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Prediction of Delirium Using Admission Inflammatory Biomarkers in Mechanically Ventilated Intensive Care Patients

Areej Fatima[1], Rameen Ali[1], Nora Maqsood[1], Tehreem Zubair[1], Hurmat Waseem Chaudhry[1]

1 Al-Aleem Medical College, Lahore, Pakistan

Correspondence to: Rameen Ali, **Email:** rameenaliahmed@gmail.com

ABSTRACT

Background: Delirium is common among mechanically ventilated intensive care patients, and is linked to longer lengths of hospital and ventilation, and higher death rates. Admission inflammatory biomarkers may allow identification of patients at increased risk.

Objective: To determine the predictive value of admission inflammatory biomarkers for delirium in mechanically ventilated intensive care patients.

Methods: This prospective observational cohort study was conducted in the department of anesthesia and intensive care at the Al-Aleem Medical College, Lahore, Pakistan from January 2025 to January 2026, involving 120 adult patients under invasive mechanical ventilation for more than 24 hours. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII) and C-reactive protein (CRP) were obtained within 6 hours of admission. Delirium was evaluated twice daily using the CAM-ICU. Receiver operating characteristic analysis and multivariable logistic regression were done.

Results: Delirium occurred in 44 patients (36.7%). Delirium was associated with more inflammation, more severity of illness and more incidences of sepsis. Systemic immune-inflammation index had the highest predictive accuracy with an area under the curve of 0.78. The best cut-off was >2,100 with sensitivity 72.7% and specificity 69.7%. An SIR ≥ 2,100 was an independent predictor of delirium (adjusted odds ratio 3.42; 95% confidence interval 1.49-7.85; p=0.004).

Conclusion: The current study concludes that the systemic immune-inflammation index at admission might be a simple and inexpensive tool for early stratification of delirium risk in critical illness in patients treated with mechanical ventilation.

Keywords: Delirium; inflammatory biomarkers; intensive care unit; mechanical ventilation; systemic immune-inflammation index

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INTRODUCTION

Delirium is an acute disturbance of attention, awareness, and cognitive function that develops over a short period and commonly fluctuates throughout the day [1]. It is one of the most frequent neurological complications encountered in intensive care units, particularly among patients receiving invasive mechanical ventilation [2]. There is a number of precipitating factors that critically ill ventilated patients are exposed to such as severe systemic illness, exposure to hypoxaemia, infection, metabolic abnormalities and organ dysfunction, sleep disturbance, immobility, pain and sedative drug use. Delirium may not be recognized in these patients, particularly when hypoactive, because they can't communicate effectively [3].

Delirium is clinically significant in mechanically ventilated patients as it is linked to longer intensive care and hospital stays, longer ventilator duration, increased healthcare costs, ongoing cognitive dysfunction and mortality [4]. Delirium can also hinder weaning from the ventilator, decrease patient co-operation, increase risk of

accidental removal of medical equipment and have long-term psychological and functional effects. Thus, it is crucial to recognize those who are at high risk at an early stage so that proper preventive measures can be taken and close neurological monitoring can be done at the proper time [5,6].

Delirium has been associated with a number of clinical factors, such as advanced age, pre-existing cognitive dysfunction, sepsis, shock, severity of illness, renal dysfunction, electrolyte disturbances, prolonged sedation and benzodiazepine exposure [7]. But many of these factors are not obvious until the patient has been in the intensive care unit for a considerable period of time. Using a simple biomarker at admission may be a useful tool for clinicians to identify vulnerable patients prior to the onset of obvious changes in mental status [8].

It is now thought that systemic inflammation plays a major role in the pathogenesis of delirium in critical illness [9]. Inflammatory mediators are released and neutrophils, platelets and vascular endothelial cells activated in severe infection, tissue injury, mechanical ventilation and circulatory instability. These inflammatory processes can lead to changes in the microcirculation in the brain, make the blood brain barrier permeable, activate microglial cells and disrupt neurotransmitter regulation. This neuroinflammatory reaction can lead to cognitive dysfunction, altered consciousness and impaired attention [10].

Several inexpensive markers of systemic inflammation can be obtained in routine blood investigations [11]. The N:L ratio represents the balance between the innate inflammatory activation and adaptive immune suppression. Platelet to lymphocyte ratio could be a marker of combined thrombotic and inflammatory activity. The systemic immune-inflammation index includes the number of neutrophils, lymphocytes and platelets and might reflect a more generalized inflammatory response. Another frequently ordered acute phase reactant is C-reactive protein, which rises with infection, trauma and inflammation throughout the body. These biomarkers are easy to obtain, are easily available and do not need specialized testing [12].

