ORIGINAL ARTICLE

Correlation of C-reactive Protein with Delirium in Obstetrics Intensive Care Unit: A Tertiary Center Experience

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Abstract

Background: Delirium is a neuropsychiatric illness. It affects critically ill patients on ventilator and increases mortality. The aim of this study was to evaluate the association of C-reactive protein (CRP) level with delirium in critically obstetrics women and its role in prediction of delirium.

Materials and methods: Arospective observational study was conducted in the intensive care unit (ICU), and the duration of study was one year. Total 145 subjects were recruited, 33 patients were excluded, and 112 subjects were studied. For study, group A ($n = 36$) includes critically ill obstetric women who had delirium on admission; group B ($n = 37$) includes critically ill obstetric women who developed delirium within 7 days; and group C ($n = 39$) that includes critically ill obstetric women who did not develop delirium after follow-up of 7 days was served as control. Disease severity was assessed by using acute physiologic assessment and chronic health evaluation (APACHE) II score, and Richmond Agitation-Sedation Scale (RASS) was used to assess awakeness. In awake patients (RASS of ≥3), delirium was assessed by the use of confusion assessment method for ICU tools. C-reactive protein measured by particle enhanced turbidimetric immunoassay—two point kinetic method.

Results: The mean ages of group A, B, and C were 26.44 ± 4.72, 27.46 ± 4.97, and 28.26 ± 5.67 years, respectively. C-reactive protein levels on the day of delirium development (group B) were found to be significantly higher than day 1 CRP levels of groups A and C. The mean Global Attentiveness Rating (GAR) was significantly lower in groups A and B as compared to that in group C ($p < 0.001$). On evaluating the correlation of CRP with GAR, it was found to be inverse and mild in strength for the correlation between CRP and GAR ($r = -0.403$, $p < 0.001$). At a cut-off value of >181 mg/L, CRP had sensitivity of 93.2% and specificity of 69.2%. The positive predictive value was 85% and the negative predictive value was 84.4% that differentiate delirium from non-delirium.

Conclusion: C-reactive protein is a useful tool for screening and prediction of delirium in critically ill obstetric patients.

Keywords: C-reactive protein, Critically ill, Delirium, Intensive Care Unit, Obstetric intensive care unit.

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Introduction

Delirium is a neuropsychiatric illness. It affects critically ill patients on ventilator, increases mortality, in intensive care unit (ICU), and significantly slows functional recovery. It lasts within a short span of time and fluctuation might be noticed during the day and night. It is characterized by decreased ability to focus, sustain, or transfer attention as well as reduced awareness.[1]

The wide range of incidence of delirium was observed in ICUs. It ranges from 20% to 80% in different study populations.[2–7] After controlling for various confounding factors, it was found that delirium is an independent predictor of mortality in ICU settings.[8]

Although obstetric women are young, still maternal mortality is high in ICUs, 5–20% in developed countries, and 15–30% in developing countries. There are currently no accurate and valid biomarkers that predict the onset of delirium. Serum biomarkers produced by delirium-related pathological processes may serve as predictors as well as diagnostic marker for delirium and aid in the selection of candidates for early, aggressive therapeutic interventions.[9]

Delirium is associated with increased mortality, prolonged hospital stay, requirement of mechanical ventilation, costs of treatment, and cognitive disorders after discharge from the ICUs.[10] Critical illness is a potentially fatal involving multiple organs that can cause significant mortality and morbidity. Acute physiologic assessment and chronic health evaluation (APACHE II) is a critical illness grading system.[11]

A nonspecific inflammatory biomarker known as C-reactive protein (CRP) increases 10,000-fold in response to an acute stimulus.[12] The inflammatory processes causes disruption of the blood–brain barrier (BBB) and allows leukocytes and astrocytes to communicate with one another, activating astrocytes that cause delirium in patients.[13]

A meta-analysis reported that if the elevation of CRP is for longer duration, then there is an increased chances of higher mortality rate.[14] Though the relation between increase in CRP levels and delirium is not well established. Various studies have reported

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correlation between CRP levels and delirium, but the results are conflicting.[15,16] This study was aimed to evaluate the association of CRP levels and delirium in obstetrics women on ventilator and its role as a predictor of delirium.

