Serum levels of BDNF in remission, but not the acute phase, may predict the development from depression to dementia.

Running Title: Serum BDNF predicts MDD–dementia transition.

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ABSTRACT

Objectives: Depression may be a risk factor or a prodromal symptom of dementia, and decreased serum levels of brain-derived neurotrophic factor (BDNF) have been observed in both depression and dementia. The aim of the present study was to determine whether serum levels of BDNF in the remitted or acute phase of depression predicted the transition from depression to dementia.

Methods: Serum levels of BDNF were measured in the acute phase of depression (n = 204) and after remission (n = 117), and we followed (mean: 24.3 months) the participants to assess the subsequent onset of dementia or mild cognitive impairment (MCI).

Results: Serum levels of BDNF after remission, but not those in the acute depressive phase, predicted the future development of dementia or MCI.

Conclusions: Patients with low serum BDNF levels, even after depression remission, might have an increased risk of developing dementia. These findings suggest a potential association between residual low serum BDNF levels after remission and the prodromal state of dementia, or the involvement of BDNF in the transition from depression to dementia. However, given that this study is low-powered and preliminary, interpretation of the results should be approached with caution.

KEYWORDS

Depression, Dementia, Brain-derived neurotrophic factor, BDNF, Serum

KEY POINTS

- Serum BDNF levels in acute depressive phase did not predict the future development of dementia or MCI.
- Serum BDNF levels after remission predicted the future development of dementia or MCI.
- Residual low serum BDNF levels after remission may reflect the prodromal state of dementia.
- BDNF may be involved in the transition from depression to dementia.

1. INTRODUCTION

Previous studies have shown that depression is a risk factor for the development of various forms of dementia, including Alzheimer's disease (AD) [1-3]. On the other hand, some studies have concluded that depression in late-life may be a prodromal symptom of dementia [2,4-6]. Although the biological mechanisms underlying the relationship between depression and dementia are unclear, a commonly observed biological change in both depression and dementia is a decrease in levels of brain-derived neurotrophic factor (BDNF) [7-9].

BDNF is a member of the neurotrophin family of growth factors and plays an important role in neurogenesis, synaptic plasticity, and long-term potentiation in the central nervous system including the hippocampus [10-15]. It has been reported BDNF is implicated in learning and memory [16]. For instance, one study demonstrated that low serum levels of BDNF were correlated with small hippocampal volume and poor memory in older adults without dementia [9].

In patients with AD, decreased BDNF levels have been reported in the brain and serum [17-21]. In the AD brain, especially in the hippocampus, decreased protein and mRNA levels of BDNF have been observed [17,19,22]. Moreover, reduced brain BDNF levels occur from the early stage of AD, and these changes correlate with a decline in cognitive function [23]. Decreased serum levels of BDNF have also been reported in AD patients. A meta-analysis (including 15 studies, n = 2067) demonstrated that serum levels of BDNF in AD patients were significantly lower than those in healthy controls [20]. The

Framingham Heart Study was a community-based, large prospective cohort study involving 2131 elderly participants without dementia (≥60 years old) who were followed for up to 10 years [24]. The study examined the relationship between serum BDNF levels at baseline and the future risk for dementia. The results showed that the risk for future dementia and AD decreased as serum levels of BDNF increased, and especially in women, elderly people (≥80 years old), and highly educated individuals, BDNF may play a role in preventing dementia and AD. This means that lower levels of BDNF may be a risk factor and predictor of the development to dementia. Decreased serum levels of BDNF have been observed not only in AD but also in other neurological disorders. For example, Ventriglia and colleagues evaluated serum levels of BDNF in patients with neurogenerative disorders and vascular dementia (VaD) [25], and found lower serum BDNF levels in patients with AD, Lewy body dementia (LBD), frontotemporal dementia (FTD), and VaD compared with healthy controls.

Lower BDNF serum levels have been reported in patients with depression compared with healthy controls [26-28], and BDNF levels have been found to increase with effective treatment of depression symptoms [29-31]. A replication study and meta-analysis also demonstrated decreased peripheral blood levels of BDNF in patients with depression [32]. However, serum levels of BDNF did not return to normal levels after remission in a group of patients with depression with a prolonged depressive phase [33]. Given that cognitive dysfunction, especially memory dysfunction, remained after remission from depression [34], the low serum BDNF levels observed after remission may be related to the persistent

cognitive dysfunction and transition to dementia [33]. Moreover, a large cohort study conducted in China and the United Kingdom demonstrated that the incidence of dementia was associated with depression severity such that participants who experienced severe depression had an increased risk of dementia [35]. As serum levels of BDNF are known to correlate with depression severity [28,30,31], serum levels of BDNF in the acute phase of depression may predict the development from depression to dementia.