Inflammatory biomarkers have been studied in a variety of medical and surgical patient cohorts, but their ability to predict delirium in mechanically ventilated intensive care patients has been poorly characterized [13]. Findings from previous studies have been variable, which may be due to the differences in patient population, timing of assessment for biomarkers, delirium assessment method, and clinical severity. In addition, there is a lack of direct comparison between more than one inflammatory index evaluated at admission and whether these markers provide additional predictive value to standard admission clinical parameters [14].

The aim of current study was to evaluate the association between delirium in patients on mechanical ventilation in the critical care unit and signs of inflammation upon admission. Additionally, it aimed to determine if the N:L ratio, P:L ratio, SII, and C-reactive protein might be utilized to improve clinical risk categorization in the early stages [15].

MATERIALS AND METHODS

The study was a prospective observational cohort study, carried out in the department of anesthesia and intensive care at the Al-Aleem Medical College, Lahore, Pakistan from January 2025 to January 2026. Ethical clearance was granted by the Institutional Review Board under the reference number IRB/AMC/2025/004. All participants gave written informed consent prior to enrolment.

The sampling technique used was non-probability consecutive sampling with a total of 120 adult patients. Patients were eligible if they were above the age of 18, required invasive mechanical breathing for at least 24 hours, and had a complete blood count and C-reactive protein level accessible within 6 hours of being admitted to the intensive care unit. The study comprised both medical and surgical critical care patients. Delirium at the first examination that could be evaluated, pre-existing dementia, stroke in the acute phase, ICP or TBI, infection of the CNS, hepatic encephalopathy, active psychosis, drug intoxication, haematological malignancy or severe hearing or visual loss were exclusion criteria. Patients who were deeply sedated or comatose during their intensive care unit stay and who were not able to be evaluated for delirium were also excluded.

Each patient's age, gender, admitting service (medical or surgical), comorbid illnesses, presence of sepsis, requirement for vasopressors, exposure to sedatives, and severity of sickness were among the clinical and demographic information gathered at the time of hospital admission. During the first 24 hours of hospitalization, the Acute Physiology and Chronic Health Evaluation II score was used to gauge the severity of the illness.

Within six hours after being admitted to the intensive care unit (ICU), one blood sample was taken and examined for serum C-reactive protein levels, total leukocyte counts, absolute neutrophil counts, absolute lymphocyte counts, and platelet counts. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC). The ratio of the absolute lymphocyte count to the platelet count was used to calculate the platelet-to-lymphocyte ratio. The platelet count was multiplied by the absolute value of neutrophils and divided by the absolute value of lymphocytes to get the systemic immune-inflammation index.

Richmond Agitation–Sedation Scale was used to assess the level of sedation prior to delirium assessment. Patients with scores of −4 or −5 were deemed too deeply sedated to assess and reassessed on improvement in

consciousness. Delirium was assessed in patients with scores between −3 and +4 using CAM-ICU.

Trained intensive care physicians or nurses conducted delirium assessments twice daily. Delirium was diagnosed if the patient had an acute or fluctuating mental status change and inattention, and either altered consciousness or disorganized thinking. Patients were followed for seven days or till the discharge of intensive care unit or extubation or death whichever came first. The main outcome was considered to be the onset of delirium at any time during the observation period. Secondary endpoints were length of mechanical ventilation, intensive care unit stay, hospital stay, and intensive care mortality.

Data analysis was done using IBM SPSS Statistics 26.0. The mean and standard deviation or median and interquartile range, depending on the situation, were used for continuous data. The number and percentage were utilized for categorical variables. For continuous variables, the independent-samples t-test or Mann-Whitney U test were used; for categorical variables, the chi-square test or Fisher exact test were used.

The predictive power of the NLR, PLR, SII, and CRP was determined using ROC curve analysis. Sensitivity, specificity, cutoff value, and area under the curve were calculated. After controlling for clinically significant variables, independent factors linked to delirium were identified using multivariable logistic regression analysis. A $p<0.05$ was deemed significant, and adjusted odds ratios (ORs) were presented with 95% confidence intervals (CI).

RESULTS

A total of 132 mechanically ventilated patients were evaluated for inclusion in the study period. Twelve patients were excluded (six with delirium at the initial examination, four with acute neurological disorders and two who were deeply sedated during the entire observation period). A total of 120 patients were evaluated. 44 patients (36.7%) had delirium, whereas 76 did not. The median period from critical care unit admission to the first occurrence of delirium was two days. Among them, 24 (54.5%) had hypoactive delirium, 8 (18.2%) had hyperactive delirium, and 12 (27.3%) had mixed delirium.

