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The Role of Gasdermin D and CRP as Risk Markers of Postoperative Delirium in Patients Undergoing Spine Surgery: A Prospective Cohort Study

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ABSTRACT

Aim: To evaluate the role of Gasdermin D and C-reactive protein (CRP) as biomarkers for predicting the risk of postoperative delirium (POD) in elderly patients undergoing spine surgery.

Material and Methods: This prospective cohort pilot study was conducted over one year at the Department of Anaesthesiology, R D Gardi Medical College Ujjain. Thirty-five patients aged ≥60 years, classified as ASA I or II and scheduled for elective spine surgery under general anaesthesia, were included. Patients with pre-existing cognitive impairment, systemic infections, or malignancies were excluded. Preoperative and 48-hour postoperative CRP and Gasdermin D levels were measured using ELISA. Delirium assessment was performed daily for seven days post-surgery using CAM or CAM-ICU. Statistical analyses included logistic regression and ROC curve analysis, with $p < 0.05$ considered significant.

Results: Out of 35 patients, 9 (25.71%) developed POD. Patients with delirium showed significantly lower MMSE scores and higher preoperative CRP (9.2 ± 1.8 mg/L) and Gasdermin D levels (55.6 ± 8.9 pg/mL) than those without delirium (CRP: 5.6 ± 1.4 mg/L; Gasdermin D: 37.8 ± 6.3 pg/mL). Postoperative levels further increased in the POD group (CRP: 16.8 ± 2.6 mg/L; Gasdermin D: 74.2 ± 9.4 pg/mL). ROC analysis showed high predictive accuracy with AUCs of 0.86 for postoperative CRP and 0.91 for postoperative Gasdermin D. Sensitivity and specificity were highest for postoperative Gasdermin D at a cut-off of >65 pg/mL (100% and 84.6%, respectively).

Conclusion: Elevated CRP and Gasdermin D levels, both pre-and postoperatively, were significantly associated with the development of POD. Gasdermin D exhibited superior predictive performance, suggesting its utility as a novel biomarker. Prolonged surgical duration and higher blood loss were additional risk factors. These findings support the integration of inflammatory biomarkers into perioperative risk assessment protocols.

Keywords: *Postoperative Delirium; Gasdermin D; C-Reactive Protein; Spine Surgery; Biomarkers*

1. INTRODUCTION

Advances in spine surgery have enabled safer procedures for elderly patients suffering from spine fractures. However, Postoperative delirium (POD) is a common and severe complication among elderly patients undergoing spine surgery. It is characterized by acute neurocognitive disturbances such as disorientation, inattention, and fluctuating mental states. The incidence of POD is significant, affecting approximately 25% of patients undergoing non-cardiac surgeries, and is associated with increased morbidity, extended hospital stays, and long-term cognitive impairments such as postoperative cognitive

dysfunction (POCD).[1-3] Recent research suggests that a pro-inflammatory state plays a critical role in the development of POD. Pro-inflammatory biomarkers such as Interleukin-6 (IL-6), C-reactive protein (CRP), and S100 calcium-binding protein β (S100β) have been implicated in neuroinflammatory processes associated with cognitive decline.[1,3,4] Elevated preoperative levels of these biomarkers correlate with a higher risk of POD, highlighting the importance of systemic inflammation as a predictive factor.[1,3]

Neuroinflammation, characterized by microglial activation and cytokine release, contributes to blood-brain barrier disruption and neuronal damage, which are key pathophysiological mechanisms of POD.[1,2,5] Biomarkers such as Gasdermin D and soluble triggering receptor expressed on myeloid cells 2 (sTREM2) have emerged as promising indicators of preoperative neuroinflammatory status.[1,2]

Understanding these biomarkers' role in POD risk stratification could pave the way for targeted preoperative interventions, ultimately improving surgical outcomes.[1]

