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Potential Inflammatory Markers Related to the Conversion to Alzheimer's Disease in Female Patients With Late-Life Depression

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ABSTRACT

BACKGROUND: Inflammation has been postulated as a mediating factor in the development of Alzheimer's disease (AD) pathology. We investigated candidate inflammatory markers related to conversion to AD among patients with depression.

METHODS: A longitudinal study was conducted with older women with depression who were at least 55 years of age, with a mean follow-up period of 5.73 years. At baseline, 9 inflammatory cytokines were measured using the immunoreactivity method. During follow-up, patients with depression who complained of cognitive impairment were evaluated and diagnosed with AD conversion. Association of the cytokines with conversion to AD was analyzed using multivariable Cox proportional hazards regression with adjusting covariates. For clinical applicability, the optimal cutoff value was determined using the minimum p value approach for the conversion to AD and was used to plot an AD-free survival curve.

RESULTS: Among 132 participants, 34 patients with depression (25.76%) developed AD during their follow-up period. Higher levels of interleukin (IL) 1β at baseline (hazard ratio = 3.30 [95% CI, 1.11–9.78], $p = .031$) and lower levels of IL-10 ($p < .001$) were significantly associated with an increased risk of progression to AD. The survival curve plotted by the cutoff value of ≥0.25 pg/mL for IL-1β and ≤0.15 pg/mL for IL-10 suggested adjusted hazard ratios of 8.96 (95% CI, 3.48–23.09; $p < .001$) for IL-1β and 10.99 ($p < .001$) for IL-10, respectively.

CONCLUSIONS: This study demonstrated that IL-1β and IL-10 were associated with conversion to AD among patients with late-life depression, suggesting their potential as predictive markers of the transition to AD from depression.

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and impaired daily functioning. It is the most common form of dementia, affecting millions of individuals worldwide and placing a substantial burden on patients, families, and society owing to its profound impact on quality of life and health care resources (1). Reliable biomarkers could aid in the timely application of preventive strategies, the selection of participants for neuroprotective trials, and disease monitoring. However, it is difficult to assess the risk of developing AD.

Growing evidence indicates that the development of AD involves more than just a neuronal aspect; it entails significant interactions with immunological mechanisms in the brain. According to previous research, neuroinflammation may be triggered by the accumulation of misfolded proteins such as amyloid-β (Aβ) plaques, a hallmark of AD. Activated microglia are involved in the clearance of Aβ. However, chronic activation of microglia can lead to the release of proinflammatory cytokines and other neurotoxic substances that contribute to disease progression and severity (2). Genome-wide analysis suggests that multiple genes associated with an increase in sporadic AD are involved in regulating the glial clearance of misfolded proteins and the subsequent inflammatory response (3). Neuroinflammation can compromise the integrity of the blood-brain barrier, allowing the entry of peripheral immune cells and inflammatory molecules into the brain. This breach of the blood-brain barrier can further amplify neuroinflammatory responses and contribute to neuronal damage (4). Longitudinal and cross-sectional studies have demonstrated elevated levels of inflammatory markers before AD onset and during the early stages of the disease (5–7).

Large number of patients with late-life depression have converted to AD (8). Because depression has also been linked to AD as a risk factor (9), identifying individuals with a high risk of dementia among those with depressive symptoms could assist clinicians in implementing timely preventive strategies. Given that depression is also influenced by neuroinflammatory responses (10), it can be inferred that depression and AD are associated through similar pathways. Depression and cognitive dysfunction may be associated with hippocampal atrophy,

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decreased total brain volume, and proinflammatory effects (11,12).

Sex differences in inflammatory biomarker systems are associated with decreased neuroplasticity, and women are at a higher risk of developing AD than men (13–15). Women become depressed more frequently than men, and a retrospective cohort study reported sex differences in some inflammatory markers in patients with depression (16,17). This indicates that both depression and AD may have sex-specific pathophysiologies of inflammation. To identify specific inflammatory markers related to the risk of developing AD in patients with depression, studies focusing on female populations should yield more focused results (15,17). In this study, we aimed to investigate the risk of AD using systemic inflammatory markers in peripheral blood samples at the time of diagnosis of major depressive disorder in a longitudinal cohort of older women.

