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Influence of plasma cytokine levels on the conversion risk from MCI to dementia in the Alzheimer's disease neuroimaging initiative database

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1. Introduction

Neurodegenerative dementia is a clinical syndrome characterized by progressive deteriorations in cognitive ability and the capacity for independent living. A recent meta-analysis estimated that 35 million individuals lived with dementia worldwide in 2010, with numbers expected to almost double every 20 years to 65 million in 2030 [1]. Neurodegenerative dementia consists of several types of causative diseases, including Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) [2].

Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia that is also caused by various neurological conditions and is clinically and psychologically defined by a measurable deficit in cognition in at least one domain in the absence of dementia or impaired activities of daily living [3]. Patients with MCI convert to dementia at a rate of 10–15% per year, which is approximately ten-fold higher than the conversion rate in healthy controls [4].

However, there are currently no effective strategies for preventing the conversion of MCI to dementia. Biomarkers that provide a more detailed understanding of the disease mechanisms and efficacy of preventive and treatment strategies are needed. To target this issue, the Alzheimer's Disease Neuroimaging Initiative (ADNI), a longitudinal and worldwide multisite observational study, was launched in 2003. ADNI data may be useful for validating AD-related biomarkers in MCI [5].

Research on the pathogenesis of neurodegenerative dementia, including AD and DLB, has been focusing more on central and peripheral inflammation [6,7]. Microglia and astrocytes both play important roles in the innate neuroimmune system and produce high levels of cytokines when stimulated by amyloid-β (Aβ) and α-synuclein, which is the pathological hallmark of these diseases [7–9]. Several cytokines, such as interleukin (IL)-1β, IL-6, IL-18, and tissue necrosis factor-alpha (TNF-α), were previously shown to be altered in the tissue and body fluids of patients with AD [10,11]. Thus, targeting cytokines has therapeutic potential in the treatment of neurodegenerative dementia. However, previous findings on cytokine levels and their effects on pathological changes associated with AD have been inconsistent among research groups. Limited information is currently available on the influence of cytokines on the development of other types of dementia. A recent review by Brosseron et al. [10] revealed greater changes in cytokine levels in patients with mild AD than in those with advanced AD, indicating that cytokine signaling primarily plays a role in the early or prodromal stages of dementia.

Previous studies reported that the levels of several cytokines correlated with the speed of cognitive decline, even in a healthy aging population and MCI patients [12–18]. However, these studies generally only examined one, or at most only a few, cytokines, and supportive evidence obtained from multivariate analyses is lacking. Therefore, exploratory and multifactorial research is needed to clarify the relationship between cytokines and disease progression in the early or prodromal stage of dementia.

In the present study, we assessed ADNI data and investigated the conversion risk from MCI to dementia based on multiple plasma cytokine levels using a multiple logistic regression analysis.

2. Materials and methods

2.1. Data source

Data used in the preparation of this study were obtained from the ADNI database (adni.loni.usc.edu) on 2 November 2018. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of the ADNI has been to investigate whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and

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[1] Data used in preparation of this manuscript were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Therefore, investigators within the ADNI contributed to the design and implementation of the ADNI and/or provided data, but did not participate in the analysis or writing of this manuscript. A complete list of ADNI investigators may be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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clinical and neuropsychological assessments may be combined to measure the progression of MCI and early AD. Each participant of the 63 ADNI sites in the United States and Canada provided written informed consent, and each ADNI site obtained local Institutional Review Board approval.

2.2. Patients and samples

Patient inclusion criteria were described previously [19] and are available on the ADNI website. In brief, a diagnosis of MCI was based on subjective or objective memory impairments evaluated by education-adjusted scores on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale–Revised. Mini-Mental State Exam (MMSE) scores were between 24 and 30 and the Clinical Dementia Rating (CDR) was 0.5.

In the present study, we included subjects who met the clinical criteria for MCI and had baseline data on plasma cytokines and follow-up data on the severity of dementia on CDR. We included 296 MCI patients and 47 subjects with normal cognition who had baseline data on plasma cytokines. Two hundred and seventy-two (91.9%) MCI subjects and 42 (89.4%) control subjects were non-Hispanic Caucasians, while the remaining subjects were Hispanic Caucasian, Asian, and black populations.

We defined MCI patients whose CDR score reached 1 or more within two years as having converted to dementia, or converted-MCI (C-MCI). MCI patients whose CDR score remained at 0.5 or reverted to 0 were defined as non-converted-MCI (NC-MCI).

We obtained demographic and clinical data, including age, sex, education attainment, the ApoE 4 genotype, MMSE scores, and Alzheimer's Disease Assessment Scale-cognitive 11-item (ADAS-11) scores from all subjects.

