The Role of High Sensitivity C-reactive Protein to Predict Delirium Persistence in Elderly Patients with Pneumonia: A Prospective Cohort Study

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ABSTRACT

***Background**: Delirium is a disorder of acute full attention, and cognitive function commonly occurs at elderly which can prolong hospitalization, dependence rate, morbidity, and mortality, with pneumonia infection as one of its risk factors. Several markers have been studied for delirium, but relationship between delirium severity and persistence remains unclear. This study aimed to examine the role of hs-CRP, pNF-H, S100B, and NLR to predict delirium persistence.* **Methods**: A prospective cohort study was conducted among 80 subjects who were admitted to the internal ward in dr. M. Djamil Hospital in Padang. Subjects were grouped based on severity of delirium using the Memorial Delirium Assessment Scale and followed up until discharged to determine delirium persistence event.* **Results**: *Mean age of subjects is 70.7±7.4 years, 39 (48.8%) male and 41 (51.2%) female,consisting of 29 mild, 26 moderate, and 25 severe delirium. Levels of hs-CRP in mild, moderate, and severe delirium are 13.36±0.79, 13.56±0.78, and 13.88±0.59 mg/L (p=0.038), respectively. Median NLR values for mild, moderate, severe delirium were 6.80 (1.00-31.00), 9.50 (3.60-46.00), and 11.90 (2.80-46.50) (p=0.026). Cut off value hs-CRP 13.61 mg/L has significant difference for delirium persistence event (OR 2,54; 95% CI 1,01-6,39). Median levels of pNF-H and S100B are not significant in different delirium severity, regardless of non-persistent or persistent.* **Conclusion**: *Hs-CRP levels exceeding 13.61 can predict risk of persistent delirium, but not with levels pNF-H, S100B, and NLR.*

***Keywords*: *Delirium persistence, hs-CRP, elderly, pneumonia*.

INTRODUCTION

Delirium is an acute global impairment of attention and cognitive function common in old age.[1] The incidence of delirium is associated with prolonged length of stay, high mortality, and risk for cognitive impairment later in life. Delirium occurs due to the interaction between predisposing factors that determine the susceptibility of the patient and precipitating factors.[1]

Infection is one of the triggers of delirium.[2] Pneumonia is the most common infection and is the leading cause of hospitalization and death in the elderly. The incidence of delirium during hospitalization in pneumonia patients is about 31%.[3] Research shows delirium is a predictor of mortality in elderly pneumonia patients.[4] Delirium conditions can be reversible but can also persist for a longer time, known as persistent delirium. Several studies set different times as a standard for persistent delirium, one of which is at the time of discharge.[5] Cole et al. found a persistent delirium proportion of 44.7% upon

discharge.[6] Lee et al.[5] found prolonged delirium in elderly patients after hip fracture surgery 20% at four weeks.[5] This persistent condition of delirium sometimes causes confusion and misunderstanding for families.

Systemic inflammation will continue to be neuroinflammatory and cause increase in blood-brain barriers' permeability leading to damage to the synapse.[7] The severity of inflammation in infection can be assessed by various markers, including high sensitivity C-reactive protein (hs-CRP) and neutrophil-lymphocyte ratio (NLR). Systemic inflammation will continue to be neuroinflammatory and cause activation of microglia and astrocytes, which will excrete S100 Beta (S100B).[8] Mietani et al. observed elevated level of phosphorylated neurofilament heavy subunits (pNF-H), the main structures of the central axons of the nervous system levels, in 30 of the 41 patients who had non-cardiac postoperative delirium under general anesthesia.[9]

It is not yet clear whether hs-CRP, pNF-H, S100B, and NLR are associated with the persistence of delirium. This study aims to determine the role of hs-CRP, NLR, S100B, and pNF-H levels in predicting risk of persistence of delirium in elderly patients with pneumonia in the acute medical ward.

METHODS

This prospective cohort study was conducted in the acute medical ward of dr. M. Djamil Hospital from February 2021 to December 2021. Subjects were recruited after obtaining approval from ethical review board. The study sample was delirium patients aged 60 years or older with pneumonia infection. Patients who consumed antipsychotic drugs, suffered Parkinson's, acute stroke, rheumatoid arthritis, head trauma, or undergoing surgery were excluded. Eligible patients were followed up until discharge. Patients who were still delirium when discharged were classified as persistent delirium.

Ethical Approval

The Research Ethics Committee of Medical Faculty Andalas University number 227/ UN.16.2/KEP-FK/2021.