C-reactive protein (CRP) is an acute-phase reactant produced by the liver in response to inflammation. It is regulated by cytokines such as Interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). CRP serves as a biomarker of systemic inflammation and is widely used in clinical practice to detect infections and inflammatory diseases and assess cardiovascular risks. Elevated CRP levels have been linked to postoperative complications, including postoperative delirium (POD). Its role in POD is attributed to its ability to amplify neuroinflammatory responses, contributing to blood-brain barrier disruption and neuronal damage.[3,4] Gasdermin D is a protein involved in the process of pyroptosis, a form of programmed inflammatory cell death. It is activated by inflammasomes in response to infection or tissue damage, leading to the release of pro-inflammatory cytokines such as IL-1β. Gasdermin D forms pores in the cell membrane, allowing the release of inflammatory mediators and driving neuroinflammation. Emerging evidence suggests its involvement in neurological disorders and cognitive dysfunction, including POD. Elevated levels of Gasdermin D in preoperative settings may indicate an underlying pro-inflammatory state that predisposes patients to POD.[1,2]

2. MATERIAL AND METHODS

The present study was conducted at the Department of Anesthesiology R D Gardi Medical college Ujjain. It was designed as a prospective cohort pilot study aimed at exploring biomarkers predictive of postoperative delirium. The total duration of the study was one year. A sample size of 35 elderly patients undergoing spine surgery under general anaesthesia was included. Since the study was exploratory and conducted as a pilot, formal sample size calculation was not required.

Inclusion Criteria and Exclusion Criteria:

Inclusion Criteria

- Adults aged ≥60 years scheduled for spine surgery under general anesthesia.
- ASA physical status I and II.
- No prior history of delirium or significant cognitive impairment.

Exclusion Criteria

- History of psychiatric disorders, systemic infections, or autoimmune diseases.
- ASA physical status III and IV.
- Malignancies affecting CRP or Gasdermin D levels.
- Use of immunosuppressive therapy or corticosteroids.
- Severe cognitive impairment or inability to cooperate.
- Unwilling patients.

3. METHODOLOGY

The study was designed as a prospective cohort study. The primary objective was to assess the role of Gasdermin D and C-reactive protein (CRP) as biomarkers for predicting postoperative delirium in elderly patients undergoing spine surgery.The study population included adults aged 60 years and above who were scheduled for spine surgery under general anesthesia. Participants were selected according to predefined inclusion and exclusion criteria. Only ASA I and II patients without a history of delirium or significant cognitive impairment were included.

Baseline demographic details such as age, gender, BMI, and comorbidities were recorded. Preoperative cognitive assessment was performed using the Mini-Mental State Examination (MMSE). Blood samples were collected within 24 hours before surgery to determine baseline CRP and Gasdermin D levels using enzyme-linked immunosorbent assay (ELISA). Intraoperative data, including the type of anaesthesia, duration of surgery, estimated blood loss, and intraoperative complications, were documented. Patients were monitored daily for the development of postoperative delirium for up to 7 days using the Confusion Assessment Method (CAM) or CAM-ICU for intubated patients. Postoperative blood samples were obtained at 48 hours to evaluate changes in CRP and Gasdermin D levels.

Blood samples were centrifuged and stored at –80°C until analysis. CRP levels were measured using high-sensitivity CRP assays, while Gasdermin D levels were quantified using specific ELISA kits. Laboratory personnel remained blinded to the

clinical outcomes to reduce observer bias. Informed written consent was obtained from all participants prior to enrollment in the study.

Statistical Analysis

Statistical analysis was carried out using SPSS software (Version 27.0). Descriptive statistics were used to summarize demographic, clinical, and laboratory parameters. Group comparisons were made using the Student's t-test or Mann-Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables. Logistic regression analysis was employed to identify independent predictors of postoperative delirium, with CRP and Gasdermin D levels considered as primary explanatory variables. Receiver operating characteristic (ROC) curve analysis was conducted to assess the predictive accuracy of these biomarkers. A p-value <0.05 was considered statistically significant.