2.3. Cytokines

We used the following data on immunological biomarkers, including several cytokines that were publicly accessible on the ADNI website: ciliary neurotrophic factor (CNTF), C-reactive protein (CRP), IL-13, IL-16, IL-18, IL-3, IL-6 receptor (IL-6R), IL-8, CXCL-10, matrix metallopeptidase-9 (MMP-9), and TNF-α. These data were obtained from the file “Biomarkers Consortium Plasma Proteomics Project RBM Multiplex Data and Primer (Zip file)”, which was downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=11&subCategoryId=33) on 2 November 2018. These biomarkers were measured using Luminex xMAP technology (Luminex Corporation, Austin, Texas, United States), the details of which were attached to the Zip file described above. Briefly, Luminex xMAP technology uses fluorescent polystyrene microspheres called beads. These beads are coated with either ligand or capture antibodies, and each bead contains a unique color-coded signature to be read by the flow-based laser apparatus.

2.4. Evaluation of CSF $A\beta_{42}$ and p-tau

In order to examine the pathological backgrounds of MCI subjects, we also collected data on cerebrospinal fluid (CSF) $A\beta_{42}$ and phosphorylated tau (p-tau) from subjects with available data.

CSF levels of $A\beta_{42}$ and p-tau were obtained from the file “UPENN CSF Biomarker Master [ADNI1,GO,2]”, which was downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=11&subCategoryId=33) on 2 November 2018. CSF $A\beta_{42}$ and p-tau levels were evaluated using a micro-bead-based multiplex immunoassay, the INNO-BIA AlzBio3 RUO test (Fujirebio, Belgium), on the Luminex platform. Details are available in the file “UPENN CSF Biomarker Master Methods (PDF)” at the website described above.

2.5. Evaluation of brain MRI data

To examine the pathological backgrounds of MCI subjects, we also collected data on hippocampal volumes and white matter hyperintensity (WMH) volumes evaluated by MRI in subjects with available data.

Data on hippocampal volumes were obtained from the file “UCSF - SNT Hippocampal Volumes [ADNI1]”, which was downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=14&subCategoryId=30) on 2 November 2018. Hippocampal volumes were evaluated on MRI using a commercially available high dimensional brain mapping tool (Medtronic Surgical Navigation Technologies, Louisville, Colorado, United States). The position of the hippocampus on individual brain MRI data was manually identified using 22 local landmark points. Fluid image transformation was then used to match individual brains to a template brain. Pixels corresponding to the hippocampus were labeled and counted to obtain volumes. Details are available in the file “UCSF - SNT Hippocampal Volumes Methods (PDF)” on the website described above.

Data on WMH volumes were obtained from the file “UCD_ADNI1_WMH”, which was also downloaded from the above-described website on 2 November 2018. WMH volumes were evaluated on MRI using a fully-automated method established by Schwarz et al. [20]. Briefly, a binary label for each image voxel that denotes either the presence or absence of a WMH established from a vector of three image intensities at that voxel was obtained using a Bayesian Markov-Random Field (MRF) approach. Details are available in the file “ADNI1_Methods_UCD_WMH_Volumes_Methods” on the website described above.

2.6. Statistical analysis

We compared demographic data, MMSE scores, ADAS-11 scores, and biomarker levels between MCI patients and subjects with normal cognition. The Student's *t*-test was used to compare mean values and the chi-squared test to compare prevalence.

We then performed a multiple logistic regression analysis to predict the risk of conversion based on age, sex, the ApoE 4 genotype, and plasma cytokine levels. Antecedently, we performed Pearson's correlation analysis among ApoE 4 genotypes and plasma cytokine levels to identify any relationships. We also conducted a single regression analysis of the conversion risk using the data for each cytokine to select those to be included in the multivariable model based upon a regression coefficient of $p < .1$. The Variance Inflation Factor (VIF) was used to check for multicollinearity.

We also compared CSF $A\beta_{42}$ and p-tau levels and hippocampal and WMH volumes among C-MCI, NC-MCI, and normal cognition subjects.

The significance of differences was set at $p < .05$. All quantitative data were analyzed using the SPSS Version 22.0 statistical package (IBM Corp., Armonk, New York, United States).

3. Results

3.1. Demographics in MCI

The demographic data of MCI and normal cognition subjects are summarized in Table 1. No significant differences were observed in age, sex, or education attainment between patients with MCI and subjects with normal cognition. The prevalence of ApoE 4 and ADAS-11 scores were significantly higher in patients with MCI than in subjects with normal cognition. Additionally, MMSE scores were significantly lower in patients with MCI than in subjects with normal cognition.

3.2. Plasma cytokine levels in MCI

Plasma biomarker levels in patients with MCI and subjects with

Table 1
Patient demographics and plasma cytokines.