The aim of the present study was to determine whether serum levels of BDNF in the remitted or acute phase of depression could predict the transition from depression to dementia. Thus, we measured serum levels of BDNF in the acute phase of depression and after remission and followed patients to quantity the subsequent onset of dementia or mild cognitive impairment (MCI).

This study was a part of the Juntendo University Mood Disorder Project (JUMP).

2. MATERIALS AND METHODS

2-1. Participants

Participants were inpatients 50 years old and over with major depressive disorder (MDD) diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders, 4th or 5th edition (DSM-IV or DSM-5). They were recruited from Juntendo Koshigaya Hospital between August 2004 and April 2016. Patients were excluded if they had a history of other psychiatric disorders, severe or acute medical illnesses, neurologic disorders, or were taking drugs that may cause psychosis or

depression. Patients showing clinical evidence of MCI, dementia, and those who had a Mini–Mental State Examination (MMSE) score <24 at the time of remission were also excluded. After all ineligible patients had been excluded, 219 inpatients with MDD (mean age = 65.7 years; age range, 50–85 years) were enrolled in the study. The number of MDD annual inpatients over the age of 50 years is estimated to be approximately 100 at this facility. As almost all eligible patients were approached and invited to enroll during the entry period, the estimated participation rate was approximately 20%. Age at onset of the first depressive episode and the number of depressive episodes were confirmed via medical records. Depressive symptoms were assessed via the Hamilton Rating Scale for Depression (HAM-D). Remission was determined as follows. When a patient no longer met the diagnostic criteria for MDD during daily examinations, the HAM-D was administered at that point. The patient was considered to be in remission if they were confirmed to have a HAM-D score of 7 or less. All patients were taking antidepressants during their hospital stay. The antidepressant doses were converted to equivalent doses of imipramine [36]. Early in the study, BDNF was measured only at admission, but measurement of BDNF after remission was added midway through the study. This resulted in a large difference between the number of patients measured at admission and the number of patients measured after remission.

The study protocol was approved by the Medical Ethics Committee of Juntendo University, was performed in accordance with the regulations outlined by Juntendo University, and conformed with

the provisions of the Declaration of Helsinki (1995). All participants provided written informed consent prior to participation.

2-2. Measurement of BDNF

Blood samples were taken before breakfast at 07:00 on the day after admission and immediately after remission, and were centrifuged immediately after blood was drawn and clotting confirmed. Serum samples were stored at -80°C until processing.

Serum levels of BDNF were measured using a Quantikine Human BDNF Immunoassay Kit (R&D Systems, Minneapolis, MN, USA) according to the instructions from the manufacturer and as previously described (Minelli et al., 2011). The detection limit was 20 pg/ml, and the intra-assay coefficient of variation was <8%.

2-3. Follow-up and diagnosis of MCI and dementia

All patients were followed up prospectively. The follow-up period began immediately after remission and lasted until MCI/dementia diagnosis or August 2018. Patients were administered the MMSE every year after discharge and when cognitive problems were clinically observed. At the time of MMSE administration, patients were assessed and given a diagnosis of MCI or dementia. The diagnosis of MCI or dementia was made by each patient's physician. The DSM-5 criteria for mild

neurocognitive impairment and major neurocognitive impairment were used to diagnose MCI and dementia, respectively. The assessment of MCI/dementia outcomes was blind to baseline BDNF levels.

2-4. Apolipoprotein E phenotype determination

Apolipoprotein E phenotypes for all samples were determined via isoelectric focusing carried out at SRL, Tokyo, Japan [37].

2-5. Statistical analysis

Patients were divided into a Low BDNF group and a non-Low BDNF group. Those in the Low BDNF group had a BDNF level lower than the mean of healthy subjects minus one standard deviation. We used BDNF serum data from healthy subjects, obtained in our previous study [28], to establish a cut-off level of 27105.5 minus 8310.2 pg/mL (18795.3 pg/mL).