4. RESULTS

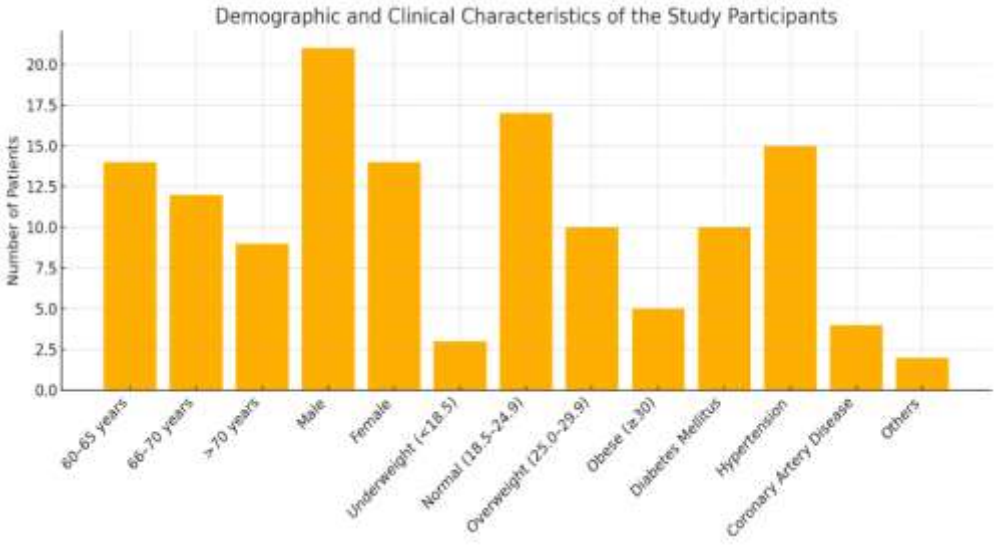
Demographic and Clinical Characteristics

The study enrolled 35 elderly patients scheduled for spine surgery, with the majority (40%) falling within the 60–65 years age group, followed by 34.29% between 66–70 years, and 25.71% over the age of 70. Males constituted a larger proportion of the study population (60%) compared to females (40%). Regarding nutritional status, nearly half of the participants (48.57%) had a normal BMI (18.5–24.9 kg/m²), while 28.57% were overweight and 14.29% were obese. A small fraction (8.57%) were underweight.

Importantly, none of the participants had a prior history of delirium or cognitive impairment, fulfilling the exclusion criteria. Among comorbid conditions, hypertension was the most common (42.86%), followed by diabetes mellitus (28.57%) and coronary artery disease (11.43%). Two patients had other comorbidities. These baseline characteristics highlight a typical elderly surgical population, with prevalent metabolic and cardiovascular risks that may influence postoperative outcomes, including delirium.

Table 1 : Demographic and clinical characteristics

Parameter	Frequency (n)	Percentage (%)
Age Group (years)		
60–65	14	40.00
66–70	12	34.29
>70	9	25.71
Gender		
Male	21	60.00
Female	14	40.00
BMI Category (kg/m²)		
<18.5 (Underweight)	3	8.57
18.5–24.9 (Normal)	17	48.57
25.0–29.9 (Overweight)	10	28.57
≥30 (Obese)	5	14.29
History of Delirium		
Yes	0	0.00
No	35	100.00
History of Cognitive Impairment		
Yes	0	0.00
No	35	100.00



