than in Group IV.

The patients in Group I were older and showed increased plasma tHcy and serum cystatin C levels, lower MMSE score, shorter survival time, and an increased percentage of pathological CT findings compared to the patients in Group II.

Distribution of Diagnoses in the Subgroups

The distribution of the main diagnoses (VaD, AD, MCI, and depression) in the four subgroups is presented in table 4. Patients with VaD were observed only in Groups I and II. Patients with AD were substantially observed in all groups, whereas only a few patients with MCI (n = 3) and depression (n = 2) were observed in Group III. Patients with VaD and an

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Table 5. Patients with AD with normal and elevated serum NT-proBNP

	n	Age years	Serum NT-proBNP ng/l	Plasma tHcy μmol/l	Serum cystatin C mg/l	MMSE score	Survival time months	Pathological CT, %
Elevated NT-proBNP	28	81 (73–91)***	528 (304–3,185)***	16.3 (11.1–29.6)*	1.08 (0.81–1.55)***	20 (12–27)	37 (3–59)	32*
Normal NT-proBNP	49	77 (64–84)	145 (61–250)	14.8 (9–19.6)	0.92 (0.74–1.17)	22 (12–27)	41 (12–61)	26

Values represent medians (10–90th percentiles).
* $p < 0.05$; *** $p < 0.001$. Patients with elevated serum NT-proBNP are compared to patients with normal serum NT-proBNP.

elevated level of serum NT-proBNP (Group I) were older ($p < 0.001$) and showed a shorter survival time ($p < 0.001$) than patients with a normal level of serum NT-proBNP (Group II).

Patients with AD in Group I were older and showed an increased serum cystatin C level (plasma tHcy was almost significantly increased, $p = 0.07$) compared to those in Group IV, whereas patients in Group II did not differ in any parameter from patients in Group IV. Patients with AD and an elevated serum NT-proBNP (Groups I and III) were older and showed increased levels of plasma tHcy and serum cystatin C as well as an increased percentage of pathological CT findings compared to patients with a normal level of serum NT-proBNP (Groups II and IV) (table 5).

Patients with MCI in Group I were older and showed increased levels of plasma tHcy and serum cystatin C, decreased MMSE score, shorter survival time, and an increased percentage of pathological CT findings compared to patients in Group IV (table 4). Likewise, patients with MCI in Group II were older and showed increased levels of plasma tHcy and serum cystatin C and an increased percentage of pathological CT findings compared to patients in Group IV. Patients with depression in Group I were older and showed increased levels of plasma tHcy and serum cystatin C and a decreased MMSE score compared to patients in Group IV, whereas patients with depression in Group II did not differ in any parameter from patients in Group IV.

Discussion

Different Forms of Vascular Disease

The present study shows that patients with different forms of vascular disease exhibited an elevated level of NT-proBNP compared to patients without vascular disease. Thus, these findings are in agreement with previous reports suggesting that the presence of cardiovascular disease increases the level of serum NT-proBNP [4–6, 16]. About half of the patients classified as having vascular disease according to their medical records showed normal levels of serum NT-proBNP. A possible reason for this discrepancy is that their vascular disease did not significantly involve the heart. The elevated levels of serum NT-proBNP in 23 patients diagnosed as having no vascular disease according to their medical records might be attributed to renal impairment and/or subclinical cardiovascular disease.

The increase of serum NT-proBNP levels in most of the different forms of vascular disease suggests similar cardiac involvement irrespective of whether the vascular disease is of cerebral or extracerebral origin, occlusive or not occlusive, or only manifests itself as hypertension. Thus, this finding indicates a generalized vascular disease also in patients diagnosed with cerebral vascular disease. The level of serum NT-proBNP was, however, particularly increased in patients with atrial fibrillations, which is in agreement with a highly elevated serum NT-proBNP level in atrial distention [4–6]. As previously shown [23], plasma tHcy was also elevated to a similar extent in the different forms of vascular disease compared to patients

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without vascular disease. Likewise, the level of serum cystatin C was increased to a similar extent in the different forms of vascular disease, which indicates similar renal impairment in all these vascular diseases. Furthermore, in patients without vascular disease but with an elevated level of serum NT-proBNP, the levels of plasma tHcy and serum cystatin C were increased compared to patients with vascular disease but a normal level of serum NT-proBNP. This finding indicates that the serum NT-proBNP level might be a better indicator of the severity of the vascular disease than solely the diagnosis and/or presence of symptoms of vascular disease.