Demographic data at admission and after remission were compared between the Low BDNF group and the non-Low BDNF group. Age, age at onset, education, number of depressive episodes, HAM-D scores, MMSE scores, antidepressant dose, duration of the follow-up period, and serum BDNF levels were compared using two-tailed unpaired Student's t-tests. The χ^2 test was used to compare sex and apolipoprotein E4 variables.

Kaplan-Meier survival curves and log-rank comparisons were used to compare the time from

remission to onset of MCI or dementia between the Low or non-Low BDNF groups. Patients were censored on loss of follow-up or at the end of the present study. Cox proportional hazard ratio (HR) estimates were used in a multivariate model with the controlled age at onset, sex, education, and HAM-D scores at admission as covariates.

3. RESULTS

3-1. Demographic characteristics of the Low versus non-Low BDNF group

Of the 219 enrolled patients, 204 were followed to assess the transition to MCI or dementia. The remaining 15 were not followed up. It is possible that some of these patients were lost to follow-up because they died. However, we do not have any information about the reasons they were lost to follow-up. The demographic and comparison data are shown in Table 1.

When comparing the Low BDNF and non-Low BDNF groups at admission, we found no differences in sex, education, the number of depressive episodes, HAM-D scores at admission and remission, MMSE scores, antidepressant dose at admission and remission, the duration of the follow-up period, or ApoE4 frequencies. The age and age at onset of the Low BDNF group was significantly higher than that of the non-Low BDNF group ($p = 0.010$, $p = 0.003$).

Immediately after remission, serum samples were collected from 117 patients. We found no

differences in age, the age at onset, sex, the number of depressive episodes, HAM-D scores at admission and remission, MMSE scores, the antidepressant dose at admission and remission, the duration of the follow-up period, or ApoE4 frequencies between the two groups. The education duration was significantly longer in the Low BDNF group compared with the non-Low BDNF group ($p = 0.044$).

3-2. Transition from MDD to MCI or dementia

The mean follow-up period was 24.3 months (standard deviation 30.6). Of the 204 patients with MDD who were followed up, nine developed MCI and 15 developed dementia (8 AD, 4 frontotemporal dementia, 1 dementia with Lewy bodes, and 2 vascular dementia). The χ^2 test showed no significant differences in the number of patients who developed MCI or dementia between the Low and non-Low BDNF groups at admission. In the Low BDNF group at remission, however, the number of patients who developed MCI or dementia was significantly higher than that in the non-Low BDNF group at remission ($p = 0.043$) (Table 1).

3-3. Incidence of MCI or dementia by survival analysis

Figure 1 displays the Kaplan-Meier survival curve showing the time to incidence of development of MCI or dementia for the two groups, divided by serum BDNF levels at admission. The cumulative

probabilities of developing MCI or dementia were not different between the Low BDNF and non-Low BDNF groups at admission (log-rank test). Cox proportional hazard ratio estimates also indicated that serum BDNF levels at admission were not associated with the incidence of development of MCI or dementia after controlling for age at onset, sex, education, and depression severity (HAM-D scores) at admission (Table 2).

Figure 2 shows the Kaplan-Meier survival curves for the two groups, divided by serum BDNF levels measured after remission. The Log-rank test showed no significant difference in the cumulative probability of developing MCI or dementia between the Low and non-Low BDNF groups at remission. However, after controlling for the age at onset, sex, education, and HAM-D scores at admission, the Cox proportional hazard ratio estimates demonstrated a significant association between BDNF levels at remission and the incidence of development of MCI or dementia (HR = 11.733; 95%CI, 1.16–119.14, p = 0.037) (Table 3). This indicates that the patients with lower BDNF levels after remission had a higher incidence of developing MCI or dementia.

4. DISCUSSION

The main finding of the present study was that serum levels of BDNF after remission, but not in acute depressive phase, may predict the transition from depression to dementia or MCI.

Given that depression severity has been associated with the future incidence of dementia (Chen et al., 2008) and serum levels of BDNF (Shimizu et al., 2003; Yoshimura et al., 2007; Satomura et al., 2011), we hypothesized that serum levels of BDNF in the acute phase of depression would predict the transition from depression to dementia. However, the results of the present study failed to substantiate our hypothesis. Therefore, serum BDNF may not be involved with or mediate the relationship between depression severity and the future incidence of dementia.