Preoperative and Postoperative Biomarker Assessment

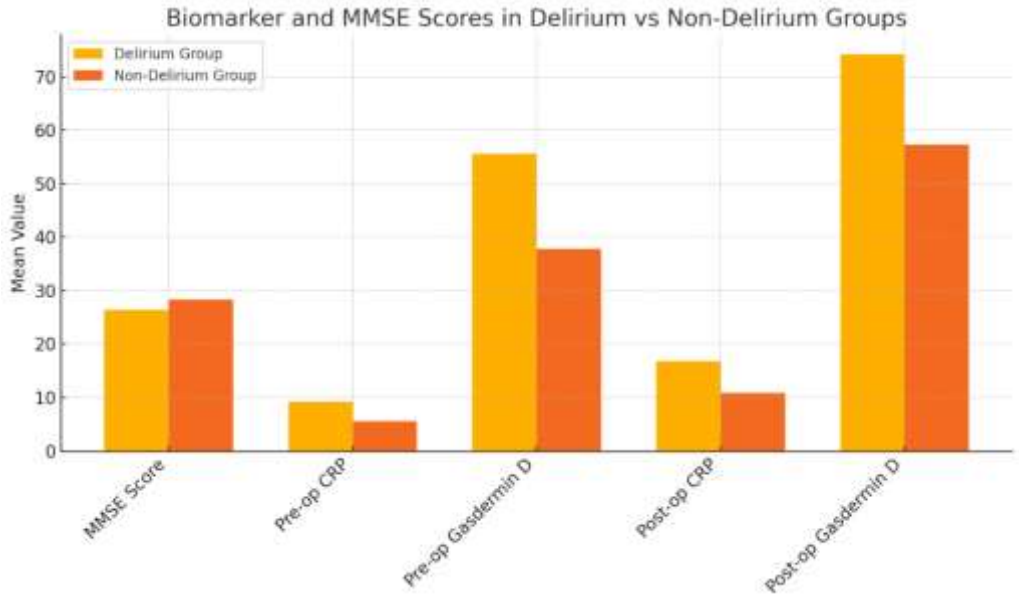
Table 2 evaluates the biomarker profiles (CRP and Gasdermin D) and cognitive function (MMSE score) in both delirium and non-delirium groups. The average MMSE score of the total population was 27.8 ± 1.6. Patients who developed POD had significantly lower MMSE scores (26.4 ± 1.2) than those who did not (28.3 ± 1.1), suggesting a subtle preoperative cognitive vulnerability.

The preoperative mean CRP level was 6.5 ± 2.1 mg/L, which was significantly higher in patients who developed delirium (9.2 ± 1.8 mg/L) compared to those who did not (5.6 ± 1.4 mg/L), with a p-value <0.01. Similarly, preoperative Gasdermin D levels were markedly elevated in the delirium group (55.6 ± 8.9 pg/mL) versus the non-delirium group (37.8 ± 6.3 pg/mL), also with a p-value <0.01.

Postoperatively, both CRP and Gasdermin D levels increased, particularly in patients with POD. Postoperative CRP levels at 48 hours rose to 16.8 ± 2.6 mg/L in the delirium group and 10.9 ± 2.8 mg/L in the non-delirium group. Similarly, postoperative Gasdermin D levels reached 74.2 ± 9.4 pg/mL in the delirium group, significantly higher than the 57.3 ± 10.7 pg/mL observed in the non-delirium group. These differences were statistically significant and reinforce the hypothesis that a heightened systemic and neuroinflammatory response is associated with POD.

Table 2: Preoperative and Postoperative Biomarker Assessment (n = 35)

Parameter	Mean ± SD	Delirium Group (n = 9)	Non-Delirium Group (n = 26)	p-value
MMSE Score	27.8 ± 1.6	26.4 ± 1.2	28.3 ± 1.1	<0.01
Preoperative CRP (mg/L)	6.5 ± 2.1	9.2 ± 1.8	5.6 ± 1.4	<0.01
Preoperative Gasdermin D (pg/mL)	42.3 ± 10.4	55.6 ± 8.9	37.8 ± 6.3	<0.01
Postoperative CRP at 48h (mg/L)	12.4 ± 3.5	16.8 ± 2.6	10.9 ± 2.8	<0.01
Postoperative Gasdermin D (pg/mL)	61.9 ± 12.3	74.2 ± 9.4	57.3 ± 10.7	<0.01