METHODS AND MATERIALS

Study Samples

Participants were eligible if they were female and at least 55 years of age. Eligible patients were enrolled from June 1995 to January 2012 at the Geropsychiatry Clinic of the Samsung Medical Center and were followed for up to 18.53 years (mean 5.73 [range 1.00–18.53] years). All participants were of unrelated Korean ancestry and underwent a semistructured diagnostic interview using the Samsung Psychiatric Evaluation Schedule. The Affective Disorder section of the Samsung Psychiatric Evaluation Schedule uses the Korean version of the Structured Clinical Interview for DSM-IV (18,19). At least one family member living with the patient was interviewed to supplement the patient's report on psychiatric symptoms, behaviors, duration of episodes, level of functioning, recent treatments, comorbid diagnoses, and cognitive function. Diagnoses were confirmed by a board-certified psychiatrist based on the Samsung Psychiatric Evaluation Schedule, case review notes, and other relevant data. A minimum baseline score of 15 on the 17-item Hamilton Depression Rating Scale was required. Participants were included if they had been diagnosed with depression, had no cognitive problems at baseline, no complaints of memory impairment, and a 28/30 or greater score in the Korean version of the Mini-Mental State Examination (MMSE) (20). Potential participants were excluded for pregnancy, significant medical conditions, abnormal laboratory baseline values, unstable psychiatric features (e.g., suicidal thoughts), a history of alcohol or drug dependence, seizures, head trauma with loss of consciousness, neurological illness, or concomitant Axis I psychiatric disorders. The protocol was approved by the ethics review board of the Samsung Medical Center (IRB No. 1999-10-14). Informed consent was obtained from all participants.

Study Protocol

Consistent with our previous study on antidepressant responses in patients with major depression, the current study was conducted in a naturalistic clinical setting (19,21). This study included 132 female patients who experienced late-life depressive episodes. Peripheral blood samples for genotyping, including apolipoprotein E (*APOE*), and biological analyses were collected at baseline around the time of the depression diagnosis, together with measurements of the initial 17-item Hamilton Depression Rating Scale. Of the patients, 64% (84/132) responded to antidepressant medication and showed improvement in depressive symptoms, 31% (41/132) experienced clinical recurrence during the study period, and 7.6% (10/132) had persistent long-term depressive symptoms. Patients were followed up every 3 months, and the scores on the Korean version of the MMSE were updated every year. At each clinic visit, when the patient (or her family member) complained of cognitive impairment, the patient underwent extensive neuropsychological, brain magnetic resonance imaging, and laboratory tests. A standardized neuropsychological battery, the Seoul Neuropsychological Screening Battery-Dementia Version, was used to assess all participants at baseline and follow-up visits. The Seoul Neuropsychological Screening Battery-Dementia Version includes quantitative measures of attention, language, visuospatial function, memory, and frontal executive function domains (22). Additionally, we administered the following assessment instruments: the Korean version of the MMSE, Clinical Dementia Rating (CDR) scale (23), Seoul-Activities of Daily Living (22), Seoul-Instrumental Activities of Daily Living (24), Korean version of the Neuropsychiatric Inventory (25), and Korean version of the Geriatric Depression Scale (26). All psychometric tests were scheduled at 12-month intervals during the follow-up period. The diagnosis of incident all-cause dementia was made in accordance with the DSM-IV criteria (27) and required objective deficits in neuropsychological testing as well as impairments in activities of daily living. Specific diagnostic criteria were used to classify patients with dementia. Probable AD was diagnosed using criteria from the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (28). Brain magnetic resonance imaging results were used as an auxiliary measure to differentiate AD from other diseases capable of producing a dementia syndrome. Board-certified neuroradiologists performed visual diagnoses. We attempted to make the clinical diagnosis as clear as possible by excluding patients with clinical presentations suspected of having non-AD degenerative dementia, such as those who showed Parkinsonian symptoms or behavioral/personality changes. In our Geropsychiatry Clinic, the interobserver diagnostic reliability of AD and non-AD dementia was 91.4%.