Unlike the result in the acute phase, lower serum levels of BDNF after remission predicted the development from depression to dementia. The Framingham Heart Study, which was a large cohort study, examined the relationship between serum BDNF levels and the risk for dementia. The results demonstrated that higher serum levels of BDNF decreased the future risk of dementia, especially in women and older individuals [24]. The participants in the present study were also older and were predominantly female (73% female), and our results from the group with low serum BDNF levels after remission supported the previous findings. Given previous evidence of lower serum BDNF levels in patients with dementia [20,25], our results suggest that patients with depression with lower serum BDNF levels after remission may have been in a prodromal state of dementia. Our previous study demonstrated that lower serum BDNF levels after remission were correlated with longer depressive episodes [33]. In that study, all patients were treated with an antidepressant. Combining the previous and present results, we speculate that elderly patients with depression who have prodromal

dementia may be treatment resistant. A recent pilot study using amyloid PET scanning demonstrated that amyloid-positive older patients with MDD had a poor antidepressant response to sequential antidepressant treatment [38]. This result suggests that depression as a prodromal state of AD may be treatment resistant.

However, it is also possible that lower serum BDNF may accelerate the development from depression to dementia. It has been suggested that serum BDNF may play a role in the development of AD, and that higher serum BDNF levels may protect against the future occurrence of dementia and AD. According to the findings of the Framingham Heart Study, the relationship between serum BDNF levels and the future occurrence of AD was independent of putative risk factors. The authors suggested that BDNF might be an active participant in the mechanisms underlying these conditions rather than an incidental risk marker [24]. Decreased serum BDNF levels have been observed in various neurological disorders [25] and have been correlated with cognitive decline in healthy subjects [39]. From these previous reports, decreased serum BDNF levels may not reflect a prodromal state of a specific neurological disease, but rather may promote neurodegeneration and decreased neurological function. Alternatively, they may deteriorate protective effects against such neurological damage. Our previous result [33] could also indicate that longer depressive episodes interrupt the normalization of BDNF serum levels by treatment. If lower serum BDNF levels after depression remission influence the development to dementia, then earlier treatments that shorten the depressive phase

might prevent residual BDNF decline after remission, and potentially prevent the transition to dementia.

The present study had several limitations. First, the power calculation using Schoenfeld's formula showed that the power (β-1) with this sample size was approximately 0.69. To achieve a power of 0.8, a total of 166 cases would be needed. Therefore, low statistical power is one limitation of this study. For this reason, we consider this study to be preliminary. Second, dementia included various subtypes, and MCI was included in the analysis. Given the small number of cases, we were unable to analyze each subtype separately. Although low serum BDNF levels have been observed in various neurological disorders [25], an analysis of each subtype is necessary to understand the relationship between depression and dementia. Third, all patients were taking antidepressants during hospitalization, and the class and dose of antidepressants were not controlled. Although other reports have yielded different results [40], it has been suggested that antidepressants might influence the later development of dementia [41-43]. Data on patients who were followed up without medication are needed. Fourth, the age difference between the healthy participants used to establish the BDNF cut-off value (mean age: 54.4 years) and the individuals with depression in the current sample (mean age: 63+ years) is also an limitation. BDNF levels are known to change with age, and this age disparity may have influenced the interpretation of our results. Further study with age-matched cohorts is warranted to validate and refine our findings. Finally, the short follow-up duration is a

limitation. We will continue to follow some of these patients and plan to report on additional cases with longer follow-up durations in the future.

5. CONCLUSION

In conclusion, we investigated the relationship between serum levels of BDNF in depression and the risk of developing dementia. Serum levels of BDNF in the remitted phase were associated with the future development to dementia, although this was not the case for BDNF levels in the acute depressive phase. Patients with low serum BDNF levels, even after depression remission, might have an increased risk of developing dementia. These findings suggest a potential association between residual low serum BDNF levels after remission and the prodromal state of dementia, or the involvement of BDNF in the transition from depression to dementia. However, given that this study is low-powered and preliminary, interpretation of the results should be approached with caution.

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Conflict of Interest

Hajime Baba received grant funding from the Japan Society for the Promotion of Science and Esai, and speaker's honoraria from Otsuka Pharmaceutical, Sumitomo Dainippon Pharma, MSD, Meiji Seika Pharma, Eli Lilly, Yoshitomi Yakuhin, Janssen Pharmaceutical, Kyowa Pharmaceutical, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Pfizer, Esai, Takeda Pharmaceutical, Lundbeck, Mochida, Sawai, Kowa, EA Pharma, Mylan EPD and Viatris. Toshihito Suzuki received speaker's honoraria from Otsuka Pharmaceutical, Sumitomo Dainippon Pharma, MSD, Meiji Seika Pharma, Janssen Pharmaceutical, Kyowa Pharmaceutical, Pfizer, Takeda Pharmaceutical, Lundbeck, Mochida, Sawai, Kowa, EA Pharma, Mylan EPD, Viatris and Mochida Pharmaceutical. The other authors declare that they have no conflicts of interest with respect to this study.