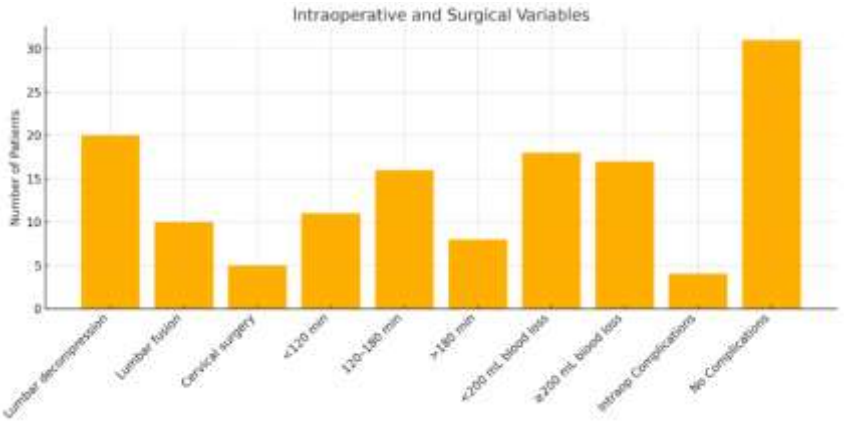
Intraoperative and Surgical Variables

Surgical variables were analyzed to evaluate their association with the development of POD in Table 3. The most commonly performed procedure was lumbar decompression (57.14%), followed by lumbar fusion (28.57%) and cervical spine surgery (14.29%). All patients received general anesthesia. Regarding surgical duration, 45.71% of surgeries lasted between 120–180 minutes, 31.43% were completed within 120 minutes, and 22.86% exceeded 180 minutes.

Estimated blood loss was nearly equally distributed, with 51.43% experiencing losses <200 mL and 48.57% with ≥200 mL. Intraoperative complications were reported in 4 patients (11.43%). These intraoperative parameters, particularly prolonged duration, significant blood loss, and complications, may act as physiological stressors contributing to postoperative neuroinflammatory responses and the onset of delirium, fulfilling one of the secondary objectives of the study.

Table 3: Intraoperative and Surgical Variables (n = 35)

Parameter	Frequency (n)	Percentage (%)
Type of Surgery		
Lumbar decompression	20	57.14
Lumbar fusion	10	28.57
Cervical surgery	5	14.29
Type of Anesthesia		
General	35	100.00
Duration of Surgery		
<120 minutes	11	31.43
120–180 minutes	16	45.71
>180 minutes	8	22.86
Estimated Blood Loss		
<200 mL	18	51.43
≥200 mL	17	48.57
Intraoperative Complications		
Yes	4	11.43
No	31	88.57



Incidence and Duration of Postoperative Delirium

Delirium assessments conducted over 7 postoperative days revealed that 9 out of 35 patients (25.71%) developed POD. The highest incidence was on postoperative day 2 (17.14%), followed by day 3 (14.29%) and day 1 (11.43%). The incidence declined gradually, with only 1 patient (2.86%) showing symptoms by day 6 and none by day 7. Most delirium cases (77.78%) resolved before discharge, while 22.22% had persistent symptoms, indicating the need for close neurological monitoring in at-risk patients.

This temporal profile of delirium onset supports the importance of serial postoperative assessments and highlights the peak risk period within the first 3 days after surgery. The findings align with the study's primary objective of associating biomarker levels with actual POD incidence.

Table 4: Incidence and Duration of Postoperative Delirium (n = 35)

Parameter	Frequency (n)	Percentage (%)
Delirium During Postoperative Days		
Day 1	4	11.43
Day 2	6	17.14
Day 3	5	14.29
Day 4	3	8.57
Day 5	2	5.71
Day 6	1	2.86
Day 7	0	0.00
Total Patients with Delirium	9	25.71
Delirium Outcome		
Resolved	7	77.78
Persistent at Discharge	2	22.22