In the delirium group, there were 26 men and 18 women, whereas in the non-delirium group, there were 49 men and 27 women. There was no statistically significant difference in the numbers of men and females in the groups. Patients with delirium were substantially older and had significantly higher Acute Physiology and Chronic Health Evaluation II scores. Additionally, those with sepsis were more likely to have delirium. The delirium group had substantially higher NLR, PLR, SII, and CRP levels upon admission, as seen in Table 1.

With an area under the curve of 0.78, the systemic immune-inflammation index was determined to have the strongest prediction potential for delirium in receiver operating characteristic curve analysis. A sensitivity of 72.7% and specificity of 69.7% were obtained when the systemic immune-inflammation index value was more than 2,100. As shown in Table 2, the neutrophil-to-lymphocyte ratio likewise exhibited respectable prediction ability, although C-reactive protein and the platelet-to-lymphocyte ratio performed worse.

The most important independent predictor of delirium, according to multivariable logistic regression, was a SII level over 2100. Patients with levels exceeding this cutoff had adjusted chances of delirium that were 3.42 times greater. Additionally, increased age, a higher Acute Physiology and Chronic Health Evaluation II score, sepsis upon admission, and exposure to benzodiazepines were all independently linked to delirium. Table 3 shows that the need for vasopressors was not statistically significant after adjustment. The Acute Physiology and Chronic Health Evaluation II score, age, sepsis, vasopressor usage, and benzodiazepine exposure were all included in the clinical prediction model, which had an area under the curve of 0.75. The addition of the systemic immune-inflammation index increased the area under the curve to 0.81. A p value of 0.624 from the Hosmer–Lemeshow test indicates that the model is well calibrated.

The median mechanical breathing time for delirious patients was 8 days compared to 5 days for non-delirious patients ($p<0.001$). The median length of stay in the intensive care unit (ICU) was 7 days for the non-delirium group and 11 days for the delirium group ($p<0.001$). Additionally, delirious patients were more likely to have a longer median hospital stay (16 vs. 12 days, $p=0.006$). 11 patients with delirium (25.0%) and eight patients without delirium (10.5%) died in the intensive care unit; this difference was statistically significant ($p=0.034$).

Table 1: Baseline characteristics and admission inflammatory biomarkers

Variable	Delirium group, n=44	Non-delirium group, n=76	p-value
Age, years	59.8 ± 13.2	52.9 ± 14.1	0.009
Male gender, n (%)	26 (59.1)	49 (64.5)	0.557
Female gender, n (%)	18 (40.9)	27 (35.5)	0.557
Acute Physiology and Chronic Health Evaluation II score	20.6 ± 5.8	16.9 ± 5.2	<0.001
Sepsis at admission, n (%)	21 (47.7)	20 (26.3)	0.017
Vasopressor requirement, n (%)	18 (40.9)	19 (25.0)	0.068
Neutrophil-to-lymphocyte ratio	11.4 (8.2–15.8)	7.6 (5.2–10.9)	<0.001
Platelet-to-lymphocyte ratio	214 (158–287)	181 (132–238)	0.041
Systemic immune-inflammation index	2,860 (1,960–4,180)	1,625 (980–2,380)	<0.001
C-reactive protein, mg/L	112 (68–181)	71 (38–126)	0.002

Table 2: Predictive performance of admission inflammatory biomarkers for delirium

Biomarker	Area under the curve	95% confidence interval	Optimal cut-off	Sensitivity, %	Specificity, %
Systemic immune-inflammation index	0.78	0.69–0.86	>2,100	72.7	69.7
Neutrophil-to-lymphocyte ratio	0.73	0.64–0.82	>9.1	68.2	67.1
C-reactive protein	0.68	0.58–0.78	>84 mg/L	65.9	61.8
Platelet-to-lymphocyte ratio	0.62	0.52–0.72	>190	61.4	57.9

Table 3: Multivariable predictors of delirium

Predictor	Adjusted odds ratio	95% confidence interval	p-value
Age, per 10-year increase	1.32	1.02–1.71	0.036
Acute Physiology and Chronic Health Evaluation II score, per-point increase	1.10	1.02–1.18	0.011
Sepsis at admission	2.18	1.01–4.71	0.047
Vasopressor requirement	1.38	0.59–3.24	0.456
Benzodiazepine exposure	2.26	1.01–5.04	0.047
Systemic immune-inflammation index greater than 2,100	3.42	1.49–7.85	0.004

DISCUSSION

The current study assessed the effectiveness of inflammatory biomarkers detected upon intensive care unit admission for predicting delirium in mechanically ventilated patients [1]. This finding suggests that delirium was frequent in the study population, as it occurred in 36.7% of the population. Patients with delirium were older, more severely ill and more likely to present with sepsis. They also had significantly higher neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, and C-reactive protein levels at admission [2].