Group	MCI (n = 296)	Normal cognition (n = 47)
Demographic data		
Age	74.73 ± 7.14	75.36 ± 5.89
Sex (female)	104 (35.1%)	23 (48.9%)
Education (years)	15.80 ± 2.92	15.62 ± 2.88
ApoE 4 **	homo: 38 (12.8%)	homo: 0 (0.0%)
	hetero: 122 (41.2%)	hetero: 4 (8.5%)
	null: 136 (45.9%)	null: 43 (91.5%)
MMSE **	26.93 ± 2.14	28.98 ± 1.09
ADAS-11 **	11.22 ± 4.72	5.81 ± 2.38
Cytokine levels		
plasma CNTF (pg/ml)	1.74 ± 0.31	1.69 ± 0.29
^{log}plasma CRP (ug/ml) **	0.06 ± 0.46	0.33 ± 0.47
plasma IL-13 (pg/ml)	1.59 ± 0.18	1.60 ± 0.15
plasma IL-16 (pg/ml) **	2.54 ± 0.17	2.62 ± 0.13
plasma IL-18 (pg/ml)	2.41 ± 0.17	2.38 ± 0.21
^{log}plasma IL-3 (ng/ml)	−1.62 ± 0.28	−1.63 ± 0.22
plasma IL-6R (ng/ml) *	1.46 ± 0.14	1.51 ± 0.12
plasma IL-8 (pg/ml)	1.00 ± 0.21	1.03 ± 0.15
plasma CXCL 10 (pg/ml)	2.64 ± 0.18	2.66 ± 0.16
plasma MMP-9 (ng/ml)	2.14 ± 0.24	2.11 ± 0.16
plasma TNF-α (pg/ml)	0.83 ± 0.27	0.85 ± 0.32

Age, education, scores of the Mini-Mental State Examination (MMSE) and the 11-item version of Alzheimer's Disease Assessment Scale (ADAS-11), and plasma cytokine levels are shown as mean ± standard deviation. Sex is shown as the number (percentage) of female participants. ApoE 4 is shown as the number (percentage) of its genotype.
log, natural log; MCI, mild cognitive impairment; *, significant difference with $p < .05$; **, significant difference with $p < .01$.

normal cognition are summarized in Table 1 and their distribution is shown in Fig. 1. There were significantly lower levels of CRP, IL-16, and IL-6R in patients with MCI than in subjects with normal cognition. No significant differences were observed in other cytokine levels between patients with MCI and subjects with normal cognition. The relationships among ApoE 4 genotypes and plasma cytokine levels and are summarized in Supplementary file 1. A correlation was not observed between plasma cytokine levels and ApoE 4 genotypes.

3.3. Conversion risk from MCI to dementia based on plasma cytokine levels

Among 296 MCI patients, 79 subjects with MCI converted to dementia in 2 years (C-MCI). Two hundred and seventeen subjects with MCI remained at the MCI state or reverted to normal cognition in 2 years (NC-MCI).

The results of the single regression analysis of the conversion risk for each biomarker are available as Supplementary file 2. IL-18 and IL-6R showed regression coefficients of $p < .1$. Therefore, we performed a multiple logistic regression analysis to predict the conversion risk from MCI to dementia based on predictive variables, including age, sex, the ApoE 4 genotype, IL-18, and IL-6R levels. None of the VIF values were greater than 2, indicating that there was no collinearity in the model.

The results of the multiple logistic regression analysis are summarized in Table 2 and shown in a forest plot (Graphical abstract). The ApoE 4 gene significantly increased the risk of conversion (OR = 1.571, 95% CI: 1.066–2.315, $p = .022$), whereas high plasma IL-6R levels significantly decreased it (OR = 0.105, 95% CI: 0.015–0.711, $p = .021$).

3.4. AD biomarkers in C-MCI, NC-MCI, and normal cognition

CSF levels of $A\beta_{42}$ and p-tau and hippocampal and WMH volumes were compared among C-MCI, NC-MCI, and normal cognition subjects and are shown in Table 3 and Fig. 2. CSF $A\beta_{42}$ and p-tau data were obtained from 42 out of 79 C-MCI patients, 117 out of 217 NC-MCI patients, and all normal cognition subjects. CSF $A\beta_{42}$ levels were significantly lower in C-MCI patients than in NC-MCI patients and subjects with normal cognition, and were lower in NC-MCI patients than in normal cognition subjects. CSF p-tau levels were significantly higher in C-MCI and NC-MCI patients than in subjects with normal cognition. No significant differences were observed in CSF p-tau levels between C-MCI and NC-MCI patients.

Data on hippocampal and WMH volumes were obtained from 77 out of 79 C-MCI patients, 214 out of 217 NC-MCI patients, and all normal cognition subjects. Right and left hippocampal volumes were significantly lower in C-MCI patients than in NC-MCI patients and subjects with normal cognition, and were lower in NC-MCI patients than in normal cognition subjects. No significant differences were observed in WMH volumes among the three groups.

3.5. Data on AD

As a reference, data on patients with AD are shown in Supplementary file 3.

4. Discussion

In the present study, we examined the plasma levels of 11 immunological biomarkers in MCI patients and investigated the risk of conversion from MCI to dementia using ADNI data. CRP, IL-16, and IL-6R levels were significantly lower in MCI patients than in subjects with normal cognition. ApoE 4 significantly increased, whereas high plasma IL-6R levels significantly decreased the conversion risk from MCI to dementia. The present study is the first to show the protective effects of IL-6R against conversion from MCI to dementia.

