Cerebrospinal fluid levels of interleukin-8 in delirium, dementia and cognitively healthy patients.

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Running title: CSF IL-8 levels in delirium

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ABSTRACT

Delirium is a common and serious complication in geriatric patients. The pathophysiology of delirium is not known. The objective of the current study was to test the hypothesis that cerebrospinal fluid (CSF) levels of inflammatory markers at the time of spinal anesthesia for hip surgery are associated with delirium.

In total 133 hip fracture patients and 125 cognitively healthy controls undergoing elective surgery, together with 73 Alzheimer's disease (AD) dementia patients, were recruited at Oslo University Hospital and Diakonhjemmet Hospital, Oslo, Norway.

Delirium was evaluated daily in hip fracture patients by the Confusion Assessment Method (CAM). Depression was evaluated by Cornell Scale for Depression in Dementia (CSDD). Tumor necrosis factor alpha (TNF-α), interleukin-1beta (IL-1β) and interleukin-8 (IL-8) levels were measured in CSF using a Mesoscale Discovery (MSD) immunoassay.

Hip fracture patients had significantly higher IL-8 levels ($p < 0.001$) compared to cognitively healthy controls or patients with stable AD dementia. Furthermore, preoperative IL-8 levels were significantly higher ($p = 0.013$) in hip fracture patients who developed delirium (incident delirium) after surgery as compared to patients with no delirium. However, subgroup analyses showed that IL-8 levels were only significantly higher in delirium patients without dementia ($p = 0.006$). In contrast, depression subgroup analysis showed that IL-8 concentration was significantly higher ($p = 0.002$) in delirium patients with depression. Both TNF-α and IL-1β were undetected in most patients.

Our study suggests that IL-8 levels are associated with delirium onset and that underlying depression or dementia influences IL-8 levels.

KEYWORDS: Delirium, Cytokines, Alzheimer's disease, Depression

List of Abbreviations: Alzheimer's disease (AD); Tumor Necrosis Factor alpha (TNF-α); Interleukin-1beta (IL-1β); Interleukin-8 (IL-8); Cerebrospinal Fluid (CSF); Confusion Assessment Method (CAM); Cornell Scale for Depression in Dementia (CSDD); Subsyndromal Delirium (SSD); Amyloid-β Precursor Protein (AβPP); Microtubule-associated protein tau (tau); phospho-tau (p-tau); Lower Detection Limit (LDL)

INTRODUCTION

Delirium is an acute neuropsychiatric syndrome characterized by fluctuating awareness, inattention and cognitive impairment [1]. A significant proportion (25-50%) of hospitalized elderly patients develop delirium [2, 3]. It is particularly common among elderly patients experiencing traumatic injury such as hip fracture [4] and is associated with increased mortality and morbidity [5].

Pre-existing dementia is a strong risk factor for delirium [6]. On the other hand, it is also increasingly evident that delirium is a risk factor for dementia [7]. Furthermore, several studies have reported that depression is a risk factor for delirium and depression is common among elderly admitted to the hospital [8, 9]. There might be overlapping features and common pathological mechanisms between delirium and dementia, such as impaired stress and inflammatory responses, altered monoamine neurotransmission and melatonergic activity [9, 10].

Pathophysiology of delirium remains unknown although many pathways have been suggested [11, 12]. Neuroinflammation is one of the most studied areas and is associated with delirium onset [13, 14]. Several studies have reported elevated levels of pro-inflammatory cytokines in the serum and CSF of delirium patients [15-21]. Neuroinflammation plays a vital role in the brain vulnerability for long-term structural and functional consequences and neuropathological changes such as microglial activation and production of pro-inflammatory cytokines accelerate upon additional systemic inflammatory response due to injury or infection [22]. These findings have been reproduced in the preclinical animal models where systemic inflammation has been reported to accelerate the existing neuropathology such as microglial priming and acute cognitive and motor deficit in ME7 models of prion disease [23, 24].