Contributions

TS and HB conceived of the study, designed the study, conducted the statistical analysis, interpreted the data, and wrote the initial draft of the manuscript. HM and SN recruited participants and collected data. NY and KS carried out the statistical analysis and interpreted the data. TS supervised the study.

All authors read and approved the final manuscript.

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Table 1. Demographic and Comparison Data between Low and non-Low BDNF Groups

	at Admission (n = 204)			at Remission (n = 117)		
	Low BDNF (n = 114) Mean(SD)	non-Low BDNF (n = 90) Mean(SD)	*P-value*	Low BDNF (n = 54) Mean(SD)	non-Low BDNF (n = 63) Mean(SD)	*P-value*
Age (years old)	66.7 (8.20)	63.7 (8.11)	0.01	66.4 (8.60)	65.7 (7.66)	0.598
Age at onset (years old)	60.5 (12.84)	54.83 (11.89)	0.003	59.9 (12.51)	56.5 (12.17)	0.175
Sex (M/F)	31/83	24/66	0.933	18/36	13/50	0.121
Education (years)	12.1 (2.51)	12.2 (2.39)	0.799	12.6 (2.63)	11.6 (1.96)	0.044
Number of depressive episodes	2.1 (1.80)	2.3 (1.37)	0.508	2.03 (1.19)	2.8 (2.39)	0.052
MMSE at remission	26.0 (2.76)	26.1 (3.00)	0.803	25.9 (3.29)	26.0 (2.69)	0.91
HAM-D at admission	24.7 (10.67)	21.5 (9.22)	0.074	21.9 (10.75)	25.7 (10.85)	0.124
HAM-D at remission	5.3 (5.15)	5.7 (5.77)	0.753	4.6 (5.52)	4.9 (4.07)	0.772
Antidepressant dose (mg/day)	132.8 (75.33)	129.9 (82.37)	0.846	133.0 (89.84)	146.5 (74.62)	0.499
ApoE4, n/total (%)	22/93 (23.66)	14/75 (18.67)	0.433	10/42 (0.24)	7/50 (0.14)	0.227
BDNF (pg/mL)	12853.2 (3994.29)	25079.4 (4612.43)	< 0.001	12667.3 (5008.48)	24913.5 (6848.90)	< 0.001
Duration of follow-up periods (Months)	24.3 (30.6)	20.5 (30.3)	0.413	29.0 (32.8)	23.4 (30.9)	0.347
Number of MCI, n/total (%)	4/114 (3.51)	5/90 (5.56)	0.303	5/54 (9.26)	1/63 (1.59)	0.096
Number of Dementia, n/total (%)	11/114 (9.65)	4/90 (4.44)		5/54 (9.26)	3/63 (4.76)	
Number of MCI or Dementia, n/total (%)	15/114 (13.16)	9/90 (10.00)	0.487	10/54 (1.85)	4/63 (6.35)	0.043

[a] Student t-test (df = 112 in Low BDNF group, df = 88 in non-Low BDNF group); b Student t-test (df = 52 in Low BDNF group, df = 61 in non-Low BDNF group); c χ 2 test (df = 1 in both groups)

MDD, major depressive disorder; HAM-D, Hamilton rating scale of depression; MMSE, Mini-Mental State Examination

Table 2. Cox proportional hazard ratio estimates for a multivariate model of predictors of MCI or dementia with serum BDNF level **at admission** as a covariate

	Hazard ratio	95% CI	p value
Age at onset	1.021	0.958 – 1.088	0.529
Sex	1.757	0.342 – 9.031	0.500
Education	1.185	0.853 – 1.645	0.311
HAM-D at admission	1.007	0.944 – 1.074	0.840
BDNF(Low/non-Low)	1.498	0.365 – 6.148	0.574

HAM-D; hamilton rating scale for depression, BDNF;brain derived neurotrophic factor