Plasma Levels of Inflammatory Cytokines

Inflammation is a complex and essential physiological response to biological, chemical, or physical stimuli and encompasses a series of cellular and molecular events that regulate interactions within the inflammatory process. During the initial stage of inflammation, immune cells move to the injury site following a precise sequence of events guided by soluble proteins such as cytokines, chemokines, and acute-phase proteins (29). Prolonged inflammation has been reported to contribute to numerous diseases including arthritis, autoimmune diseases, diabetes, cancer, depression, neurodegenerative disorders such as AD, and aging (29). We selected the circulating soluble proteins produced by

peripheral immune cells, microglia, and astrocytes in the brain as candidate inflammatory markers for the development of AD in participants with depression. Interleukin (IL) 1, IL-6, IL-12, tumor necrosis factor α (TNF-α,), interferon gamma (IFN-γ), and granulocyte-macrophage colony stimulating factor (GM-CSF) are well characterized as proinflammatory cytokines, whereas IL-4 and IL-10 are recognized as anti-inflammatory cytokines (30). Additionally, we included C-reactive protein (CRP), an acute-phase protein that is the most commonly used inflammatory marker.

Venous peripheral blood (10 mL) was drawn from participants using vacutainer tubes containing EDTA-K_2 anticoagulant (Becton Dickins) at 8:00 AM–10:00 AM. Plasma were collected and aliquoted after centrifugation at 3000 rpm for 10 minutes and stored at −80 °C until use. Inflammatory marker levels were measured concurrently on the day of the experiment. Cytokine analyses of IL-1β, IL-4, IL-6, IL-10, IL-12, GM-CSF, IFN-γ, and TNF-α were conducted using Luminex Performance Human Sensitivity Cytokine Panel A (LHSCM; R&D Systems) according to the manufacturer's instructions. A Luminex Human Discovery Assay (LXSAHM; R&D Systems) was used for CRP analysis. All analyses were conducted using a Bio-Plex 200 system (Bio-Rad). All the samples were measured in duplicate, and standards were loaded together on each plate for standard curve. The intra-assay of (%) coefficients of variation for assayed measures of IL-1β, IL-4, IL-6, IL-10, IL-12, GM-CSF, IFN-γ, TNF-α, and CRP in 2 samples were 1.04, 1.43, 0.65, 0.68, 0.65, 0.26, 0.30, 0.40, and 0.27, respectively. Samples that were below the limit of detection had cytokine levels that were too low to be distinguishable from background noise (<0.01 pg/mL); therefore, these samples were treated as having 0 levels of that cytokine (31–33).

Statistical Analysis

Data distribution and normality were assessed using box plots, Q-Q plots, and Shapiro-Wilk's tests. Log transformations were performed on 5 analytes of inflammatory markers (CRP, IL-1β, IL-6, IL-10, TNF-α) due to skewed distributions. Regarding the remaining 4 analytes (IL-4, IL-12, IFN-γ, and GM-CSF), numbers of participants were observed below assay detection limits; these were analyzed as binary variables (0 or larger than 0) (31–33). Univariate analysis was conducted for demographic variables, clinical variables, and the 9 biomarker analytes. Cox proportional hazards regression analysis was used to determine the association with conversion to AD after assessing the proportional hazard assumption using Schoenfeld residuals. Thereafter, Cox proportional hazards regression for multivariable analysis was used for the inflammatory markers and covariates that showed p values $< .2$ (rounded off to the second decimal) in the univariate analysis (34). No correction for multiple testing was applied for the 9 inflammatory markers analyzed.

For the significant analytes of inflammatory markers from the multivariate analysis, the optimal cutoff score of the raw value was determined using the minimum p value approach of the log-rank test for the AD-free survival rate (35). For significant analytes, AD-free survival curves for the 2 groups divided by the cutoff value were estimated using the Kaplan-Meier method. To assess the clinical prediction performance of the multivariable model, the area under the time-dependent receiver operating characteristic curve at 60 and 120 months after enrollment were estimated by Uno's method (36). p Values $< .05$ were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.).

RESULTS

Participant Characteristics

A total of 132 female participants of Korean descent were included in this study. Baseline characteristics associated with the conversion to AD are summarized in Table 1. The mean (SD) age at sample collection and years of education of the patients with depression were 69.84 (7.22) and 7.92 (4.55) years, respectively. Of the 132 female patients with major depression, 34 (25.76%) developed AD during the mean follow-up period of 5.73 years (range 1.00–18.53 years). Patients with higher hazards for AD were significantly older (converted vs. nonconverted: 70.24 ± 8.11 years vs. 69.70 ± 6.93 years; p = .034; hazard ratio [HR] [95% CI] = 1.06 [1.01–1.12]) and less educated (7.15 ± 5.16 years vs. 8.19 ± 4.32 years; p = .035; HR [95% CI] = 0.92 [0.85–0.99]) than those who did not convert. No other statistical differences were observed at baseline between patients who did and did not convert, including the initial severity of depression (Hamilton Depression Rating Scale score), age at onset of depression, number of *APOE* ε4 alleles, and comorbidities (hypertension, diabetes, hyperlipidemia, cardiac disease, and cerebrovascular disease).