Several attempts have been made to understand the role of inflammation by studying inflammatory markers and pro-inflammatory cytokines such as TNF-α, interleukin (IL)-1β, IL-6 and IL-8 in relation to delirium onset in hip fracture patients. Elevated blood levels of inflammatory markers and pro-inflammatory cytokines including TNF-α, IL-1β, IL-6 and IL-8 of hip fracture patients that developed delirium have been reported [16, 18, 19, 25]. One study reported higher CSF IL-8 levels in delirium patients in a small cohort of hip fracture patients [26], while another study in which CSF cytokines levels were examined in patients with or without postoperative delirium and found no significant change in pro-inflammatory cytokines including IL-8 [27]. In fact, this study suggested that delirium onset is due to dysfunctional neuroinflammatory response that result in reduced anti-inflammatory cytokines rather than an increase in pro-inflammatory cytokines.

The role of pro-inflammatory cytokines and chemokines has also been extensively studied in cellular and animal models of AD. These studies have reported that pro-inflammatory cytokines and chemokines are associated with altered amyloid-β precursor protein (AβPP) processing that result in increased Aβ production, protein aggregation and hyperphosphorylation of microtubule-associated protein tau (p-tau) [28]. In addition to this, levels of several pro-inflammatory cytokines/chemokines have been reported to be elevated in the blood and CSF of AD patients, although, these finding are fairly contradicting [29]. Moreover, AD associated polymorphisms of TNF-α, IL-1β, IL-8 among other cytokines have also been identified [30, 31].

One the other hand, the role of cytokines and chemokines are not so well explored in the CSF of depressed geriatric patients. One study suggested elevated CSF levels of IL-6 and IL-8 in geriatric female patients with current depression [32]. In the contrary, Stubner et al., 1999 reported decreased CSF IL-6 and soluble IL-6 receptor levels in depressed geriatric patients [33]. Moreover, elevated levels of pro-inflammatory cytokines such as IL-1β and IL-6 have been reported in the

CSF of non-geriatric patients with depression disorders [34-36], although, some contradictory findings have also been reported [37, 38].

In summary, CSF pro-inflammatory cytokines levels in hip fracture patients with delirium have been reported with contradictory data [26, 39]. Therefore, we aimed to elucidate the role of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-8 in CSF in delirium in a larger cohort and with additional control groups such as cognitively healthy controls and patients with stable AD.

MATERIAL AND METHODS

CSF was collected from patients admitted to Oslo University Hospital and Diakonhjemmet Hospital, Oslo Norway.

HIP FRACTURE PATIENTS

Hip fracture patients were recruited from the Oslo Orthogeriatric Trial (inclusion 2009 – 2012), a randomized controlled trial evaluating the effect of orthogeriatric care on cognitive function [40-42]. Participants with CSF available (n=137) were included in the current study. Patients were assessed daily for delirium, preoperatively and until the fifth postoperative day, by the Confusion Assessment Method (CAM), which is a diagnostic algorithm consisting of four items: 1) acute onset and fluctuation course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness. The diagnosis of delirium requires the presence of item 1 and 2 and either 3 or 4. [43]. The CAM scores were based on a 10-30 minutes interview with the patient, in combination with information from nurses, close relatives and hospital records reporting symptoms during the last 24 hours. Patients were regularly assessed on weekdays only, but staff members that had been working during weekends were interviewed every Monday and the case notes were scrutinized in

order to reveal potential episodes of delirium. Delirium was categorized into different subcategories such as preoperative, incident (patients who were free from delirium when CSF was taken, but developed delirium later), and subsyndromal (SSD, defined as at least two positive CAM features [pre- or postoperatively] but never fulfilled criteria for full delirium). SSD patients were included as a part of no delirium group in the analyses unless otherwise stated. Each participant's fulfillment of ICD-10 criteria for dementia was evaluated by two consultants (one geriatrician and one geriatric psychiatrist) prior to the fracture, based on all existing data (except delirium status during admission), as described previously [40]. Cornell Scale for Depression in Dementia (CSDD) was used to assess symptoms of depression and score of 8 or more was considered the cutoff of depression [44]. Delirium status of three hip fracture patients were missing and therefore excluded from the analyses.

COGNITIVELY HEALTHY CONTROL GROUP

We recruited 172 participants (≥ 65 years) in the COGNORM-study during 2012 and 2013 at Oslo University Hospital and Diakonhjemmet Hospital, Oslo, as described previously [45]. These participants were undergoing elective gynecological, orthopedic or urological surgery in spinal anesthesia. The participant's cognitive functions were tested by using a multi-domain battery of cognitive tests before surgery and at yearly follow up controls. Patients without CSF samples (n=13), suspected undiagnosed dementia any time within the first 5 years of follow up (n=15) or Mini Mental State Examination (MMSE) score <28 at baseline (n=19) were excluded from this study.