Delirium Assessment

Delirium was assessed using the Confusion Assessment Method-Intensive Care Unit instrument. Delirium was diagnosed if there is a change in mental status with acute onset or fluctuating course, inattention, disorganized thinking, or altered level of consciousness.[10] A geriatrician carried out delirium assessments. The severity of delirium was assessed with the Memorial Delirium Assessment Scale (MDAS), which has ten items with four scales and a maximum value of 30. An MDAS score of 13-16 indicates mild delirium, a score of 17-24 moderate, and severe delirium if the score >24. [11]

Specimen Collection and Methods of Analyses

A 3 ml blood sample was collected within 24 hours of hospitalization in an acute medical ward. Serum was separated within 2 hours and stored at a temperature of -80^{0}C until later analysis. Examination of hs-CRP, S100B, and pNF-H is carried out at the Biomedical Laboratory of the Faculty of Medicine, Universitas Andalas. Serum concentrations of hs-CRP, pNF-H, and S100B were measured by the Enzyme-Link Immunosorbent Assay (ELISA) by BioRad. Hs-CRP was measured using high sensitivity human ELISA kits (DBC Canada), Abbexa for pNF-H, and LSBio reagent for S100B analyzed. Each examination was carried out duplo. The NLR assessment was carried out by calculating the differential count of leukocytes at the Central Laboratory of dr. M. Djamil hospital Padang.

Statistical Analysis

Differences in hs-CRP levels at varying severity of delirium were analyzed with ANOVA, while differences in NLR values, pNF-H levels, and S100B were analyzed with the Kruskal Wallis test because the data were not normally distributed. The role of these markers in predicting persistent delirium is done by first establishing a cut-off point using the receiver operating characteristic curves. The analysis continued with multivariate logistic regression. Furthermore, the odds ratio of each marker is determined in predicting risk of persistent delirium. The odds ratio not crossing one is said to be significant.

RESULTS

Of the 170 patients initially screened for the study, 15 patients were excluded and 75 patients died before discharge. Thus, 80 patients completed the study and were included in the analysis. Thirty-two (40%) subjects were still in delirium at discharge and classified as persistent delirium (**Figure 1**).

The average age of the study subjects was 70.7±4 years. About half of the subjects were women (51.2%), comorbidities were chronic kidney disease (52.50%), diabetes mellitus (50%), and hypertension (50%). (**Table 1**).

Table 2 shows differences in hs-CRP, pNF-H, S100B, and NLR levels at varying severity of delirium. There were significant differences in hs-CRP and NLR levels between mild, moderate, and severe delirium, with the highest value in severe delirium.

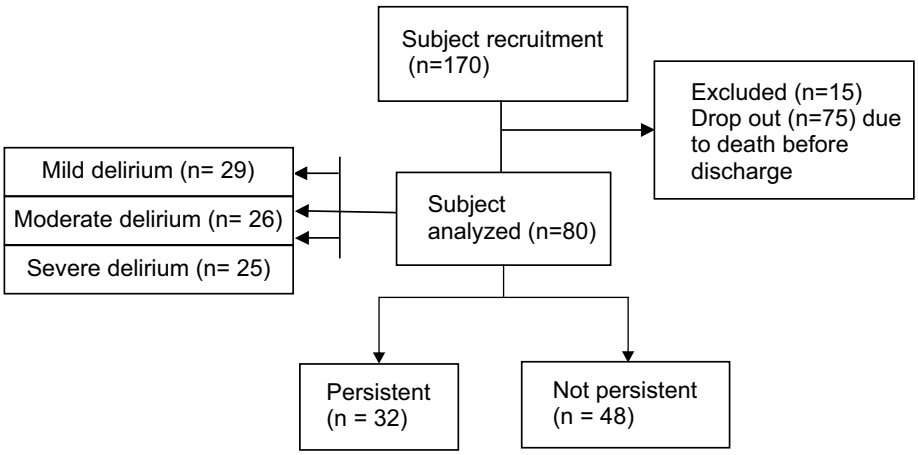

Figure 1. Subject recruitment flow.

Table 1. Subject characteristics (n=80).

Characteristics	Total	Persistent delirium (n=32)	Non-persistent delirium (n=48)
Age (mean ± SD)	70.7±7.4	71.5±7.3	70.2±7.6
Gender			
Male (n, %)	39 (48.8)	12 (37.5)	27 (56.3)
Female (n, %)	41 (51.2)	20 (62.5)	21 (43.8)
Comorbidities (n, %)			
Diabetes	40 (100.0)	18 (45.0)	22 (55.0)
Hypertension	40 (100.0)	18 (45.0)	22 (55.0)
Cardiac disease	26 (100.0)	14 (53.8)	12 (46.2)
Chronic kidney disease (CKD)	42 (100.0)	19 (45.2)	23 (54.8)
Delirium severity			
Mild	29 (100.0)	2 (6.9)	27 (93.1)
Moderate	26 (100.0)	9 (34.6)	17 (65.4)
Severe	25 (100.0)	21 (84.0)	4 (16.0)

SD, standard deviation

Table 2. Hs-CRP, pNF-H, S100B, and NLR levels at the baseline.