4.1. Plasma cytokine levels in MCI

We found that CRP, IL-16, and IL-6R levels were significantly lower in MCI patients than in subjects with normal cognition. Table 4 compares the present results with previous findings on CRP, IL-16, and IL-6R levels in MCI and AD patients.

4.1.1. CRP

In the present study, CRP levels were significantly lower in patients with MCI than in subjects with normal cognition.

Regarding MCI, O'Bryant et al. [21] reported that plasma CRP levels were significantly lower in MCI patients than in healthy controls in the non-Hispanic Caucasian population of Texas, USA. On the other hand, King et al. [22] found no significant differences in plasma CRP levels between MCI patients and healthy controls in North East England. CRP is a non-specific inflammatory cytokine that rapidly changes in response to inflammation. Plasma CRP levels fluctuate in relation to eating habits [23] and increase the risk of vascular dementia due to atherosclerosis [24]. Based on similarities in the present results and the previous findings reported by O'Bryant et al., in which more than 90% of MCI subjects were non-Hispanic Caucasians, socio-demographic factors including race, lifestyle habits, and/or residential area may explain the inconsistencies observed in CRP levels among MCI patients.

In the present study, no significant differences were observed in plasma CRP levels between C-MCI and NC-MCI, or in WMH volumes among AD, C-MCI, NC-MCI, and subjects with normal cognition. Since MCI was not subdivided biologically, the present results were insufficient to evaluate the extent to which plasma CRP levels affected degeneration or vascular factors. Further studies are needed to clarify the influence of plasma CRP on each factor promoting dementia.

Regarding dementia, two meta-analyses reported that there was no significant difference in plasma CRP levels between AD and healthy controls [25,26]. In line with these findings, no significant differences were observed in CRP levels between AD patients and subjects with normal cognition in the ADNI cohort (See Supplementary file 3).