Materials and Methods

A prospective observational study was carried out at the Department of Obstetrics and Gynecology in collaboration with Pathology, King George's Medical University, Lucknow, from September 2021 to August 2022 (reference code: III PGTSC-IIA/P5). A total of 145 subjects were recruited out of which 33 patients were excluded and only 112 subjects were enrolled for the study. Subjects were further divided into three groups: group A (n = 36) includes critically ill obstetric women who had delirium on admission, group B (n = 37) includes critically ill obstetric women who developed delirium within follow-up of 7 days, and group C (n = 39) includes critically ill obstetric women who did not develop delirium after follow-up of 7 days was served as control.

Sample Size Calculation

The difference in mean Serum C-reactive protein (S. CRP) levels (mg/L) between delirium and non-delirium group (μ1−μ2) was 88 (delirium group = 254 and non-delirium group = 166), and the population variance (σ) was 114.[17]

Sample size (n) = 2 $(Z\alpha/_2 + Z_{[1-\beta]})^2 \times \sigma^2/(\mu1-\mu2)^2$

By assuming 0.05 level significance, $Z_{\alpha/2}$ = 1.96, and 90% power $Z_{[1-\beta]}$ = 1.28. n was 35 in each group of the study.

$$n = 2\ (Z\alpha/_2 + Z_{[1-\beta]})^2 \times \sigma^2\ (\mu1-\mu2)^2$$

$$n = 2\ (1.96 + 1.28)^2 \times (114)^2\ (254-166)^2$$

$$n = 35$$

After obtaining informed consent and clearance from the institutional ethical committee, 112 critically ill obstetric women enrolled for the study. Disease severity was assessed by using APACHE II score.[18] Further, the Richmond Agitation-Sedation Scale (RASS) was used to assess awakeness. In awake patients (RASS of ≥3), confusion assessment method for ICU (CAM-ICU) was used. In all patients, CRP and routine investigations were sent on admission. Patients who do not have delirium on day of admission were followed for 7 days to assess the development of delirium. Those patients who developed delirium within 7 days, samples were obtained and CRP was measured again on the day of development of delirium (*B*). Those patients who were on sedation, daily sedation vacation was done for up to 2 hours in the morning. Every day, the RASS was applied followed by CAM-ICU that was used in both mechanically and nonmechanically ventilated patients. The severity of delirium was assessed by Global Attentiveness Rating (GAR). Patients were managed according to the institutional protocol.[14,19]

The inclusion criteria includes critically ill women admitted in obstetric ICU who developed delirium within 7 days of follow-up, and critically ill obstetrics women admitted in the ICU of the same duration of stay who do not develop delirium (considered as controls).

The exclusion criteria for the study were pregnant women having history of dementia, delirium, and depressive illness before pregnancy, having history of severe visual, auditory, immunosuppressive, neurological problems, malignancy, and chronic inflammatory diseases.

For the assessment of the severity of critical illness, APACHE II score was used. The RASS was used to assess agitation and sedation level, and the confusion assessment method for ICU (CAM-ICU) was used to assess presence of delirium in alert patients.[14,18,19]

Richmond Agitation-Sedation Scale (RASS) is an instrument to assess sedation and agitation in adult ICU patients (+1 to +4) and one level denoting a calm and zero level denoting an alert state. The scale also includes five levels to assess the level of sedation ranging from −1 to −5. A score of −4 indicates that the patient is unresponsive to verbal stimulation, and a score of −5 indicates an unarousable state. It is an ideal tool to assess sedation and agitation in patients. Patients who had −3 up to +4 on RASS were evaluated for delirium. Patients of scores −4 and −5 considered as comatose and excluded from the study. The severity of delirium was assessed by GAR. All patients were managed according to the institutional protocol (Fig. 1).[14,18–22]