STABLE AD DEMENTIA PATIENTS

The 73 AD dementia patients were included at the memory clinic at Oslo University Hospital between 2009 and 2014. They all went through a comprehensive examination according to a standardized research protocol including cognitive assessment (among others MMSE, the clock drawing tests and the trail making test A and B), and physical examination with blood sampling, lumbar puncture, and magnetic resonance imaging (MRI). The patients were diagnosed according to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for Alzheimer's disease [46]. Depressive symptoms were assessed with the CSDD as stated earlier.

CSF SAMPLING AND HANDLING

CSF was collected in polypropylene tubes before administration of the anesthetic agent in all patients undergoing surgery and as part of the diagnostic work up for the AD patients. CSF samples were centrifuged, aliquoted and stored at – 80° C. Samples were analyses at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital (Mölndal, Sweden). CSF concentrations of IL-8, TNF-α and IL-1β was analyzed using a Mesoscale Discovery (MSD) immunoassay (V-PLEX Human Proinflammatory Panel I), following the recommendations by the manufacturer.

STANDARD PROTOCOL APPROVAL, REGISTRATION AND PATIENT CONSENTS

The study was conducted in accordance with the Declaration of Helsinki. The data and CSF samples were collected after informed consent from the patient and/or proxy (if patients were unable to consent due to cognitive impairment), as approved by the Regional Committee for Medical and Health Research Ethics (REK 2009/450, 2011/2052, and 2017/371).

STATISTICS

SPSS version 25 was used for statistical analysis and figures were drawn in GraphPad prism version 7.04. Data were not normally distributed and therefore non-parametric tests were performed. Mann-Whitney *U* test and Kruskal-Wallis test were used for continuous variable. Chi-square and Fisher's exact test were used for categorical variables. Both dementia and depression are risk factors for delirium and therefore we conducted subgroup analyses on dementia or depression status. Since SSD has been reported to be clinically closer to delirium as compared to no delirium, we analyzed our data with and without SSD as a part of the no delirium group [47]. CSF IL-8 concentrations were natural log-transformed for linear regression analysis.

RESULTS

IL-8, IL-1β and TNF-α (pg/mL) were measured in the CSF of 134 hip fracture patients, 125 elective surgery patients (cognitively healthy controls) and 73 patients with stable AD dementia (table 1). IL-1β and TNF-α could be detected in less than 10% of the patients (table 1). Therefore, we only proceeded with IL-8 concentration of different patient groups for further analysis. IL-8 was detected in all samples except from one patient in the hip fracture group. This patient was excluded from all analyses. Hip fracture patients were significantly older (median (IQR) 84 (79-89) years) compared to the cognitively healthy (71 (68-76.5) years) and AD dementia (66 (60-70.5) years) group (both p<0.001) and more hip fracture patients were female (73 % vs 50 % vs 58 %, see table 1 for details).

CSF IL-8 IN HIP FRACTURE PATIENTS

Overall, there was a trend towards higher CSF IL-8 levels in hip fracture patients with incident delirium (118.1 (79.7-183.3) pg/mL) and preoperative delirium (99.5 (72.8-133.4) pg/mL) compared to those without delirium (85.8 (62.7-130.1) pg/mL, $p = 0.057$) (figure 1a). When SSD patients were excluded, IL-8 was significantly higher in incident delirium compared to no delirium (118.1 (79.7-183.3) pg/mL vs 78.6 (59.7-127.4) pg/mL, p=0.013, figure 1b) and the association was upheld when adjusted for age (table 2).

In order to understand the role of underlying dementia pathology and CSF IL-8 concentration, we performed subgroup analyses of hip fracture patients according to delirium and dementia status. The CSF IL-8 concentration was significantly higher in delirium when compared to no delirium in patients without dementia (129.8 (91.8-172.8) pg/ml vs 85.8 (60.6-131.6) pg/ml, $p = 0.006$) and the association was upheld when adjusted for age (table 2). In patients with dementia, there was no difference in IL-8 between those with and without delirium (89.6 (68.3-125.3) pg/ml vs 86.8 (74.3-135.1) pg/ml, $p = 0.851$).