After an average of 5.73 years, the patient group that converted to AD showed a mean MMSE score (SD) of 17.68 (5.35), a mean CDR score of 1.26 (0.57), and a mean CDR sum of boxes score of 6.58 (3.61) at diagnosis, while non-converted patients had a mean score of 27.28 (2.67) on the MMSE, a mean score of 0.13 (0.22) on the CDR, and a mean score of 0.88 (0.85) on the CDR sum of boxes. Age, education, cardiac illness, onset of depression, and number of *APOE* ε4 alleles were selected as covariates for the multivariable analysis, which showed a p value $< .2$ (rounded off to the second decimal) in the univariate analysis (Table 1).

Associations of Inflammatory Markers With Conversion to AD in Depression

Table 2 shows plasma IL-1β, IL-6, IL-10, TNF-α, and CRP levels, which were log-transformed due to skewed distributions, and IL-4, IL-12, IFN-γ, and GM-CSF, which were analyzed as binary variables (no detection vs. larger than 0.01 pg/mL) due to the assay detection limit (31–33,37).

Patients with higher plasma levels of IL-1β had significantly higher hazards for conversion to AD (p = .013; HR [95% CI] = 1.96 [1.15–3.34]). Plasma IL-4, IL-6, IL-10, IL-12, GM-CSF, IFN-γ, TNF-α, and CRP showed no statistically significant difference in the univariable analysis between patients who converted to AD and patients who did not convert (Table 2).

For the multivariable analysis, we determined the potential biomarkers related to the conversion to AD in patients with depression among 5 candidate inflammatory markers, IL-1β, IL-6, IL-10, IL-12, and IFN-γ, which all showed p values $< .2$ in

Table 1. Demographic and Clinical Characteristics of 132 Female Patients With Late-Life Depression

		Converted to AD			
	Total, *N* = 132	No, *n* = 98	Yes, *n* = 34	Hazard Ratio (95% CI)	*p* Value[a]
Baseline					
Demographic					
Age, years	69.84 ± 7.22	69.7 ± 6.93	70.24 ± 8.11	1.06 (1.01–1.12)	.034[b]
Education, years	7.92 ± 4.55	8.19 ± 4.32	7.15 ± 5.16	0.92 (0.85–0.99)	.035[b]
Depression					
Initial severity of depression, HAMD	19.08 ± 4.12	19.07 ± 3.68	19.10 ± 5.43	0.96 (0.88–1.06)	.429
Age of depression onset, years	61.86 ± 12.27	61.16 ± 11.94	63.85 ± 13.15	1.02 (0.99–1.05)	.197[b]
Comorbidities					
Hypertension	77 (58.33%)	60 (61.22%)	17 (50.00%)	1.01 (0.50–2.05)	.975
Diabetes mellitus	31 (23.48%)	25 (25.51%)	6 (17.65%)	1.18 (0.48–2.91)	.722
Hyperlipidemia	29 (21.97%)	21 (21.43%)	8 (23.53%)	1.28 (0.58–2.85)	.545
Cardiac illness	24 (18.18%)	15 (15.31%)	9 (26.47%)	1.58 (0.73–3.41)	.247[b]
Cardiovascular disease	12 (9.09%)	7 (7.14%)	5 (14.71%)	1.12 (0.43–2.93)	.812
APOE Genotype					
Number of *APOE* ε4 alleles	–	–	–	–	.105[b]
APOE ε4 allele, 1	24 (18.18%)	16 (16.33%)	8 (23.53%)	0.94 (0.40–2.19)	>.999
APOE ε4 allele, 2	3 (2.27%)	1 (1.02%)	2 (5.88%)	4.76 (1.10–20.63)	.074
APOE ε4 allele, 0	105 (79.55%)	81 (82.65%)	24 (70.59%)	–	Reference
On Diagnosis of AD Transition					
Neuropsychological Test					
MMSE	–	27.28 ± 2.67	17.68 ± 5.35	–	–
CDR	–	0.13 ± 0.22	1.26 ± 0.57	–	–
CDR-SB	–	0.88 ± 0.85	6.58 ± 3.61	–	–

Values are presented as mean ± SD for continuous variables and frequency, *n* (%), for categorical variables.

AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CDR-SB, sum of boxes of the CDR; HAMD, 17-item Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination.

[a]Cox proportional hazards regression analysis for AD-free survival rate was used to determine the association between demographic and clinical factors.

[b]For the multivariable analysis, covariates were determined by *p* value < .2 (rounded off to the second decimal) in the univariable analysis.

Table 2. Plasma Levels of Inflammatory Cytokines and Association of Cytokines With Conversion to AD Among Female Patients With Late-Life Depression

		Converted to AD		Univariable Analysis[a]		Multivariable Analysis[a,b]	
Cytokines	Total, *N* = 132	No, *n* = 98	Yes, *n* = 34	Hazard Ratio (95% CI)	*p* Value	Hazard Ratio (95% CI)	*p* Value
IL-1β, Log pg/mL	−0.96 ± 0.69	−1.02 ± 0.71	−0.77 ± 0.62	1.96 (1.15–3.34)	.013	3.30 (1.11–9.78)	.031
IL-4[c]	42 (31.82%)	31 (31.63%)	11 (32.35%)	1.07 (0.52–2.23)	.852	–	–
IL-6, Log pg/mL	−0.24 ± 0.35	−0.25 ± 0.36	−0.18 ± 0.33	1.94 (0.72–5.20)	.188	0.84 (0.17–4.30)	.835
IL-10, Log pg/mL	−0.45 ± 0.39	−0.44 ± 0.37	−0.51 ± 0.45	0.62 (0.28–1.38)	.241	0.19 (0.08–0.49)	<.001
IL-12[c]	13 (9.85%)	7 (7.14%)	6 (17.65%)	2.28 (0.93–5.59)	.072	1.10 (0.24–5.09)	.903
GM-CSF[c]	21 (15.91%)	16 (16.33%)	5 (14.71%)	0.70 (0.27–1.81)	.458	–	–
IFN-γ[c]	15 (11.36%)	10 (10.20%)	5 (14.71%)	2.44 (0.92–6.48)	.074	2.68 (0.44–16.20)	.282
TNF-α, Log pg/mL	0.62 ± 0.22	0.62 ± 0.21	0.63 ± 0.26	1.45 (0.29–7.20)	.649	–	–
CRP, Log pg/mL	5.76 ± 0.53	5.77 ± 0.53	5.76 ± 0.54	1.10 (0.57–2.14)	.777	–	–

Values are presented as mean ± SD for continuous variables and frequency, *n* (%), for categorical variables. IL-1β, IL-6, IL-10, TNF-α, and CRP were analyzed after log-transformation due to skewed distribution.

AD, Alzheimer's disease; CRP, C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon gamma; IL, interleukin; TNF-α, tumor necrosis factor α.

[a]Cox proportional hazards regression analyses were used for the association with inflammatory cytokines and conversion to AD.

[b]The multivariable analysis included inflammatory markers selected by *p* value < .2 in the univariable analysis and covariates such as age, education, cardiac illness, age of depression onset, and number of *APOE* ε4 alleles.

[c]IL-4, IL-12, IFN-γ, and GM-CSF were defined by binary variables (0 or larger than 0) due to assay detection limits. Frequency refers to the number of participants with a plasma level > 0 (pg/mL).

the univariable analysis. When we controlled preselected demographic and clinical covariates (age, education, onset of depressive episode, comorbidity of cardiac illness, and number of *APOE* ε4 alleles), we found significant differences between patients who had converted to AD and patients who had not converted in IL-1β (p = .031; HR [95% CI] = 3.30 [1.11–9.78]) and IL-10 ($p < .001$; HR [95% CI] = 0.19 [0.08–0.49]) (Table 2). The *APOE* allele, which has the potential for genetic biomarkers among covariates, also had a significant impact on AD conversion (overall p = .043; *APOE* ε4 allele 1 vs. 0: p = 1.000; HR [95% CI] = 1.12 [0.44–2.89]; *APOE* ε4 allele 2 vs. 0: p = .025; HR [95% CI] = 11.12 [1.68–73.61]) (data not shown).