Variables	Total	Mild delirium (n=29)	Moderate delirium (n=26)	Severe delirium (n=25)	P value
hs-CRP (mg/L)	13.59±0.75	13.36±0.79	13.56±0.78	13.88±0.59	0.038
pNF-H (pg/mL)	598 (18.36-4759.94)	605.86 (18.36-3309.20)	542.12 (25.28-4759.94)	643.27 (82.09-4669.88)	0.813
S100B (pg/mL)	21.73 (17.49-531.16)	22.74 (17.91-36.99)	21.53 (18.13-99.23)	20.89 (17.49-37.68)	0.074
NLR	9.35 (1.00-46.50)	6.80 (1.00-31.00)	9.50 (3.60-46.00)	11.90 (2.80-46.50)	0.026

Table 3. Relationship of hs-CRP, pNF-H, S100B, and NLR levels with delirium persistence.

			Bivariate analysis		Multivariate analysis	
Variable	**Cut off**	**AUC (95% CI)**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
hs-CRP (mg/L)	13.61	0.627 (0.504-0.751)	2.54 (1.01-6.39)	0.045	2.54	0.047
pNF-H (pg/mL)	549.00	0.508 (0.370-0.640)	0.75 (0.30-1.83)	0.523		
S100B (pg/mL)	21.58	0.459 (0.326-0.592)	0.53 (0.21-1.31)	0.167	0.74	0.583
NLR	9.35	0.538 (0.409-0.668)	1.52 (0.62-3.74)	0.361		

AUC *area under the curve*, OR *odd ratio*

The analysis results showed that hs-CRP was significantly associated with persistent delirium events. Subjects with hs-CRP levels exceeding 13.61 had a 2.5-fold increased risk of delirium persistence, whereas pNF-H, S100B, and NLR levels showed no significant association with delirium persistence.

DISCUSSION

The study found high levels of hs-CRP (exceeding 13.61 mg/L) can predict the risk of persistent delirium (OR 2.54, 95%CI 1.01-6.39), but this is not the case with pNF-H, S100B, and NLR.

In systemic inflammatory conditions, neutrophils activate and cross endothelial cells in the vascular brain, and release reactive oxygen species (ROS) and proteases, which will cause the destruction of endothelial cell arrangement. Disruption of the blood-brain barrier will increase the transport of cytokines to the brain. These cytokines will activate microglia that produce inflammatory markers and reactive oxygen species (ROS).[12,13] The formation of ROS by neutrophils and microglia causes oxidative stress that leads to neuronal damage and apoptosis.[14] Endothelial dysfunction will cause impaired blood flow and the release of various biochemical mediators resulting in delirium.[15] Systemic inflammation will continue to be neuroinflammatory and cause various activation of microglia and astrocytes which will excrete S100B, a calcium-bound protein that will increase neuronal inflammatory conditions and blood-brain barriers' permeability. Damage to the blood-brain barrier will increase the transport of cytokines to the brain leading to damage to the synapse.[7]

High sensitivity-CRP is a relatively stable marker for a long time and has high sensitivity, in contrast to S100B, which has a short half-life so that within 24 hours, it returns to normal levels.[16] Evident in this study, S100B levels are generally normal (<100 pg/mL).

Ischemia and neuron apoptosis lead to neuronal damage characterized by high pNF-H levels in delirium subjects. The pNF-H levels found in neuron axon damage can last up to 21 days. Almost all delirium patients in this study had positive pNF-H levels and did not differ in those who were persistent or not. Hayakawa et al. concluded that S100B could be used as an early marker, while pNF-H is used as a delayed marker in neuronal injury.[17]

Research on the relationship between CRP and persistent delirium is still lacking. Some existing studies only link CRP levels to the occurrence of delirium. Zhang, who examined CRP levels in ICU patients, found an increase in CRP >8.1 mg/L in 24 hours associated with a 4-fold increased risk of delirium. Patients with delirium had a longer treatment duration than patients without delirium. This study did not record the incidence of persistent delirium.[18] Research on patients undergoing vascular surgery also showed CRP as a marker for an increased risk of post-surgical delirium events.[19] (Pol). Vasunilashorn's study (2017) found high CRP levels associated with delirium duration.[20] McGrane (2011) found a link between hs-CRP levels and the shorter duration of delirium free in critically ill patients.[21]

This study supports the role of hs-CRP as an inflammatory marker in predicting the risk of persistent delirium. Further research with larger sample size and different subjects is needed to support this finding. High levels of hs-CRP also indicate the severity of the inflammatory process occurring in delirium patients. The limitation of this study is the definite onset of delirium was unclear because patients had had delirium when admitted to the ward.

CONCLUSION

High sensitivity of c-reactive protein but not pNF-H, S100B, and NLR could be used to predict the risk of persistent delirium.

CONFLICT OF INTEREST

All authors declare no conflict of interest related to this study.

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