Since depression has been associated with pro-inflammatory cytokines, we also run analyses on delirium subgroups according to depression status. We found that in patients with depression (n = 21) IL-8 was higher in delirium compared to those without delirium (92.9 (67.9-134.5) pg/ml vs 50.4 (42.1-69.2) pg/ml, $p = 0.002$). However, the association did not hold up when adjusted for age, possibly due to lack of statistical power (table 2). On the other hand, in patients without depression, (n = 100) there was no significant difference in IL-8 concentration between patients with and without delirium (99.6 (72.2-140.4) pg/ml vs 92.9 (69.7-136.8) pg/ml, $p = 0.565$).

CSF IL-8 IN COGNITIVELY HEALTHY AND IN PATIENTS WITH STABLE AD DEMENTIA

In order to further explore the interplay between dementia and delirium on CSF IL-8 levels, we included two additional control groups; patients with stable AD dementia and cognitively healthy controls (table 1). Both AD dementia patients (42.1 (36.2-50.2) pg/mL) and cognitively healthy controls (46.9 (40.1-54.4) pg/mL) had significantly lower levels of CSF IL-8 concentration when compared to hip fracture group (91.8 (69.6-136.3) pg/mL, p <0.001 for both groups, table 1).

CSF IL-8 AND AGE

Since there is a significant difference in age between different patient groups (table 1), we conducted a spearman rank correlation analysis between age and IL-8 concentration within each patient group. There was no significant correlation between IL-8 concentration and age in any of the patients groups (supplementary table 1).

DISCUSSION

To our knowledge this is the first study that compares CSF IL-8 levels in delirium patients, cognitively healthy controls and AD dementia patients side by side. Our data supports the neuroinflammatory hypotheses in delirium. However, in most samples we could not detect TNF-α and IL-β. This could be due to sensitivity of the assays for both IL-1β and TNF-α, although similar findings were reported previously in hip fracture patients [26].

There is some evidence in the literature that supports the role of pro-inflammatory cytokines in the pathophysiology of delirium, especially in studies examining cytokine levels in blood

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samples. However, there is an ambiguity with pro-inflammatory cytokines levels, including IL-8, in the CSF of hip fracture patients.

We found that IL-8 concentration seemed to be impacted by delirium status at the time of sampling, with the highest levels in those about to develop delirium after surgery (incident delirium). It is well-established that IL-8 is an acute pro-inflammatory marker [48, 49] and has also been shown to be elevated in the CSF of multiple sclerosis (MS) [50], AD and Parkinson's disease (PD) patients as compared to age matched controls [51]. Highest IL-8 levels in incident delirium suggest a role of an acute inflammatory response in phase prior to a clinically evident delirium and this increase in CSF IL-8 concentration is not associated with age. In addition to this, underlying conditions such as dementia increase the vulnerability for preoperative delirium whereas non-demented patients are more likely to get incident delirium [52], and that suggests the involvement of different inflammatory pathways associated with delirium subtypes. Thus, these observations are relevant for our study.

IL-8 concentration was significantly higher in incident delirium only when SSD patients were excluded (figure 1b). It has been suggested that SSD falls between no delirium and delirium [53]. Recently a study by Yamada and colleagues further supports this idea where they showed that 33.9% of critically ill patient in an ICU setting had SSD and 9.5% of these patients later developed delirium [54]. Our data supports that SSD is clinically relevant. Dementia subgroup analyses revealed that the observed differences in IL-8 in delirium were confined to patients free from pre-fracture dementia (figure 2a). This observation is consistent with an earlier study that showed decreased IL-8 CSF and serum levels in patients with AD. They also showed that IL-1β levels negatively correlates with MMSE score and suggested that pro-inflammatory markers such as IL-1β and IL-8 may have separate pathogenic mechanisms involved in AD [55]. Moreover, IL-