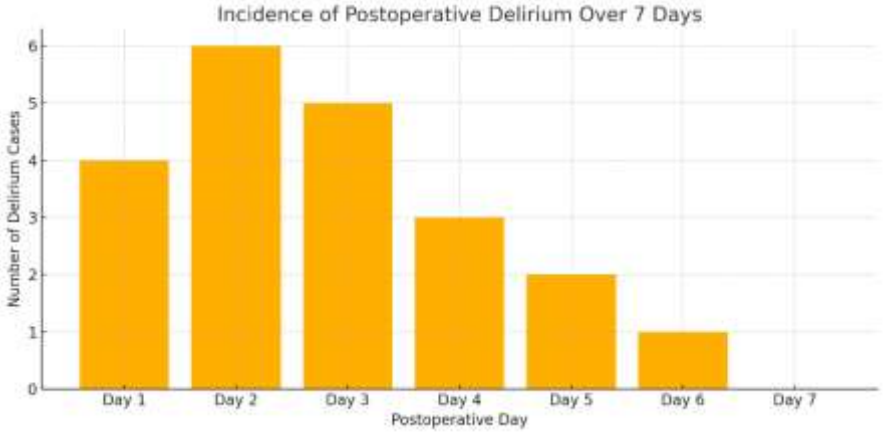
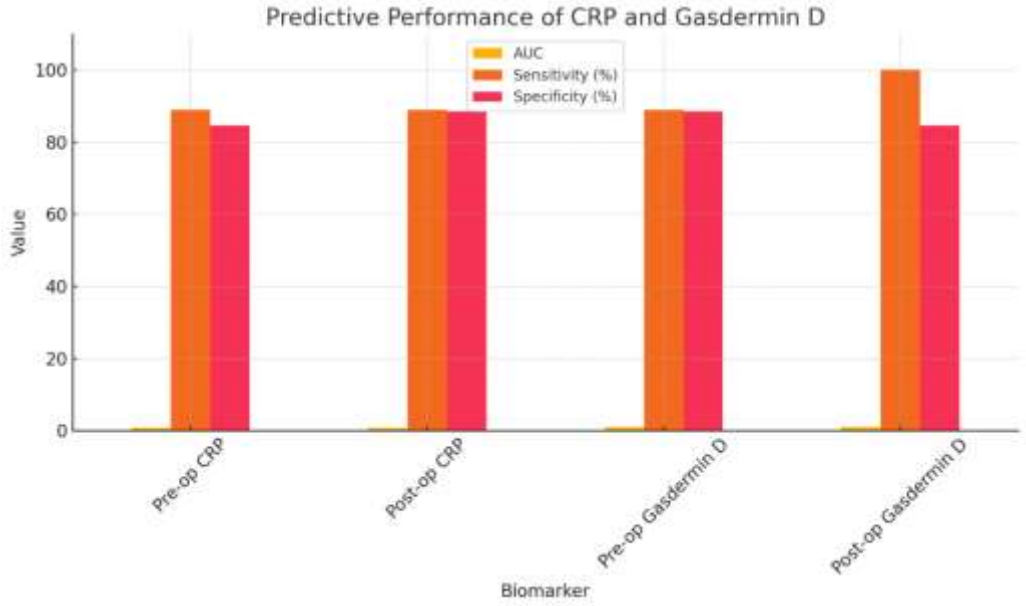


Table 5: Predictive Performance of CRP and Gasdermin D

Receiver operating characteristic (ROC) curve analysis demonstrated strong predictive capability for both CRP and Gasdermin D. Preoperative CRP had an area under the curve (AUC) of 0.82, with a cut-off >7.5 mg/L yielding 88.9% sensitivity and 84.6% specificity. Postoperative CRP performed slightly better, with an AUC of 0.86 at a cut-off >13 mg/L. Preoperative Gasdermin D was even more predictive with an AUC of 0.88 at >45 pg/mL, while postoperative Gasdermin D showed the highest predictive value (AUC = 0.91) at a threshold of >65 pg/mL, achieving 100% sensitivity and 84.6% specificity. All results were statistically significant ($p < 0.001$).

Table 5: Predictive Performance of CRP and Gasdermin D for POD (n = 35)

Biomarker	AUC (95% CI)	Cut-off Value	Sensitivity (%)	Specificity (%)	p-value
Pre-op CRP	0.82 (0.70–0.95)	>7.5 mg/L	88.9	84.6	<0.001
Post-op CRP	0.86 (0.74–0.97)	>13.0 mg/L	88.9	88.5	<0.001
Pre-op Gasdermin D	0.88 (0.77–0.98)	>45 pg/mL	88.9	88.5	<0.001
Post-op Gasdermin D	0.91 (0.82–0.99)	>65 pg/mL	100.0	84.6	<0.001



5. DISCUSSION

In the present study, the mean age of patients was predominantly between 60–70 years, with 25.71% above 70 years. Males made up 60% of the cohort, and 42.86% had hypertension while 28.57% had diabetes. This reflects a typical elderly spine surgery population. Notably, none of the participants had prior delirium or cognitive impairment, which reduced diagnostic ambiguity in assessing new-onset POD.These findings are comparable to those reported by Lozano-Vicario et al. (2024), who also studied elderly patients undergoing orthopedic surgery and found hypertension and diabetes to be major comorbidities linked with increased CRP and delirium risk.[6] Similarly, Watne et al. (2023) identified older age and vascular comorbidities as critical contributors to POD, reinforcing the clinical importance of comprehensive preoperative evaluation in this demographic.[7]