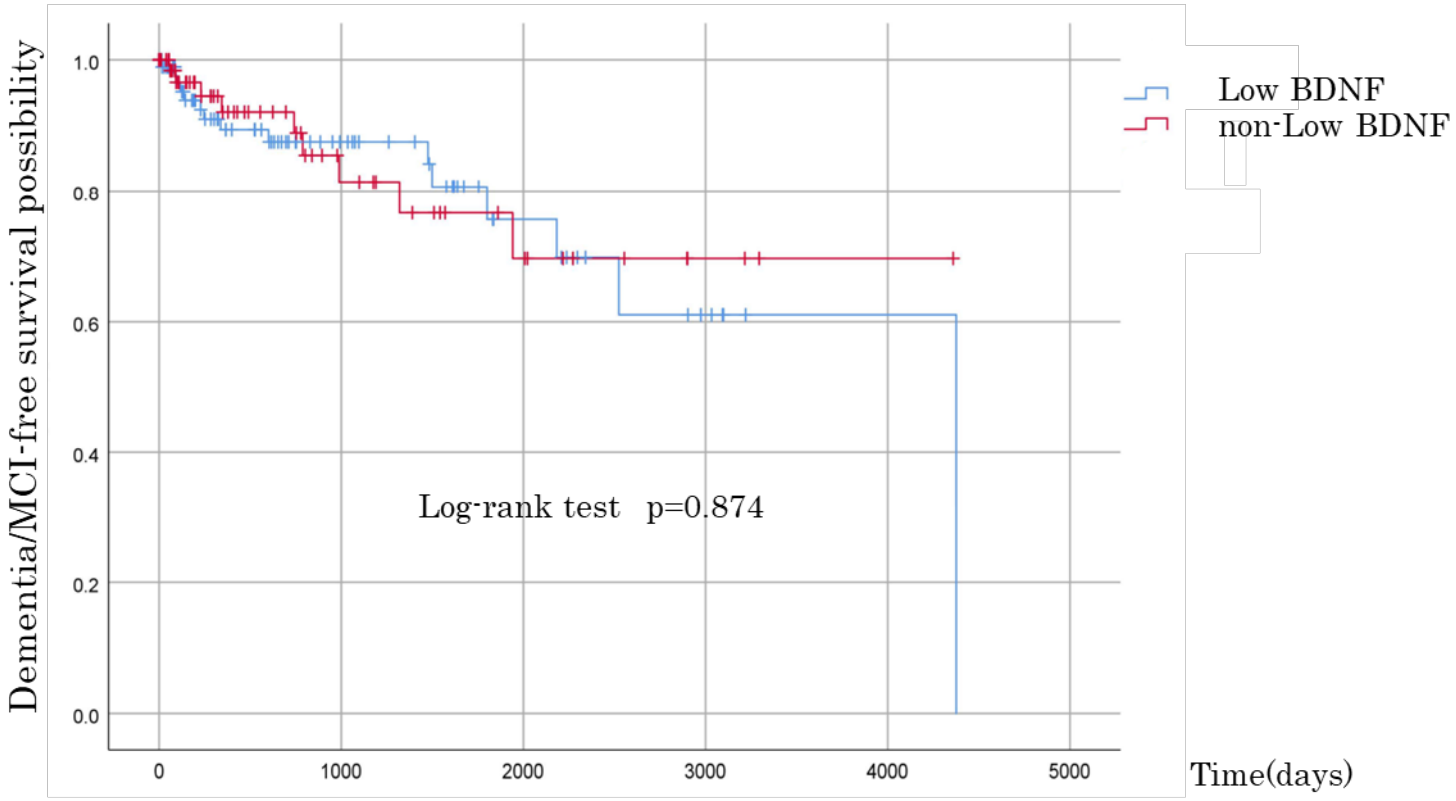
MCI; mild cognitive impairment, CI; confidence interval

Table 3. Cox proportional hazard ratio estimates for a multivariate model of predictors of MCI or dementia with serum BDNF level **after remission** as a covariate

	Hazard ratio	95% CI	p value
Age at onset	0.980	0.920 – 1.044	0.529
Sex	4.18	0.479 – 36.490	0.196
Education	0.885	0.596 – 1.315	0.545
HAM-D at admission	1.025	0.955 – 1.100	0.497
BDNF(Low/non-Low)	11.733	1.155 – 119.137	0.037