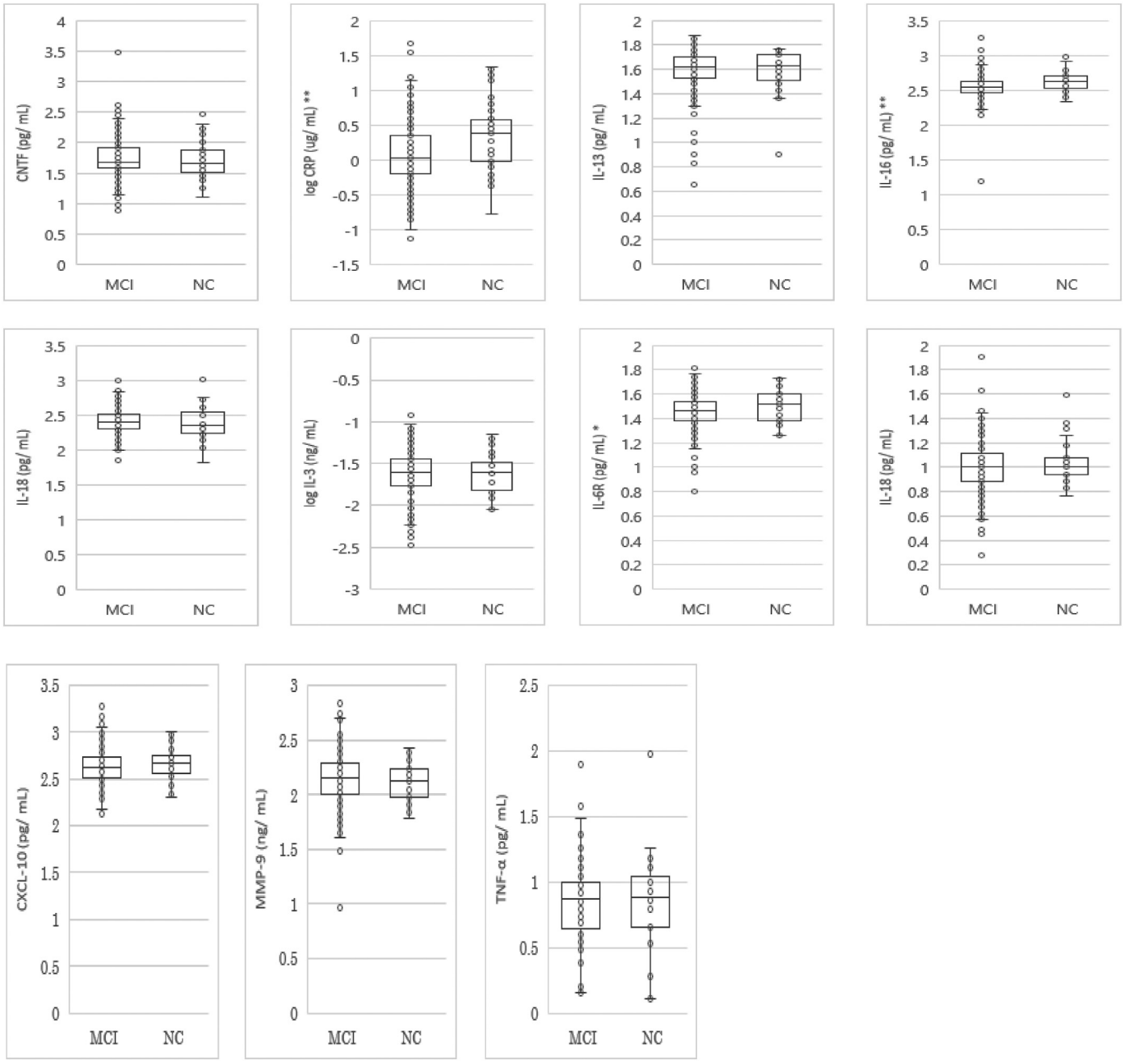

Fig. 1. Distribution of plasma cytokine levels in MCI and normal cognition.
Distribution of cytokine levels in MCI and control subjects are shown in box and dot-plots. The vertical axis shows the cytokine level, and the horizontal axis shows the patient groups.
NC, normal cognition; *, statistically significant difference between MCI and NC with $p < .05$; **, statistically significant difference between MCI and NC with $p < .01$.

4.1.2. IL-16

We found that IL-16 levels were significantly lower in patients with MCI than in subjects with normal cognition. IL-16 levels were also significantly lower in AD patients than in normal cognition subjects (See Supplementary file 2).

IL-16 is an immunomodulatory cytokine that contributes to the regulatory process of CD4+ T cell recruitment and activation at sites of inflammation in association with asthma and several autoimmune diseases. Based on the findings of *in vivo* studies, it is hypothesized that IL-16 in the central nervous system may serve as a signaling molecule and as a scaffolding protein possibly involved in anchoring ion channels in the membrane. However, the potential role of IL-16 in the brain remains unclear [27]. IL-16 levels have not yet been investigated in detail in AD, and there is currently no information on its levels in subjects with MCI. Motta et al. [28] reported that IL-16 levels were significantly elevated in patients with mild AD and progressively decreased in patients with moderate AD. These findings on IL-16 are insufficient and inconsistent to allow for any interpretation of the relationship between IL-16 and AD. Brosseron et al. [10] proposed several different patterns for changes in plasma cytokine expression levels over time; for example, some increase slightly and steadily over time, others reach a peak at some point and then decrease, and some remain unchanged during the disease course. Therefore, further research with longitudinal data on IL-16 is needed to clarify the pathological association with AD progression.

Table 2
Multiple logistic regression model to predict conversion from MCI to dementia.

	B	*SE*	*p*	OR (95% CI)
Age	0.031	0.021	0.135	1.031 (0.990–1.074)
Sex	0.096	0.289	0.739	1.101 (0.625–1.939)
ApoE 4	0.452	0.198	0.022	1.571 (1.066–2.315)
IL-18	−1.038	0.808	0.199	0.354 (0.073–1.727)
IL-6R	−2.258	0.978	0.021	0.105 (0.015–0.711)
Constant	1.989	2.890	0.491	7.305

The results of multiple regression analysis to predict conversion from MCI to dementia based on age, sex, ApoE4, and plasma cytokine levels are summarized.
B, unstandardized coefficient; SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval (lower limit – upper limit); *p*, *p*-value.

4.1.3. IL-6R

In the present study, patients with MCI showed significantly lower IL-6R levels than those in normal cognition subjects. No significant differences were observed in IL-6R levels between AD patients and subjects with normal cognition (See Supplementary file 2). Previous studies reported that IL-6R levels were significantly lower in AD patients than in healthy controls [29–31], whereas no changes in IL-6R levels were also observed in AD patients [32,33]. This is the first study to examine IL-6R levels in subjects with MCI.

High interindividual variance and a large overlap in IL-6R levels between controls and patients may explain inconsistencies in the results obtained on IL-6R levels in AD patients. Regarding differences in technical approaches, IL-6R levels have not yet been examined in AD patients, MCI patients, or healthy controls using Luminex xMAP technology.

In the present study, a significant decrease was observed in IL-6R levels in MCI patients, but not in AD patients. In support of these results, previous studies reported that the plasma levels of other cytokines, such as IL-12, IL-16, TGF-β, and MCP-1, were significantly altered in MCI and mild AD, whereas no significant differences were observed between severe AD patients and controls [14,28]. These findings indicate that the levels of some cytokines are altered around the pre-dementia phase. Therefore, the immunological mechanism of each cytokine on disease progression needs to be investigated separately in each phase.