The current study demonstrated significantly elevated preoperative CRP (9.2 ± 1.8 mg/L) and Gasdermin D (55.6 ± 8.9 pg/mL) levels in patients who developed POD. These levels increased further postoperatively to 16.8 ± 2.6 mg/L and 74.2 ± 9.4 pg/mL, respectively. In contrast, patients without delirium had substantially lower levels. Additionally, the MMSE scores were lower in the POD group (26.4 ± 1.2) compared to those without POD (28.3 ± 1.1), suggesting subtle cognitive vulnerability.These results align with the findings of Yang et al. (2022), who observed that preoperative CRP levels above 7.8 mg/L significantly predicted delirium after lumbar spinal fusion surgery.8 Likewise, Lozano-Vicario et al. (2024) found a similar trend, where CRP >8 mg/L correlated with a higher incidence of POD in hip fracture patients. However, this study adds to the literature by including Gasdermin D—a novel pyroptosis-related marker—which demonstrated even higher discriminative power.[6] This is supported conceptually by Androsova et al. (2015), who emphasized the emerging role of inflammasome-related proteins in postoperative neurocognitive disorders.[9]

Intraoperative factors such as prolonged surgery (>180 minutes in 22.86% of cases) and blood loss ≥200 mL (48.57%) were more frequent in patients who developed POD. Although not statistically isolated in this analysis, their co-occurrence with

elevated biomarkers points to a cumulative physiological burden contributing to neuroinflammation.These findings resonate with the CONFESS study by Müller et al. (2023), where longer surgeries and hemodynamic instability were identified as modifiable intraoperative risk factors for delirium.[10] Mahanna-Gabrielli et al. (2019) similarly advocated for intraoperative monitoring protocols to mitigate delirium risk by minimizing hypoxia, hypotension, and inflammatory triggers.[11]

The incidence of POD in this study was 25.71%, peaking between postoperative days 1–3. Among affected patients, 77.78% recovered by discharge, while 22.22% had persistent delirium. These rates and trends are consistent with the global literature. Gou et al. (2021) reported delirium in 20–30% of elderly surgical patients, especially within the first 72 hours.[12] Similarly, Rudolph et al. (2008) highlighted the association between early POD and persistent cognitive dysfunction, underscoring the need for early recognition and supportive care.[13]

In ROC analysis, the AUC for preoperative CRP was 0.82, and for postoperative CRP, 0.86. For Gasdermin D, the AUC was 0.88 preoperatively and 0.91 postoperatively, with 100% sensitivity at >65 pg/mL. These values are significantly higher than those reported in studies evaluating only CRP. For instance, Lozano-Vicario et al. (2024) found CRP's AUC for predicting POD to be around 0.75, while Yang et al. (2022) reported 0.78. The current study surpasses these by incorporating Gasdermin D, which likely reflects its more specific link to pyroptosis and neuroinflammatory processes.[6,8]These findings align with the mechanistic hypothesis of van Gool et al. (2010), who described the cascade from systemic inflammation to acetylcholine depletion and cognitive failure.[14] Furthermore, Watne et al. (2023) discussed the role of quinolinic acid and similar inflammatory markers in acute delirium and neurodegeneration, supporting the idea that markers like Gasdermin D are mechanistically more direct indicators of delirium risk.[7]

6. CONCLUSION

This study demonstrated that elevated levels of CRP and Gasdermin D, both preoperatively and postoperatively, might be associated with the development of postoperative delirium in elderly patients undergoing spine surgery. Gasdermin D showed superior predictive accuracy, suggesting its potential as a novel biomarker for early identification of high-risk patients. Intraoperative factors such as prolonged surgery and higher blood loss may further contribute to delirium risk. Incorporating these biomarkers into perioperative assessment protocols could enhance risk stratification and improve patient outcomes

REFERENCES

[1] Ruhnau J, Müller J, Nowak S, Strack S, Sperlich D, Pohl A, et al. Serum biomarkers of a pro-neuroinflammatory state may define the pre-operative risk for postoperative delirium in spine surgery. Int J Mol Sci. 2023;24(12):10335. doi: 10.3390/ijms24121033.