Among the biomarkers evaluated, the systemic immune-inflammation index exhibited the best prediction [3]. An index value >2,100 yielded a good sensitivity and specificity and continued to be independently associated with delirium after adjusting for relevant clinical factors. Patients whose scores exceeded this threshold had over three times the odds of delirium. The results indicate that the simultaneous inflammatory information of the three types of blood cells (neutrophil, lymphocyte and platelet) could be used for risk discrimination than only one of the parameters of the blood cells [4].

Possible explanation for the systemic inflammation - delirium association is critical illness effects upon central nervous system [5]. Stimuli which can lead to the release of inflammatory mediators include severe infection, tissue injury, hypoxaemia and circulatory instability. These alterations can lead to a disruption of cerebral microcirculation, blood–brain barrier permeability and initiation of neuroinflammatory signaling. This disruption of the regulation and function of neurotransmitters can lead to changes in consciousness, inattention, and disorganized thinking [6].

The N/L ratio was also found to have good predictive power. Raised neutrophils are a sign of engagement of innate immune system and low lymphocytes can be a sign of physiological stress and a defect in adaptive immunity [7]. These changes together, may then, mark an increased systemic inflammatory load in patients. But it had lower predictive ability than the systemic immune-inflammation index, perhaps due to its lack of platelet-mediated inflammatory and thrombotic activity [8].

C-reactive protein levels also were significantly higher in those who developed delirium, but the overall discrimination was modest [9]. C-reactive protein is a non-specific marker of inflammation and can rise in response to the presence of infection, trauma, surgery and tissue injury. It was not as accurate as the systemic immune-inflammation index, and its lack of specificity has been cited as a potential reason for this. Comparably, the platelet-to-lymphocyte ratio was the least predictive biomarker evaluated, and may not be a useful single biomarker for delirium risk assessment [10].

Age and Acute Physiology and Chronic Health Evaluation II score were independently associated with delirium [11]. Older patients may have diminished neurological reserve and be more susceptible to inflammatory and metabolic disturbances. The greater the severity score the more likely the individual has widespread organ dysfunction and is physiologically unstable, both of which can be associated with a risk of cerebral dysfunction [12]. Delirium was also independent of sepsis, reinforcing the importance of inflammatory response, endothelial dysfunction and reduced cerebral perfusion in the pathogenesis of sepsis [13].

Another independent predictor was benzodiazepine exposure. These drugs can cause excessive sedation, disruption of sleep patterns and interfere with normal cognitive functions [14]. Therefore, their use should be carefully considered in mechanically ventilated patients, especially patients with increased inflammatory biomarkers or other risk factors for delirium. Delirium risk can be minimized by reducing unnecessary exposure to benzodiazepines through sedation strategies [15].

The addition of the systemic immune-inflammation index to the clinical prediction model increased the area under the curve from 0.75 to 0.81 [16]. This finding

suggests that inflammatory markers can be used to gain insight in addition to traditional clinical parameters. The systemic immune-inflammation index does not require special laboratory testing and is also not an extra charge since it is derived from a routine complete blood count. It can therefore be used for early bedside risk stratification, such as in resource scarce intensive care environments [17].

Delirium was associated with longer mech. ventilation and ICUs and hospital lengths of stay. Mortality also was greater in the delirium group. Delirium can make weaning from ventilator difficult, decrease cooperation, lead to more exposure to sedatives, and delay mobilization. This was an observational study, however, and it was not possible to determine if delirium actually caused these adverse outcomes, or simply served as an indicator of greater underlying illness severity [18,19].

There were several points about this study that were strong. Biomarkers were assessed early upon admission to the intensive care unit (ICU), prior to the onset of delirium. Delirium was evaluated twice daily with a standardized instrument and clinically important confounders were taken into account in the multivariable analysis. Several inflammatory markers which are available on a routine basis were also compared directly [20].

There were also limitations to the study. This was carried out in one centre and the sample was quite small, so the results might not apply to other centres. Inflammatory biomarkers are non-specific and can be influenced by infection, medication, malignancy and other clinical conditions. Evaluations for delirium were not possible during periods of deep sedation and brief periods between scheduled assessments might not have been observed or recorded. Furthermore, the proposed cut-off values need to be validated in large multicentre trials before they can be used in clinical practice [15-20].

CONCLUSION

Mechanically ventilated intensive care patients were very likely to have delirium, and older age, higher illness severity, sepsis, benzodiazepine exposure, and higher inflammatory biomarkers at admission were all associated with the presence of delirium. The systemic immune-inflammation index had the best predictive ability and was an independent predictor of delirium. This is a simple, cheap marker which can be used as part of the admission examination to enhance the early detection of high-risk patients. There is a need for larger multicentre studies to confirm the threshold and its clinical relevance.

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Data Availability: Data are available from the corresponding author upon reasonable request.

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