Clinical Applicability of Candidate Inflammatory Markers

We searched for a cutoff value of a raw plasma level of 2 potential inflammatory markers using a minimum p value approach for clinical applicability to predict the risk of conversion to AD (0.25 pg/mL for IL-1β, and 0.15 pg/mL for IL-10) (Figure 1A and B) (35). Progression-free rates for groups with different baseline risk burdens are graphically depicted in Figure 2. There was a greater hazard for AD among those with higher baseline IL-1β levels (≥0.25 pg/mL) and lower baseline IL-10 levels (≤0.15 pg/mL) (Figure 2A, B) in female patients with depression. We found an approximately 10-fold increased HR for probable AD in patients with depression with higher baseline IL-1β levels ($p < .0001$; adjusted HR [95% CI] = 8.96 [3.48–23.09]) and lower baseline IL-10 ($p < .0001$; adjusted HR [95% CI] = 10.99 [4.00–30.18]) in multivariable analysis with adjusting covariates. Patients with depression with baseline plasma IL-1β ≥ 0.25 pg/mL had decreased cognitive function with an AD-free survival rate of 56.18% (95% CI, 29.39–76.23) compared with those with IL-1β < 0.25 pg/mL of 82.94% (95% CI, 71.67–90.03) 60 months after enrollment and 40.13% (95% CI, 15.91–63.54) and 74.45% (95% CI, 61.07–83.82) at 120 months, respectively. Patients with plasma IL-10 ≤ 0.15 pg/mL had an AD-free survival rate of 48.40% (95% CI, 22.37–70.36) compared with those with plasma IL-10 > 0.15 pg/mL of 83.13% (95% CI, 72.13–90.08) at 60 months and 29.04% (95% CI, 7.92–54.72) and 74.68% (95% CI, 61.49–83.92) at 120 months, respectively. For the multivariable model, the area under the time-dependent receiver operating characteristic curve at 60 and 120 months were estimated by 82.12% (95% CI, 55.32–100.00) and 84.83% (95% CI, 57.20–100.00), respectively (Figure S1).

A comparative analysis of inflammatory cytokines in older female (N = 132) and male (n = 23) patients with depression was also conducted. No significant differences were observed between older male and female patients with depression in the plasma levels of inflammatory cytokines (Table S1).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the potential of peripheral blood surrogate markers related to the conversion to AD in patients with depression. The results highlight that older women with depression with increased proinflammatory IL-1β or decreased anti-inflammatory IL-10 at their first visit had a higher risk of developing AD later. The survival curve was validated using the cutoff value calculated for clinical application, indicating the potential utility of circulating inflammatory biomarkers in the diagnosis of AD in female patients with late-life depression.

We found that increased IL-1β in older patients with depression was associated with transition to AD in later life, which is consistent with previous studies that demonstrated the involvement of inflammation in the development of AD (33,38). As a proinflammatory cytokine, IL-1β plays a crucial role in the inflammatory response in the central nervous system (39). It is produced by activated microglia, astrocytes, and other immune cells in the brain. Inflammatory dysregulation and sustained elevation of IL-1β levels can contribute to neuroinflammation, disrupt normal brain functions, and promote neurodegenerative processes. Furthermore, IL-1β has been