4.2. Comparison of AD biomarkers among C-MCI, NC-MCI, and normal cognition groups

Although we attempted to clarify the pathological backgrounds of MCI subjects by examining AD biomarkers, CSF data were only available for 53% of MCI subjects. Thus, the results obtained on CSF biomarkers need to be carefully interpreted.

As summarized in Table 3, CSF $A\beta_{42}$ levels and hippocampal volumes were significantly lower in C-MCI patients than in NC-MCI patients and subjects with normal cognition, and lower in NC-MCI patients than in normal cognition subjects. CSF p-tau levels were significantly higher in C-MCI and NC-MCI patients than in subjects with normal cognition. No significant differences were observed in WMH volumes among the three groups. These results imply that some C-MCI subjects were pathologically characterized with AD. The aim of the present study was to focus on clinically and psychologically diagnosed MCI with the untested possibility of heterogeneous pathology. However, future studies that focus on biologically confirmed MCI are needed.

4.3. ApoE 4 and conversion risk from MCI to dementia

The results of the multiple logistic regression analysis showed that ApoE 4 significantly promoted the conversion from MCI to dementia. ApoE 4 is the strongest known genetic risk factor for AD [34]. Recent studies demonstrated that ApoE 4 also increased the risk of other types of dementia, including DLB [35,36]. The results of the present study were consistent with previous findings showing that ApoE 4 increased the conversion risk from MCI to dementia.

4.4. IL-6R and conversion risk from MCI to dementia

The results of the multiple logistic regression analysis also showed that high plasma IL-6R levels significantly decreased the conversion risk from MCI to dementia. Teunissen et al. [31] reported that a logistic model, including IL-6R in combination with protein α1 fraction, cysteine, and cholesterol concentrations, facilitated the discrimination between AD and healthy controls. The present study is the first to report a relationship between IL-6R levels and chronological changes in MCI patients.

The role of IL-6 signaling *via* IL-6R in the pathogenesis of AD has been attracting attention [37,38]. Recent reviews showed that the effects of IL-6 signaling on Aβ are bidirectional [11,39]. Aβ promotes IL-6 expression, which triggers the differentiation of microglia to a phagocytic M2 phenotype [40] and activates astrocytes, both of which are capable of removing Aβ [41]. On the other hand, previous *in vitro* and animal studies indicated that IL-6 signaling promotes the progression of AD by stimulating the transcription of amyloid precursor protein (APP) and consequent Aβ production [42] and also by enhancing neurotoxicity caused by Aβ [43]. Chakrabarty et al. [44] demonstrated extensive gliosis and increased microglia-mediated phagocytosis, which attenuated the deposition of Aβ in their experiments using IL-6 over-expressing mice. This IL-6-induced neuroinflammation had no effect on APP processing or Aβ levels in young mice. They hypothesized that IL-6 signaling may be beneficial early in the disease process by enhancing Aβ plaque clearance rather than mediating a neurotoxic feedback loop that exacerbates amyloid pathology.

Table 3
Comparison of CSF biomarkers and MRI findings between C– MCI, NC-MCI and normal cognition groups.

Group (number of subjects)	C-MCI (*n* = 79)	NC-MCI (*n* = 217)	Normal cognition (*n* = 47)
CSF biomarkers/sample number (%)	42 (53.2%)	117 (53.9%)	47 (100%)
CSF $A\beta_{42}$ (pg/ml) [a, b, c]	142.83 ± 38.29	165.37 ± 57.78	249.40 ± 25.17
CSF p-tau (pg/ml) [b, c]	37.17 ± 14.62	34.22 ± 17.39	21.26 ± 8.49
MRI findings/sample number (%)	77 (97.5%)	214 (98.6%)	47 (100%)
Rt Hippocampus (mm^3) [a, b, c]	3156.43 ± 566.19	3392.52 ± 552.06	3638.60 ± 492.14
Lt Hippocampus (mm^3) [a, b, c]	2998.75 ± 554.21	3198.00 ± 516.35	3517.99 ± 388.01
WMH (cm^3)	0.93 ± 1.85	0.63 ± 1.27	0.74 ± 1.81

The amyloid β-42 ($A\beta_{42}$) and phosphorylated tau protein (p-tau) concentrations in cerebrospinal fluid (CSF), and the volumes of the right and left hippocampus and white matter hyperintensity (WMH) evaluated on MRI are shown as mean ± standard deviation.
n, number of subjects; MCI, mild cognitive impairment; Rt, right; Lt, left; WMH, white matter hyperintensity; a, significant difference between C-MCI and NC-MCI patients; b, significant difference between C-MCI patients and subjects with normal cognition; c, significant difference between NC-MCI patients and subjects with normal cognition.