8 levels have also been reported to be elevated in CSF samples of AD patients [51, 56, 57] and this contradiction in the literature may well be due to the difference in sensitivity and robustness of the assay used and/or difference in patient cohorts in terms of pathology. Although, there was no significant difference observed in IL-8 levels between dementia and dementia free hip fracture patients (supplementary table 2). In order to further explore the role of IL-8 in delirium and dementia, we compared CSF IL-8 levels of cognitively healthy controls or stable AD patients with hip fracture group. Our analysis showed that patients with stable AD or cognitively healthy controls had significantly lower levels of IL-8 as compared to hip fracture patients (table 1). IL-8 has been shown to be elevated in both acute and chronic inflammatory diseases and we postulate that IL-8 levels are acutely elevated in hip fracture patient as compared to AD dementia patients and cognitively healthy controls. This could be due to acute nature of the fracture that as a result recruited immune cells particularly neutrophils, lymphocytes and monocytes responsible for producing pro-inflammatory cytokines including IL-8. It would be interesting to know how IL-8 levels are regulated in chronic neuroinflammatory condition like AD as compared to more acute scenario such as hip-fracture. However, this was not possible in this study since we didn't have samples from hip-fracture patients at different intervals after surgery.

To our knowledge, the role of pro-inflammatory cytokines in delirium and depression has never been studied together in the CSF of hip fracture patients. We showed that in hip fracture patients with depression, patients with delirium had significantly higher IL-8 levels as compared to those without delirium. An earlier study reported higher CSF IL-6 and IL-8 levels in geriatric female patients with current depression [32]. This observation suggest that IL-8 levels are regulated by underlying depression pathology and the difference in IL-8 level may be influenced by underlying depression and/or dementia state in a more complex fashion in hip fracture patients.

Strengths of this study are the use of fairly large cohort of hip fracture patients with additional control groups that allowed us to understand the role of IL-8 and delirium in a broader context. Also, all of the analyses were conducted simultaneously and this allowed us to compare different groups side by side in order to understand the interplay between delirium, dementia and depression in hip fracture patients. We have conducted subgroup analyses since there is a significant overlap between delirium, dementia and depression. We anticipated that the relationship between IL-8, delirium, dementia and depression are crucial for cellular and molecular mechanisms for normal brain functions. It is important to interpret the data carefully and further experiments may be required for more thorough understanding of IL-8 in complex pathological scenario. A limitation is that we did not have access to follow-up samples during and after the procedure. CSF levels of IL-8 are known to increase dramatically hours after initiation of non-neurological surgery [58, 59], and it would have been highly interesting to examine this change in relation to delirium incidence. Unfortunately, we were unable to detect the TNF-α and IL-1β levels in the majority of the samples. Hence, there is a need to develop more sensitive and robust assays to analyze these two markers in delirium patients CSF samples.

In summary, our study showed that preoperative IL-8 was higher in hip fracture patients that developed delirium after surgery. Both preoperative dementia status and depression status seemed to influence the association between IL-8 and delirium, suggesting that the association between IL-8 levels and delirium are dependent on underlying pathology.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

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Table 1: Background characteristics and CSF inflammatory markers comparison between hip fracture patients, cognitively healthy controls and Alzheimer's disease (AD) dementia patients

	Hip fracture group (n=133)	Cognitively healthy controls (n=125)	AD dementia group (n=73)	*P* value[a]	*P* value[b]
Age years, Median (IQR)	84 (79-89)	71 (68-76.5)	66 (60-70.5)	< 0.001	< 0.001
Gender, F (%)	97 (73)	63 (50)	42 (58)	< 0.001[¤]	0.024[¤]
Dementia cases, n (%)	63 (47%)	0	73 (100 %)	-	-
Depression, n (%)[#]	21 (17%)	-	15 (23%)	-	-
IL-8 pg/mL, median (IQR)	91.8 (69.6-136.3)	46.9 (40.1-54.4)	42.1 (36.2-50.2)	< 0.001	< 0.001
IL-1β pg/mL, n (% detectible)	12 (9 %)	5 (4%)	3 (4%)	0.133[$]	0.266[$]
TNF-α pg/mL, n (% detectible)	13 (9.8%)	1 (0.8%)	0	0.001[$]	0.005[$]

[a] Comparison between cognitively healthy and hip fracture patients

[b] Comparison between hip fracture patients and AD patients

[¤] Chi-Square p value was reported for both genders

[$] Fisher's Exact p value was reported

Depression defined as ≥ 8 on Cornell scale in hip fracture patients and AD dementia patients. Data on depression was missing for 12 patients in hip fracture group and 8 patients in the AD dementia group. Mann-Whitney U test was perform to compare two different groups