Renal Function and Vascular Disease

Renal impairment is known to increase the serum level of NT-proBNP [4–6], and it is therefore expected that patients with an elevated level of serum NT-proBNP also show a lowered renal function (as judged by serum cystatin C) compared to patients with a normal level of NT-proBNP. Cystatin C is a sensitive marker of renal impairment, and chronic renal disease is known to be an important cardiovascular risk factor [24, 25]. This fact is in agreement with our findings from previous studies [7, 8] and from the present study, where we observed that serum cystatin C is associated with serum NT-proBNP and plasma tHcy levels, the presence of vascular disease, and pathological CT findings (indicating cerebrovascular disease).

Subgroups of Vascular Disease

As described in the Results section, all patients were divided into four groups according to their level of serum NT-proBNP and the presence or absence of vascular disease as indicated in the medical records. Patients in Group I could be regarded as having a more severe form of vascular disease than those in Group II, which was supported by the findings that patients in Group II were younger, showed lower plasma tHcy and serum cystatin C levels, higher MMSE score, a lower percentage of pathological CT findings, and a longer survival time than patients in Group I. All patients in Groups I–III could be regarded as patients with vascular disease, even if the cardiovascular disease in Group III was only manifested as an elevated level of serum NT-proBNP. Patients in Group IV represent a group of patients without any signs of vascular disease. Consequently, patients in Groups I–III showed higher plasma tHcy and serum cystatin C levels and a shorter survival time, and patients in Groups I and II also showed a lower MMSE score and higher percentage of pathological CT findings than patients in Group IV. These findings indicate that the presence or absence of vascular disease according to the medical records means that some patients with cardiovascular disorders are classified as having no vascular disease despite an elevation of their serum NT-proBNP levels.

Distribution of Diagnoses in the Four Subgroups

The distribution of the main diagnoses (VaD, AD, MCI, and depression) in the different groups of vascular disease shows that patients with VaD in Group I exhibited a somewhat higher age and a shorter survival time than patients in Group II. Furthermore, an elevated level of serum NT-proBNP in patients with VaD in Group I indicates that these patients also suffer from cardiovascular disease in addition to their cerebral vascular disease. The shorter survival time in these patients might thus be attributed to a more generalized vascular disease.

Subgrouping of the other main diagnoses (AD, MCI, and depression) in these four subgroups showed that plasma tHcy, renal function (as judged by serum cystatin C), MMSE score, survival time, and percentage of pathological CT findings differed between the groups. These findings indicate that the determination of serum NT-proBNP might be useful in the evaluation of vascular disease in elderly patients with mental illness. Few patients with MCI or depression were observed in Group III, which indicates a significant agreement between

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serum NT-proBNP level and the presence or absence of vascular disease according to medical records. However, patients with AD were substantially represented in all four groups, and serum cystatin C was elevated in Groups I and III compared to Group IV, whereas plasma tHcy showed a tendency to increase ($p = 0.07$) only in Group I. It is particularly interesting that a substantial proportion of the patients with AD (Group III) without vascular disease had an elevated level of serum NT-proBNP, indicating subclinical cardiovascular disease. Patients with AD in Groups I and III might have a more severe form of vascular disease than the patients in Group II, which is reflected by the fact that, although there was no significant decrease in the MMSE score and survival time, patients with AD and elevated serum NT-proBNP level (Groups I and III) were older, showed lower renal function, an increased plasma tHcy level, and a higher percentage of pathological CT findings compared to patients with AD and a normal level of serum NT-proBNP (Groups II and IV). This finding supports the hypothesis that neurovascular interactions in the development and/or progression of AD have been underappreciated [26]. Therefore, it is important to determine the serum NT-proBNP level in patients with AD to detect those in need of treatment of their vascular disease in order to prevent or delay cognitive impairment.

Conclusion

The main finding in the present study is that serum NT-proBNP levels are similarly increased in most of the different forms of vascular disease, which suggests similar cardiac involvement irrespective of whether the vascular disease is of cerebral or extracerebral origin, occlusive or not occlusive, or only manifests itself as hypertension. Furthermore, patients with vascular disease and an elevated serum NT-proBNP level (Group I) had a lower cognition level, shorter survival time, lower renal function, and a higher percentage of pathological CT findings than patients with vascular disease and a normal NT-proBNP level (Group II). Thus, an elevated serum NT-proBNP level might detect patients who have a more severe cardiovascular disease and therefore a higher risk of rapid progression of their vascular disease and mental illness. These patients are in need of more intensive control and treatment of their vascular disease to prevent or delay cognitive impairment.

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