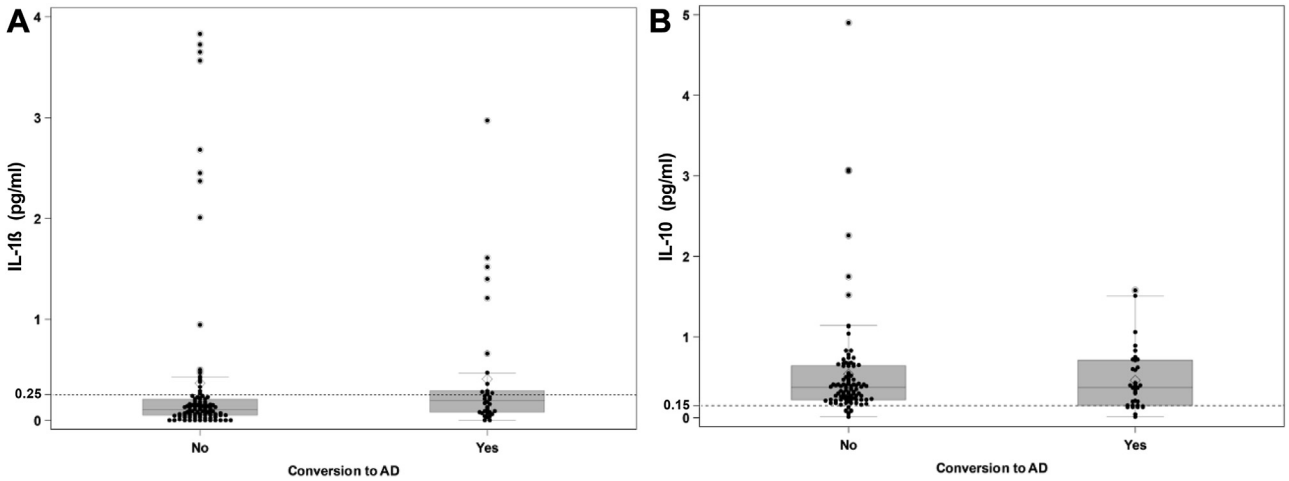

Figure 1. Plasma levels of inflammatory cytokines associated with development of AD. Box plots of **(A)** IL-1β and **(B)** IL-10 in female patients with late-life depression according to the risk of conversion to AD. The dotted line represents the cutoff value of the plasma level using the minimum p value approach for clinical applicability. AD, Alzheimer's disease; IL, interleukin.

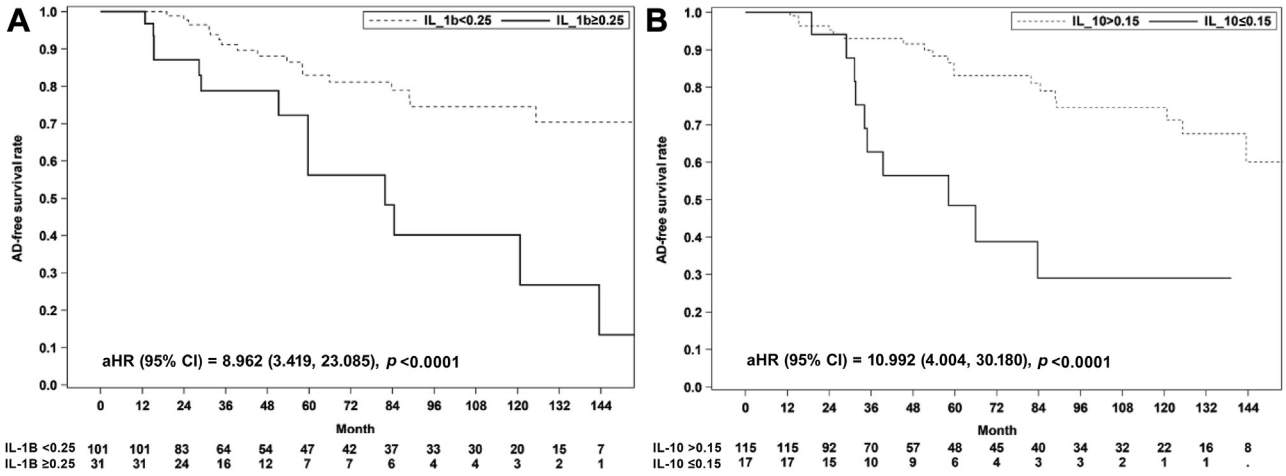

Figure 2. Progression-free rates for groups with different baseline risk burdens of inflammatory cytokines associated with AD. Kaplan-Meier AD-free survival curves by baseline risk burden of **(A)** IL-1β and **(B)** IL-10 plasma levels. aHR for IL-1β and IL-10 with the covariates age, number of years of education, cardiac illness, onset age of depressive episode, and number of *APOE ε4* alleles and *p* value by Cox proportional hazards regression model. AD, Alzheimer's disease; aHR, adjusted hazard ratio; IL, interleukin.

implicated in the regulation of Aβ production and clearance, which is a hallmark feature of AD (40). Moreover, IL-1β can inhibit the phagocytic activity of microglia, thereby impairing the clearance of Aβ plaques in the brain, which is a critical event in the pathogenesis of AD (41). Studies have shown that IL-1β can inhibit neurogenesis, the process of generating new neurons in the brain, and impair synaptic plasticity, which is essential for learning and memory (42–44). By interfering with neurogenesis and neuroplasticity, IL-1β can further contribute to the cognitive impairments observed in AD and may be a key player connecting depression to dementia.