Estimation of CRP

On admission, 5 mL of venous blood was collected from all groups, and in group B, an additional blood sample was collected on the day of delirium development. After retrieving, blood samples were centrifuged for 30 min at 3000 rpm and serum samples were stored at −70°C till final analysis was done. Particle-enhanced turbidimetric immunoassay—two-point kinetic method was used for the estimation of CRP. Specific rabbit anti-human CRP coated latex particles were agglutinated after mixing with samples having CRP. After agglutination, changes in absorbance were noticed, which depend on the amount of CRP present in patient samples. C-reactive protein concentration can be quantified by comparing with calibrators of known CRP concentration.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) Version 21.0 was used for statistical analysis. Categorical variables were measured as number and percentage (%) and continuous variables were measured as mean ± SD. Quantitative variables were compared using an unpaired *t*-test between two groups. Analysis of variance (ANOVA) test was used to compare more than two groups. Chi-square/Fisher's exact test was used for comparison between quantitative variables. p-value was considered statistically significant if <0.05.

Results

The distribution of patients and age is comparable in all the three groups. The mean age of group A was 26.44 ± 4.72; group B was 27.46 ± 4.97; and group C was 28.26 ± 5.67. Only severe pre-eclampsia and antepartum eclampsia showed significant differences in the three study groups. Other risk factors such as acute kidney injury (AKI), shock, anemia, jaundice, antepartum hemorrhage (APH), heart disease, etc., did not show any significant association with the three groups. Severe preeclampsia was observed in a higher number of group B women (45.9%) as compared to group A (27.8%) and group C (20.5%) women (p = 0.049). Antepartum eclampsia (APE) was found in higher proportion in group A (41.7%) as compared to group B (21.6%) and group C (17.9%) (p = 0.047). Above data indicate that association of delirium with severe preeclampsia (SPE) and APE was high in Group A and group B (Fig. 2).

A total of 62 (55.4%) patients had more than two morbidities. Proportion of those with more than two morbidities was 50%, 56.8%, and 59% in groups A, B, and C, respectively (p = 0.721). Though the