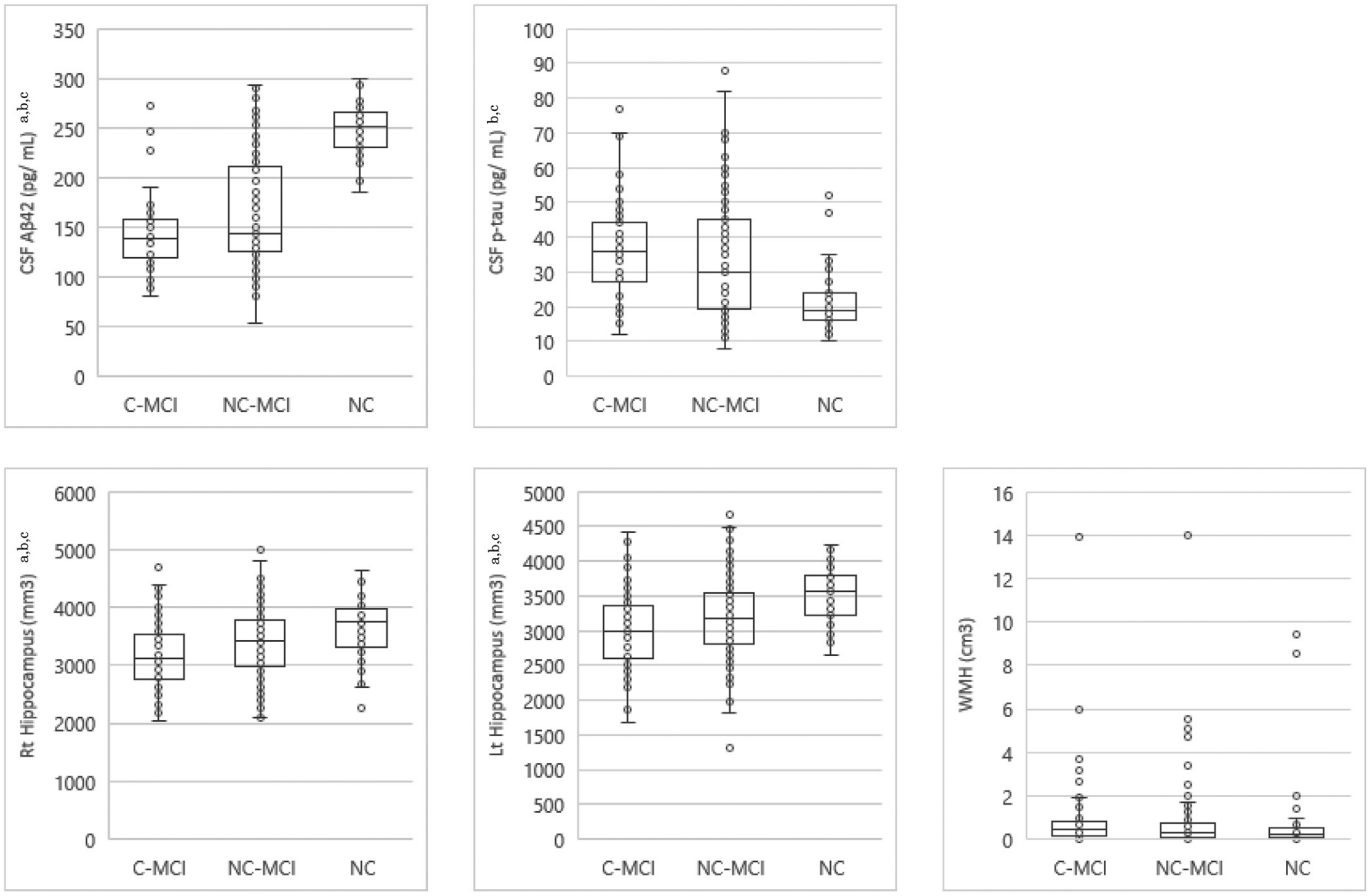

Fig. 2. Distribution of CSF biomarkers and MRI findings in C-MCI, NC-MCI, and normal cognition.
Distribution of CSF biomarkers and MRI findings in C-MCI, NC-MCI and normal cognition subjects are shown in box and dot-plots. The vertical axis shows the CSF biomarkers and MRI findings, and the horizontal axis shows the patient groups.
NC, normal cognition; a, significant difference between C-MCI and NC-MCI patients; b, significant difference between C-MCI patients and NC; c, significant difference between NC-MCI patients and NC.

IL-6 signaling strongly depends on the presence of soluble IL-6R, which is produced by T cells [45–47]. Bagli et al. [48] reported that plasma IL-6R levels of AD patients were associated with polymorphisms of the gene encoding IL-6. Haddick et al. [49] demonstrated that the common p.D358A variant in IL-6R affected the activation of IL-6 signaling and was associated with onset age of AD. Since we showed that high plasma IL-6R levels decreased the risk of conversion in MCI patients, high IL-6R levels may slow the progression of dementia by increasing Aβ plaque clearance through IL-6 signaling in some subjects at the early or prodromal stage of dementia.