In contrast, IL-10, an anti-inflammatory cytokine, is known for its immunoregulatory properties (45,46). Recent studies have demonstrated that IL-10 can reduce Aβ production and may facilitate the clearance of Aβ plaques by microglia and astrocytes (47) as well as inhibit tau hyperphosphorylation, a process associated with the formation of neurofibrillary tangles related to AD (48). Moreover, IL-10 may help maintain brain homeostasis and limit neuroinflammation associated with AD by suppressing excessive microglial activation and reducing the release of proinflammatory mediators (49). In our study, plasma IL-10 was significantly associated with the transition from depression to AD after adjusting for the effects of covariates and other proinflammatory markers in the multivariate analysis, despite showing no significance in the univariate analysis (Table 2). This could be due to the interaction between IL-10 and other AD-related proinflammatory cytokines rather than IL-10 alone, consistent with previous studies (49). The purely protective effect of plasma IL-10 on conversion to AD may be more evident after adjusting for other variables. Previous reports have also demonstrated that patients with depression had lower blood levels of IL-10 (50), and chronically lower IL-10 levels were reported to expose participants to greater vulnerability to inflammation-related diseases such as AD (47).

Although future studies should elucidate the relationship between peripheral inflammatory cytokines and neuroinflammation of the brain, our results suggest that chronic higher plasma levels of proinflammatory IL-1β or chronic lower plasma levels of anti-inflammatory IL-10 may increase the risk of AD in older patients with depression.

We observed that raw plasma levels of inflammatory cytokines had a skewed distribution or were lower than the detection limit; therefore, we confirmed values for each plate using standard substances including low concentrations, applied log-transformation to our data with a skewed distribution (32,37), and defined cytokines showing lower levels than the detection limit as binary variables if precise quantification was not possible (31–33). These plasma inflammatory cytokine levels and their distribution patterns in human subjects, including patients with depression or AD, are consistent with those reported in previous studies (31,33). In future studies, the development of more precise methods for measuring these cytokines will be useful for identifying other associated inflammatory markers.

Limitations of the current study should be considered. First, it focused on a specific sample of female patients with depression, which may limit the generalizability of the findings to broader populations including male patients with depression, and it was conducted in an exclusively Korean population. Additional information from a comparison analysis of plasma cytokines in male and female patients with late-life depression (Table S1) suggests that the inflammatory markers IL-1β and IL-10, which were associated with AD conversion, may not be specific to women. The inclusion of participants from diverse demographic (including ethnic) backgrounds would enhance the external validity of the study. However, this female-specific study allowed for the observation of the phenotype in a more homogeneous population. Second, no correction for multiple testing was applied across the 9 inflammatory markers, and these results need to be replicated in an independent sample to validate the findings. Third, although the most well-known genes and comorbid chronic illnesses were included, this study did not include

lifestyle factors or acute or chronic inflammatory diseases as covariates that could have influenced the development of AD or baseline inflammatory markers. Therefore, the presence of uncontrolled confounding variables might have affected the results. However, the participants were a well-characterized and relatively homogeneous patient cohort. We used a standardized protocol at a university hospital and followed the participants over an extended period (~18.53 years) originating from a major depressive episode in a longitudinal study. The longitudinal design using standardized comprehensive clinical evaluations strengthened the validity of our measurement of the risk of developing AD over an extensive period from baseline plasma inflammatory markers in individual patients. Developing blood surrogate markers to predict the conversion from depression to AD may be an appealing option for the accessibility and convenience of early diagnosis and large-scale screening.

Conclusions

In conclusion, we demonstrated that plasma levels of IL-1β and IL-10 were associated with the conversion to AD among patients with late-life depression. These findings underscore the potential of plasma-based inflammatory markers for predicting the development of AD in older patients with depression.

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DKK and S-WL had full access to all data used in this study. All authors agreed to submit this manuscript for publication. DKK, S-WL, JHP, SSH, and M-JK designed the study. S-WL and SJL conducted the biochemical experiments. DKK, JHP, YKM, and SSH acquired the clinical data. M-JK performed the statistical analyses. JHP, SSH, M-JK, YKM, S-WL, and DKK analyzed the data and wrote the original draft of the manuscript with input from all co-authors. DKK and S-WL acquired the funding, provided resources and infrastructure, and supervised the study.

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