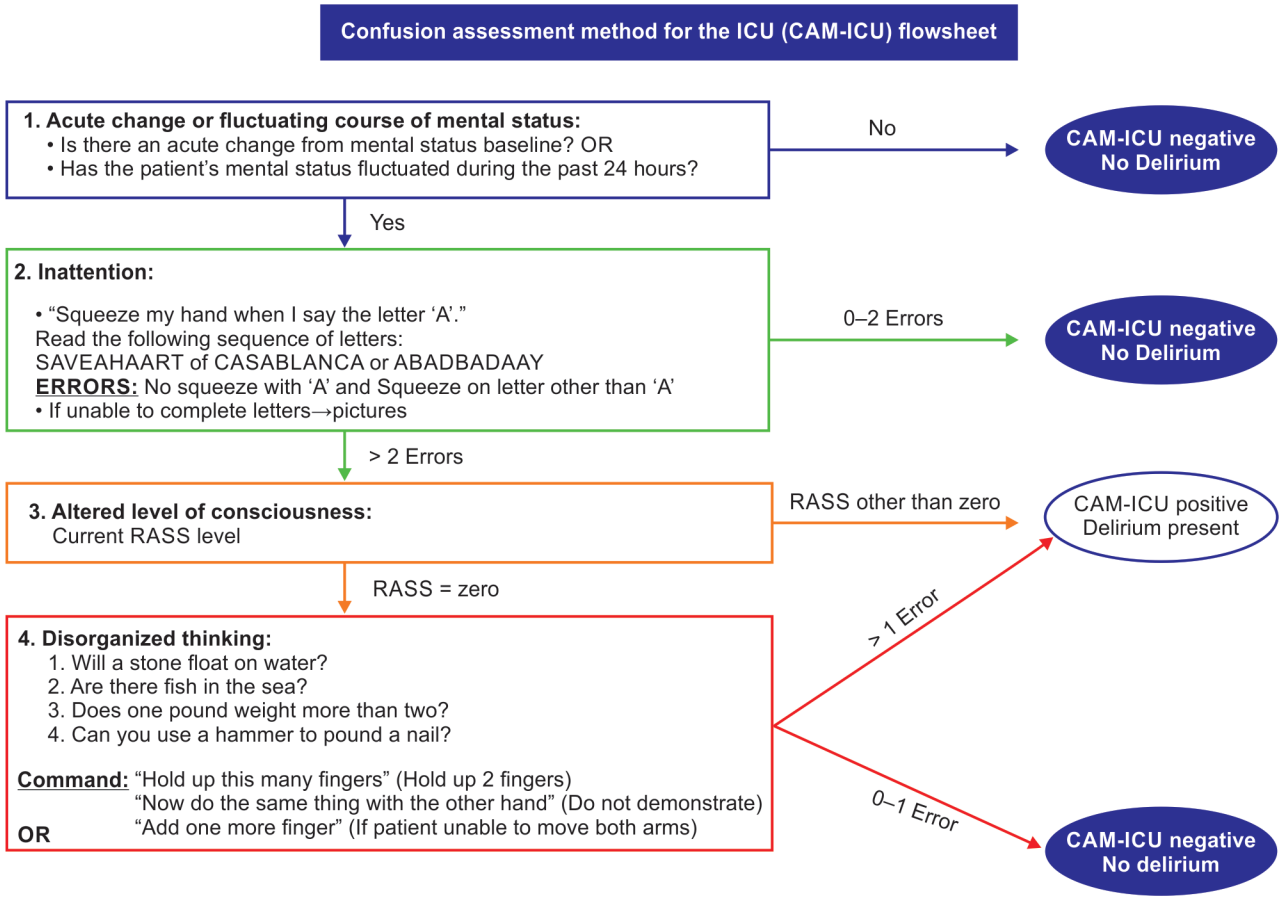

Fig. 1: The CAM-ICU scale

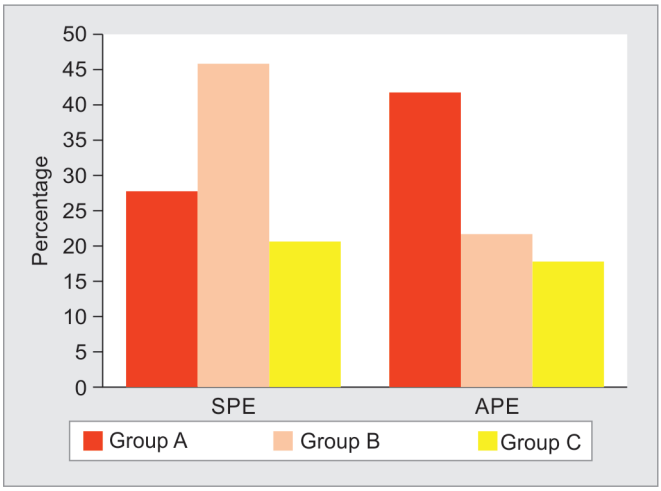

Fig. 2: Comparison of risk factors showing significant intergroup differences

duration of hospital stay and requirement of ICU care days of group B patients were higher as compared to groups A and C, this difference was nonsignificant. Acute physiologic assessment and chronic health evaluation (APACHE II) score of group C was significantly lower as compared to groups A and B. Two groups (A and B) had comparable APACHE II scores ($p = 0.118$). Significant difference was observed in APACHE II score between group B vs group C ($p < 0.001$). In relation to mortality, no significant difference was observed among groups. Out of 112 women enrolled in the study, 39 (34.8%) had sepsis, 41 (36.6%) required blood transfusion, and 6 (5.4%) were administered dialysis. No differences were observed between groups for sepsis and requirement for dialysis. Requirement of blood transfusions was significantly higher in groups A (38.9%) and B (43.2%) as compared to C (23.1%) (Table 1).

The day 1 CRP level was highest in group B followed by group A and minimum in women who did not develop delirium within 7 days, i.e., group C. A significant difference in CRP level between group A vs groups C and B vs group C was found.

In group B, there was a significant rise (approximately 111%) in the value of CRP on the day of development of delirium in comparison to baseline (day 1) value, which brought us to the conclusion that CRP levels definitely increase in critically ill women who developed delirium later on.

C-reactive protein levels on the day of delirium development (group B) were found to be significantly higher than day 1 CRP levels of groups A and C.