Table 2: Regression analysis of CSF IL-8 concentration (dependent variable) as a function of age and delirium (independent variables). CSF IL-8 values were transformed with the natural logarithm for approximation of residuals to Gaussian distribution.

| Predictor variables	CSF IL-8 (pg/mL) of no delirium and incident delirium patient groups (n = 61)	CSF IL-8 (pg/mL) of dementia free hip fracture patients (n = 70)	CSF IL-8 (pg/mL) of hip fracture patients with depression (n = 21)
	B (95% CI)	B (95% CI)	B (95% CI)
Age	0.007 (-0.012 - 0.026)	0.007 (-0.006 - 0.020)	0.028 (-0.024 - 0.080)
Delirium	0.435 (0.068 - 0.802)	0.351 (0.089 - 0.614)	0.528 (-0.519 - 1.575)
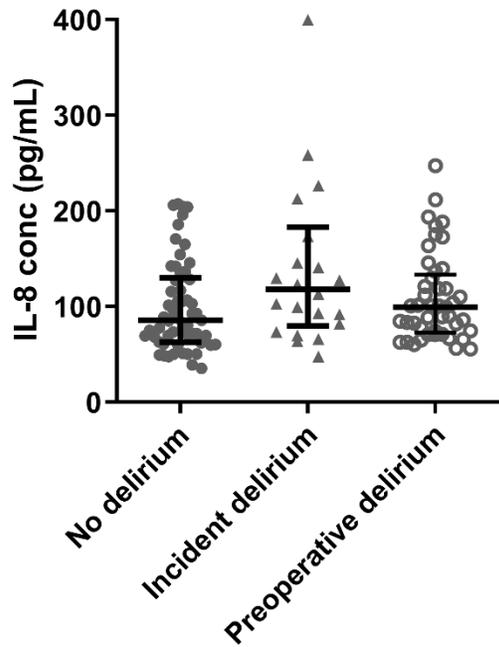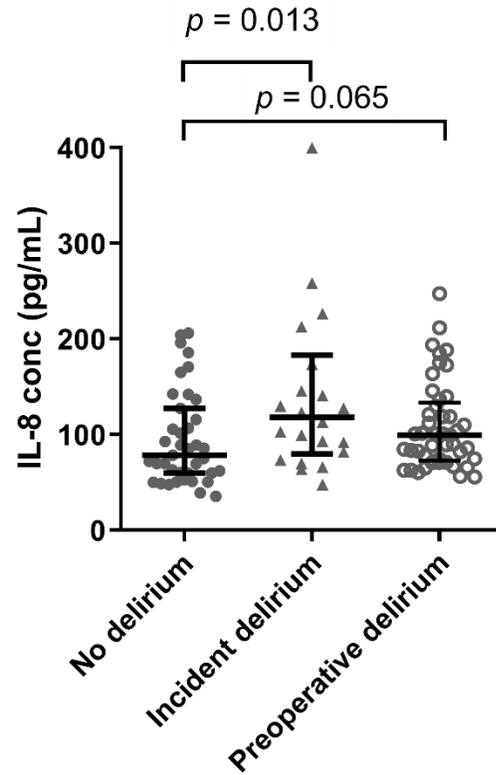
Figure 1: IL-8 concentrations in the CSF of hip fracture patients according to delirium subgroups.