However, the independent effects of IL-6 and IL-6R levels or genes on AD pathology, such as Aβ and tau, in humans have not yet been elucidated in detail. The National Institute on Aging-Alzheimer's Association (NIA-AA) proposed a research framework stating that MCI needs to be classified by biomarkers including β amyloid deposition, pathological tau, and neurodegeneration, which are known as the ATN classification system [50].

There were a few limitations in the present study. We did not examine IL-6 levels, which are not publicly available from the ADNI database. We also only assessed CSF Aβ and p-tau levels in about 50% of MCI subjects and lacked amyloid PET findings. Moreover, we did not obtain longitudinal data on plasma cytokine levels, CSF biomarkers, or MRI findings. The relationship between plasma cytokine levels and the conversion risk from MCI to dementia was investigated based on changes in CDR scores over time and plasma cytokine levels at baseline. Therefore, the present results did not clarify the mechanisms by which IL-6R exerted beneficial effects on MCI patients or whether changes in plasma cytokine levels precede neurodegeneration.

As proposed by the NIA-AA, a biological diagnosis using the ATN classification is necessary for avoiding the over- and underdiagnosis of AD, even in the MCI stage, and obtaining a more detailed understanding of the pathogenesis of AD [51]. Based on these concepts, non-AD biomarkers, such as α-synuclein and TDP-43, also need to be considered when investigating the mechanisms responsible for the beneficial effects of IL-6R on MCI. Furthermore, in consideration of previous findings indicating that peripheral inflammation observed at the MCI stages is attenuated by the progression of neurodegenerative dementia [10,22], the temporal sequence of cytokine changes and neurodegeneration is also an important topic. Thus, longitudinal investigations on cytokines using the biomarker-based classification in preclinical, MCI, and dementia patients are needed in the future.

5. Conclusion

In the present study, we found that plasma CRP, IL-16, and IL-6R levels were significantly lower in patients with MCI than in subjects with normal cognition. A multiple logistic regression analysis showed that high plasma IL-6R levels significantly decreased the conversion risk from MCI to dementia. To elucidate the role of cytokines, including IL-6R, in the development of dementia, further longitudinal investigations using biomarker-classified preclinical, MCI, and dementia subjects are needed.

Table 4
Comparison of CRP, IL-16, and IL-6R levels in AD and MCI patients between previous studies and the present study.

Cytokine/study	Subjects	Methods	Results
CRP			
Ng et al. (2018)	1645 AD 14,363 HC	meta-analysis	No difference between AD and HC
Gong et al. (2015)	1025 AD 1068 HC	meta-analysis	No difference between AD and HC
O'Bryant et al. (2013)	284 AD 251 MCI 557 HC	luminex-based HumanMAP 1.0 platform (Myriad RBM, USA)	MCI < HC (only in non-Hispanic white) AD < HC No difference between AD and MCI.
King et al. (2018)	20 AD 20 MCI 20 HC	V-PLEX Neuroinflammation Panel 1 Human Kit (Meso-Scale Discovery)	No difference among AD, MCI, and HC.
Abe et al.	296 MCI 47 HC	Luminex xMAP technology	MCI < HC
Abe et al.	69 AD 47 HC	Luminex xMAP technology	No difference between AD and HC. (See supplementary file 2)
IL-16			
Motta et al. (2007)	51 AD (11 severe, 22 moderate, 18 mild) 20 HC	ELISA (R&D Systems, USA)	mild AD > HC (progressive decrease in moderate AD)
Abe et al.	296 MCI 47 HC	Luminex xMAP technology	MCI < HC ($p < .01$)
Abe et al.	69 AD 47 HC	Luminex xMAP technology	AD < HC ($p < .01$) (See supplementary file 2)
IL-6R			
Angelis et al. (1997)	41 AD 32 HC	ELISA (R&D Systems, USA)	AD < HC
Hampel et al. (1998)	41 AD 20 HC	ELISA (R&D Systems, USA)	AD < HC
Hasegawa et al. (2000)	25 AD 48 HC	ELISA (Medgenix, Belgium)	No difference between AD and HC.
Teunissen et al. (2003)	34 AD 61 HC	ELISA (Eurogenetics S.A., Belgium)	AD < HC
Richartz et al. (2005)	20 AD 21 HC	ELISA (R&D Systems, Germany)	No difference between AD and HC.
Abe et al.	296 MCI 47 HC	Luminex xMAP technology	MCI < HC ($p < .05$)
Abe et al.	69 AD 47 HC	Luminex xMAP technology	Tended to be decreased in AD. (See Supplementary file 2)

Overview of the results of the previous studies reporting plasma CRP, IL-16, and IL-6R levels in MCI and AD patients are summarized and compared with the present study. The authors with published year in round brackets, number of subjects, methods to measure cytokines levels with the name of institution in round brackets, and changes in cytokines in AD and MCI are listed.
AD, Alzheimer disease; MCI, mild cognitive impairment; HC, healthy controls; ELISA, enzyme-linked immunosorbent assay.

Declarations of Competing Interest

None.

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Appendix A. Supplementary data

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