The mean GAR was significantly lower in groups A and B as compared to that in group C ($p < 0.001$). On evaluating the correlation of CRP with GAR, it was found to be inverse and mild in strength for the correlation between CRP and GAR ($r = -0.403$, $p < 0.001$, Table 2). None of these biochemical and Arterial blood gas analysis (ABG) parameters showed significant association with delirium (Table 3).

After receiver operator curve analysis (ROC), the area under curve of CRP for prediction of delirium was found to be 0.873 ± 0.03. At a cut-off value of >181 mg/L, CRP discriminates delirium from

Table 1: Intergroup comparison of various characteristics between groups

Characteristics	*Group A (n = 36)*	*Group B (n = 37)*	*Group C (n = 39)*	*Test/p*
Hospital stay (days)				
Days (mean ± SD)	9.44 ± 2.98	10.84 ± 6.64	8.77 ± 3.79	ANOVA/0.237
Requirement of ICU care (days)				
Days (mean ± SD)	2.72 (2.11)	3.68 (3.36)	2.41 (1.04)	ANOVA/0.056
APACHE II score				
Score (mean ± SD)	16.64 (5.92)	19.24 (4.49)	13.15 (6.15)	ANOVA/<0.001
Mortality				
Number (%)	3 (8.3)	4 (10.8)	4 (10.3)	χ^2/0.933
Complications				
Sepsis (No./%)	14 (38.9)	16 (43.2)	9 (23.1)	χ^2/0.150
Blood transfusion (No./%)	15 (41.7)	18 (48.6)	8 (20.5)	χ^2/0.029
Dialysis (No./%)	3 (8.3)	1 (2.7)	2 (5.1)	χ^2/0.564

Table 2: Comparison of association of CRP in between different groups

Characteristics	*Group distribution*	*CRP mean (mg/L)*	*SD*	*p*
CRP levels on day 1	Group A	398.8	379.4	ANOVA
	Group B	478.1	384	$p = 0.001$
	Group C	196.3	145.1	
	Total = 112	354.5	33.90	
CRP difference between groups on day 1	Group A vs Group B	79.3	74.9	Paired *t*/0.542
	Group A vs Group C	202.5	74.9	Paired *t*/0.020
	Group B vs Group C	281.8	73.9	Paired *t*/0.001
Change on day 1 CRP levels to on DDD (group B)	Day 1	478.1	384	Paired *t* test,
	DDD*	1007.3	450.9	$p = 0.001$
	Change	529.2	284.8	
Comparison of CRP levels on the DDD* in group B and day 1 CRP levels of groups A and C	Group B (DDD*) vs Group A (day 1)	608.4	81.3	*t*-test/0.001
	Group B (DDD*) vs Group C (day1)	811.0	79.7	*t*-test/0.001
		Score (mean)	*SD*	
Comparison of GAR scores and their correlation with CRP	Group A	3.53	2.05	ANOVA,
	Group B	3.89	2.01	$p < 0.001$
	Group C	8.64	1.14	
	Total = 112	5.43	2.94	
Correlation of GAR* with CRP	$r = 0.403$, $p < 0.001$			

DDD*, day of delirium development; GAR*, Global Attentiveness Rating scores

Table 3: Intergroup comparison of biochemical and ABG parameters

		Group A (n = 36)		*Group B (n = 37)*		*Group C (n = 39)*		*ANOVA*	
S. No.	*Parameters*	M_n	*SD*	M_n	*SD*	M_n	*SD*	*F*	*p*
1	Hb (g/dL)	8.68	1.50	9.12	1.41	9.21	2.03	1.030	0.361
2	TLC (cells/mm^3)	22.77	6.57	22.09	8.30	20.27	8.32	1.037	0.358
3	HCT (%)	28.04	5.97	31.28	5.40	29.52	7.32	2.412	0.094
4	S. Urea (mg/dL)	46.56	24.52	38.12	22.29	46.79	26.49	1.508	0.226
5	S. Creatinine (mg/dL)	1.20	0.77	1.03	0.45	1.13	0.66	0.659	0.519
6	SGPT(IU/L)	98.95	136.93	99.71	107.25	106.05	126.23	0.038	0.963
7	pH	7.31	0.11	7.33	0.10	7.35	0.09	1.603	0.206
8	PCO_2	35.90	9.78	33.50	9.52	37.30	20.89	0.654	0.522
9	PO_2	107.81	33.91	100.55	21.95	105.21	26.97	0.635	0.522
10	$PHCO_3$	24.02	6.11	26.02	6.97	25.45	6.35	0.915	0.404