SSD – Subsyndromal delirium
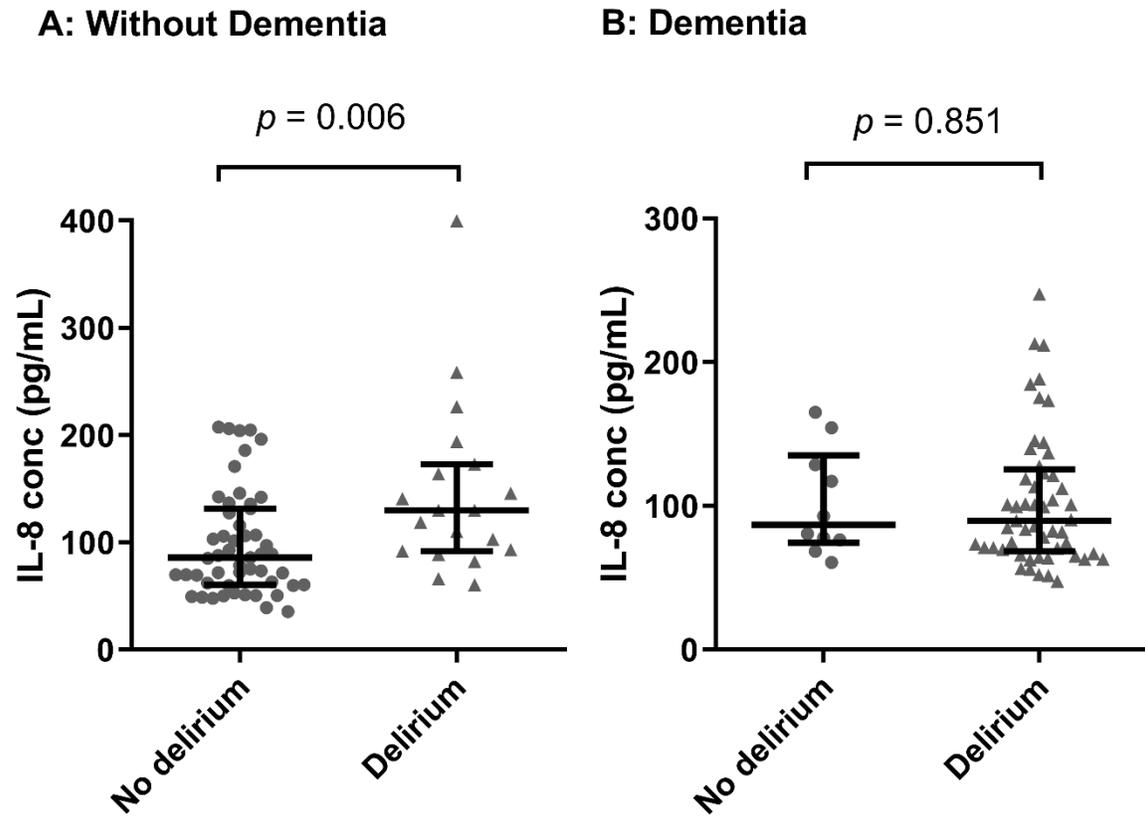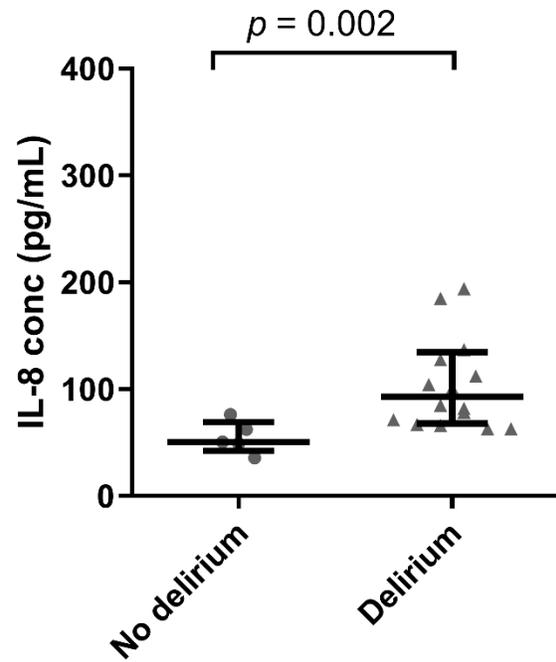
Figure 2: IL-8 concentration in the CSF of hip fracture patients according to delirium and dementia subgroups.