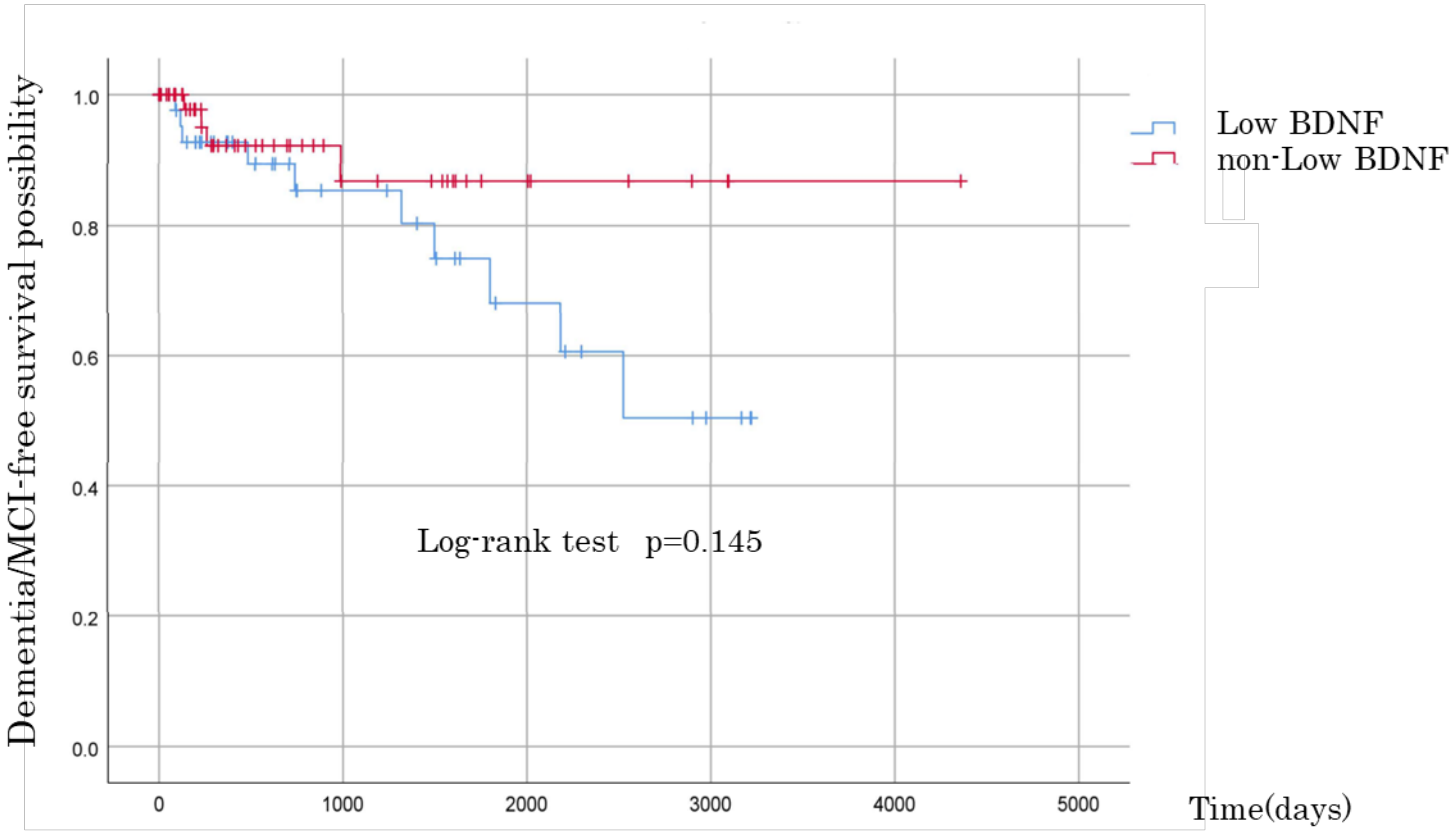
HAM-D; hamilton rating scale for depression, BDNF;brain derived neurotrophic factor

MCI; mild cognitive impairment, CI; confidence interval



Low BDNF	114	33(9)	13(12)	5(14)	1(14)	0(15)
Non-Low BDNF	90	20(7)	10(9)	3(9)	1(9)	0(9)

Fig.1 Kaplan-Meier survival curve of time to incidence of MCI or dementia by serum BDNF levels **at admission**



Low BDNF	54	18(5)	9(8)	3(10)	0(10)	
Non-Low BDNF	63	15(4)	7(4)	3(4)	1(4)	0(4)

Fig.2 Kaplan-Meier survival curve of time to incidence of MCI or dementia by serum BDNF levels **after remission**