HCT, hematocrit; SGPT, serum glutamic pyruvic transferase; TLC, total leukocyte count

Table 4: ROC Analysis for derivation of cut-off value of CRP for the prediction of delirium

Parameter	*AUC ± SE (p-value)*	*J-Index for selection of optimum cut-off value*	*Selected cut-off value*	*Projected sensitivity*	*Projected specificity*	*PPV*	*NPV*
CRP	0.873 ± 0.03 ($p < 0.001$)	0.624	>181.0	93.2%	69.2%	85%	84.4%

Table 5: Association of CRP levels with different major outcomes

		CRP (mg/L)	
S. No.	*Outcome*	*Mean*	*SD*
1.	Mortality		
	Yes ($n = 11$)	853.9	556.1
	No ($n = 101$)	493.9	470.8
	Statistical significance	$t = 2.366$, $p = 0.020$	
2.	ICU stay >2 days		
	Yes ($n = 48$)	511.7	452.6
	No ($n = 64$)	542.5	517.9
	Statistical significance	$t = 0.329$, $p = 0.743$	
3.	Intubation need		
	Yes ($n = 72$)	589.2	531.4
	No ($n = 40$)	421.4	384.9
	Statistical significance	$t = 1.756$, $p = 0.082$	
4.	Vasopressor use		
	Yes ($n = 36$)	565.4	481.7
	No ($n = 76$)	512.2	494.7
	Statistical significance	$t = 0.536$, $p = 0.593$	
5.	Morbidities		
	<2 ($n = 62$)	48.44	48.11
	>2 ($n = 50$)	58.50	49.80
	Statistical significance	$t = 1.083$, $p = 0.281$	

Table 6: Correlation of CRP with other ICU severity markers

	CRP	
Marker	*r*	*p*
APACHE II	0.391	<0.001
pH	−0.068	0.475
Bicarbonate	−0.006	0.954

non-delirium cases with sensitivity of 93.2% and specificity of 69.2%. The positive predictive value (PPV) and negative predictive value (NPV) of CRP were found to be 85% and 84.4% (Table 4).

On evaluating, the association of CRP with ICU outcomes, such as mortality, ICU stay for more than 2 days, intubation need and vasopressor need, and higher CRP showed a significant association with mortality whereas association with outcomes were not significant. Though CRP levels were higher in patients with more than two morbidities as compared to those with less than and equal to two morbidities, difference was nonsignificant ($p > 0.05$, Table 5).

C-reactive protein showed significant correlation with APACHE II, whereas with pH and bicarbonate levels have only weak inverse correlation (Table 6).

Discussion

During the study period, a total of 650 critically ill obstetrics women were admitted to the ICU, out of which delirium was diagnosed in 225 women. Thus, the incidence of delirium was 346 per 1000 ICU admissions. Meta-analysis reported that out of total admission in ICUs only one-third of patients developed delirium.[23]

The risk factors in ICU-admitted obstetric women were evaluated, and only SPE and APE showed significant differences in the three study groups. Higher number of patients had SPE in group B, while in group A higher number of patients had APE as compared to the other two groups.

In eclampsia, two major theories suggest that sudden hypertension leads to autoregulation failure, resulting in vasodilation and edema, while vasoconstriction is responsible for brain ischemia and subsequent edema.[31]

Donkin psychoses are eclamptic psychoses without seizures.[24] Symptomatic psychosis usually results from cerebral endothelial damage. Theories explain that there may be lucid intervals between eclampsia and the eruption of psychosis. These patients have the same features as eclamptic psychoses, with the onset of disease during pregnancy or in early puerperium, especially in primigravida women, but these are of short duration and in these patients full recovery is expected. Usually, the clinical picture is almost similar to delirium.[24] Similarly, our study also showed that the occurrence of delirium is more in eclampsia patients.