A: No Depression   **B: Depression**
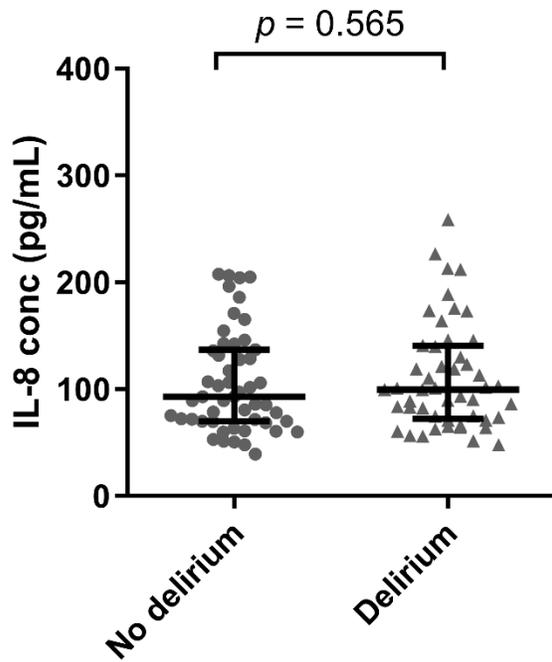
p = 0.565   *p* = 0.002

Figure 3: IL-8 concentration in the CSF of hip fracture patients according to delirium and depression subgroups.

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Figure 1: IL-8 concentration in the CSF of hip fracture patients according to delirium subgroups. A) IL-8 concentration by delirium subgroups where the subsyndromal delirium (SSD) subgroup is part of the no delirium group ($n = 61$, no delirium; n = 22, incident delirium; n = 45, preoperative delirium). Kruskal-Wallis test did not show significant difference between different groups ($p = 0.057$). One outlier ($y = 3131$) in the incident delirium had a value above the y-axis of this figure and was removed for visual purposes but not from the statistical analysis. B) IL-8 concentration by delirium subgroups without the SSD subgroup ($n = 39$, no delirium; $n = 22$, incident delirium; n = 45, preoperative delirium). Kruskal-Wallis test showed significant difference between different groups ($p = 0.023$). Mann-Whitney U test was conducted for comparison between no delirium and incident delirium ($p = 0.013$) or no delirium and preoperative delirium ($p = 0.065$). Delirium subcategories data was not available for five patients.

Figure 2: IL-8 concentration in the CSF of hip fracture patients according to delirium status and dementia subgroups. A) IL-8 concentration by delirium status in dementia free patients ($n = 51$, no delirium; $n = 19$, delirium group). Mann-Whitney U test showed significant difference between no delirium and delirium groups ($p = 0.006$). B) IL-8 concentration by delirium status in dementia patients ($n = 10$, no delirium; $n = 53$, delirium group). Mann-Whitney U test was conducted for statistical analysis and there was no significant difference between no delirium and delirium groups ($p = 0.851$). One outlier ($y = 3131$) in the delirium group had a value above the y-axis of this figure and was removed for visual purposes but not from the statistical analysis.

Figure 3: IL-8 concentration in the CSF of hip fracture patients according to delirium status and depression subgroups. A) IL-8 concentration in hip fracture patients by delirium status without

depression ($n = 51$, no delirium; $n = 49$, delirium; $p = 0.565$). B) IL-8 concentration in hip fracture

patients by delirium status with depression ($n = 5$, no delirium; $n = 16$, delirium; Exact $p = 0.002$).

One outlier ($y = 3131$) in the delirium group had a value above the y-axis of this figure and was

removed for visual purposes but not from the statistical analysis. Depression data was not available

for 12 patients ($n = 5$, no delirium; $n = 7$, delirium patients). Mann-Whitney U test was conducted

for comparison between no delirium and delirium group.

Supplementary Table 1: Correlations between CSF IL-8 and age in different patient groups

Patient groups	r_s	p-value	n
Cognitively healthy controls	0.143	0.113	125
Hip fracture group	0.113	0.195	133
AD dementia patients	0.015	0.899	73

Supplementary table 2: Comparison between dementia and dementia free patients in hip-fracture group

	Hip fracture patients		
	No – dementia (n=70)	Dementia (n=63)	p-value
Age years, Median (IQR)	84 (76 - 88)	85 (80 - 90)	0.029*
Gender, F (%)	51 (73 %)	46 (73 %)	0.984[#]
Depression, n (%)[a]	5 (8 %)	16 (27 %)	0.006[#]
IL-8 pg/mL, median (IQR)	93 (68.6 -141.2)	89.6 (69.7-127.5)	0.815*

*Mann-Whitney U test was performed.

a) Data on depression was missing for 4 patients in the dementia group and 8 patients in the no-dementia group.

[#] Chi-Square p-values were reported.