[2] Michopoulos V, Norrholm SD, Jovanovic T. Diagnostic biomarkers for posttraumatic stress disorder: promising horizons from translational neuroscience research. Biol Psychiatry. 2015;78(5):344–53. doi: 10.1016/j.biopsych.2015.01.005.

[3] Dillon ST, Vasunilashorn SM, Ngo L, Otu HH, Inouye SK, Jones RN, et al. Higher C-reactive protein levels predict postoperative delirium in older patients undergoing major elective surgery: a longitudinal nested case-control study. Biol Psychiatry. 2016;81(2):145–53. doi: 10.1016/j.biopsych.2016.03.2098.

[4] Moldovan F, Ivanescu AD, Fodor P, Moldovan L, Bataga T. Correlation between inflammatory systemic biomarkers and surgical trauma in elderly patients with hip fractures. J Clin Med. 2023;12(15):5147. doi: 10.3390/jcm12155147.

[5] Tomaszewski D. Biomarkers of brain damage and postoperative cognitive disorders in orthopedic patients: an update. Biomed Res Int. 2015;2015:402959. doi: 10.1155/2015/402959.

[6] Lozano-Vicario L, Muñoz-Vázquez ÁJ, Cedeno-Veloz BA, Romero-Ortuno R, Galbete A, Fernández-Irigoyen J, et al. The role of C-reactive protein as a risk marker of postoperative delirium in older hip fracture patients: a prospective cohort study. Eur Geriatr Med. 2024;15(6):1929–35. doi: 10.1007/s41999-024-01046-2.

[7] Watne LO, Pollmann CT, Neerland BE, Quist-Paulsen E, Halaas NB, Idland AV, et al. Cerebrospinal fluid quinolinic acid is strongly associated with delirium and mortality in hip-fracture patients. J Clin Invest. 2023;133(6):e163472. doi: 10.1172/JCI163472.

[8] Yang JS, Lee JJ, Kwon YS, Kim JH, Sohn JH. Preoperative inflammatory markers and the risk of postoperative delirium in patients undergoing lumbar spinal fusion surgery. J Clin Med. 2022;11(14):4085. doi:

10.3390/jcm11144085.

[9] Androsova G, Krause R, Winterer G, Schneider R. Biomarkers of postoperative delirium and cognitive dysfunction. Front Aging Neurosci. 2015;7:112. doi: 10.3389/fnagi.2015.00112.

[10] Müller J, Nowak S, Weidemeier M, Vogelgesang A, Ruhnau J, von Sarnowski B, et al. Duration of surgery and intraoperative blood pressure management are modifiable risk factors for postoperative neurocognitive disorders following spine surgery: results of the prospective CONFESS study. Spine (Phila Pa 1976). 2023. doi: 10.1097/BRS.0000000000004722.

[11] Mahanna-Gabrielli E, Schenning KJ, Eriksson LI, Browndyke JN, Wright CB, Culley DJ, et al. State of the clinical science of perioperative brain health: report from the American Society of Anesthesiologists Brain Health Initiative Summit 2018. Br J Anaesth. 2019;123(4):464–78. doi: 10.1016/j.bja.2019.07.004.

[12] Gou RY, Hshieh TT, Marcantonio ER, Cooper Z, Jones RN, Travison TG, et al. One-year Medicare costs associated with delirium in older patients undergoing major elective surgery. JAMA Surg. 2021;156(5):430–42. doi: 10.1001/jamasurg.2020.7260.

[13] Rudolph JL, Marcantonio ER, Culley DJ, Silverstein JH, Rasmussen LS, Crosby GJ, et al. Delirium is associated with early postoperative cognitive dysfunction. Anaesthesia. 2008;63(9):941–7. doi: 10.1111/j.1365-2044.2008.05523.x.

[14] van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet. 2010;375(9716):773–5. doi: 10.1016/S0140-6736(09)61158-2.