In our study, though the duration of stay in hospital, sepsis, requirement of dialysis, and mortality were higher in obstetric women admitted to the ICU with delirium and who developed delirium as compared to controls, but it was statistically not significant.

Various studies and meta-analysis reported that the need of mechanical ventilation, duration of stay in the ICU, and mortality was significantly higher in patients with delirium as compared to patients without delirium.[23]

Another systematic review including 41 studies reported the longer ICU stay in patients who developed delirium.[25] Another study showed significant mortality in delirious vs non-delirious.[26] Sepsis-associated delirium is a combination of multiple factors. Neuroinflammation and disturbances in cerebral perfusion could be responsible for neurological impairment as well as disturbances in BBB and neurotransmission might be responsible for the development of delirium.[27]

The results of our study were different from other studies because in our study young obstetric women were enrolled who had acute complications rather than chronic problems. In present study, shorter ICU stay and shorter follow-up only for 7 days, with small sample size, and multiple confounding factors might be the reason for the difference in results.

In our study, APACHE II score of group B who developed delirium was significantly higher as compared to patients who did not developed delirium. Similar results were observed by another author.[28] A multivariate study done by another author reported that social determinants of health do not affect delirium in ICU patients in the Dutch region.[29]

C-reactive protein is a reliable indicator of inflammatory response and tissue damage.[30] Increased levels of CRP were associated with increase in BBB permeability.[31] Thus, CRP increases in patients

of delirium and is itself an independent predictor of delirium. Similar results were observed by another author after univariate analysis. Patients with delirium showed significantly higher CRP values as compared to those who do not develop delirium after adjusting for confounding variables.[32] In the logistic regression model, it was found that CRP remained as an independent predictor of delirium as compared to patients who do not develop delirium, and those who developed delirium showed longer stay in ICU and increased duration of mechanical ventilation. Another study reported that serum interleukin-6 and CRP levels were considerably higher in postoperative delirium patients as compared to nonpostoperative delirium patients, indicating that early serum inflammatory markers might be a predictor of postoperative delirium.[33]

The area under the curve (AUC) and values of CRP for the prediction of delirium were found to be 0.873 ± 0.03 ($p < 0.001$) after ROC analysis. At a cut-off value of >181 mg/L, CRP discriminates delirium from non-delirium cases with sensitivity of 93.2% and specificity of 69.2%. Thus, CRP has good sensitivity and can be used for the screening as well as prediction of delirium.

Our results are slightly different from the prospective observational study done by another author on postpartum ICU women and found that patients who developed delirium had higher CRP levels.[17] They were identified as independent predictors of delirium in postpartum women who admitted to the ICU.[34] On ROC analysis, at the cut-off value of CRP 206 mg/L, it had a sensitivity of 87.1% and specificity of 66.7%. This is almost similar to our results. Another study reported a positive correlation of serum elevation from before surgery to after surgery (D-CRP) with the development of postoperative delirium, similar to our study.[34]

C-reactive protein increases with the APACHE II score. The APACHE II score increases with the severity of disease in ICU patients. C-reactive protein showed increase in APACHE II score. Thus, CRP had association with the severity of disease. Another author concluded that the high level of CRP at the time of admission to ICU was associated with the subsequent development of delirium during the stay in the ICU. The risk of delirium increases by 7% with every 10 mg/L increase in CRP.[32] Patients with higher APACHE II scores had higher CRP values. The present study has been done on young obstetric patients whereas most of the previous studies had been done on older or diverse age groups.

Conclusion

The incidence of delirium in our study was found to be 34.6%. C-reactive protein is an inflammatory marker, and in delirium there is an inflammation of astroglial and oligodendroglial cells. Patients with delirium had high CRP levels. There was also significant rise in CRP value who developed delirium later on and showed positive correlation with delirium. The ROC analysis showed a high sensitivity and specificity. C-reactive protein might be useful as a screening tool and has good predictive value for delirium in critically ill obstetric patients admitted on ventilators.

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