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C - Reactive Protein Levels and Its Correlation with Infections, Mortality and Organ Failure in Critically ILL Patients

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Abstract: ***Introduction: A number of inflammatory cells and mediators involved in the inflammatory response have their role as potential markers of the presence and severity of the inflammatory response and organ failure in critically ill patient. Serum levels of C-reactive protein (CRP), markedly increase within hours after infection or inflammation. Aims and Objectives: To study the association between early serum CRP concentrations and the development of organ failure and mortality in ICU patients. Design: Prospective cohort study. Material and Method: The study carried out in emergency medical ward Hamidia between April to November 2011. Patient divided in 3 groups based on CRP at time of admission. In gp 1 CRP<1mg/dl gp2 1-10mg/dl & gp 3 >10mg/dl. Results: Patients with high CRP levels at ICU admission had more severe organ dysfunction and higher mortality rates. CRP concentrations were correlated with the presence and number of organ failures. The incidence of infection was directly related to the CRP level on ICU admission [gp1 27.77% vs gp2 57.57% vs gp3 73.07% p<.05] .The incidence of Coagulation failure was directly related to the CRP level on ICU admission [gp1 0% vs gp2 3.03% vs gp3 15.38%p<.05] Conclusions: Trends of CRP concentrations during the first 48 h of ICU admission can be important in predicting the outcome and perhaps timely modifying the therapeutic interventions.***

Keywords: ICU; outcome; sepsis marker; sequential organ failure assessment

1. Introduction

A number of inflammatory cells and mediators involved in the inflammatory response have been assessed, for their role as potential markers of the presence and severity of the inflammatory response and organ failure in critically ill patient[1-8]. Serum levels of C-reactive protein (CRP), an acute-phase protein synthesized by the liver following stimulus by various cytokines including tumor necrosis factor-and interleukin (IL)-6, markedly increase within hours after infection or inflammation[9].Many studies shows increased CRP in patients with sepsis[10-15].

C-reactive protein (CRP) was first discovered in 1930, when a protein in the serum of patients with Streptococcus pneumonia was found to precipitate and bind to the C-polysaccharide derived from the pneumococcal cell wall (16). It has been known for a long time that CRP is one of many non-specific acute phase reactants that are elevated during an inflammatory process. Because the CRP response to an inflammatory process is non-specific, many clinicians have not adopted its use as a predictive and prognostic test in intensive care medicine. Furthermore, the role of CRP as a predictor of infection, instead of inflammation, has become even more controversial since the introduction of procalcitonin as a test in this regard. Comparing CRP with other inflammatory markers such as procalcitonin can be difficult because of their different kinetics and many studies have looked at different types of patients (17). The overall evidence suggests that procalcitonin has much faster kinetics, both in its onset and offset, and may also be more specific than the CRP in diagnosing some infections (18-20). Because the CRP test is widely available and relatively cheap, it is likely to be widely used in many institutions in the foreseeable future.

Multi organ failure is major cause of death in intensive care unit patient [21-22]. A few studies have suggested that CRP may be an indicator of organ failure[23-27]. Pinilla et al[23] demonstrated a strong correlation between the ratio of CRP to prealbumin and the severity of organ dysfunction in critically ill patients. Other investigators have reported CRP levels to be associated with multiple organ dysfunction in patients with acute pancreatitis [25-27]. This study was planned to assess relationship between early CRP measurements and its association with morbidity and mortality in critical ill patients.

2. Aims and Objectives

To study the association between early serum CRP concentrations and the development of organ failure and mortality in ICU patients.

3. Material and Method

The study was conducted in the Departments of Medicine at Gandhi Medical College & Hamidia Hospital, Bhopal from April 2010 to Nov 2011. The study subjects selected from patients who are admitted in the emergency medical wards at Hamidia Hospital

Type of Study

Prospective cohort study

Inclusion Criteria

Patients with acute inflammatory condition like Myocardial Infarction, Stroke, Systemic Inflamatory Response Syndrome Sepisis and Other Critiecal Illness

Exclusion Criteria

1) Patient with alcohol consumption more than 20 gm per day
2) Patient with chronic inflammation like rheumatoid arthritis, gout.

The APACHE (acute physiologic and chronic health evaluation) II score was calculated on ICU admission. Organ function was evaluated according to the sequential organ failure assessment (SOFA) score. For each of the six organ systems included in the SOFA score (respiratory, cardiovascular, neurologic, renal, hematologic, and hepatic), organ failure was defined as a score of six.Infection was diagnosed according to usual clinical, laboratory, and microbiological parameters.

Systemic Inflammatory Response Syndrome (SIRS)

Two or more of the following:

- Temperature of >38^{o}C or <36^{0}C
- Heart rate of >90
- Respiratory rate of >20
- WBC count >12 x 10^{9}/L or <4 x 10^{9}/L or 10% immature forms (bands)

Organ dysfunction defined on basis of SOFA score

The Sequential Organ Failure Assessment (SOFA) Score

Each organ is graded from 0 (normal) to 4 (the most abnormal), providing a daily score of 0 to 24 points.

Sequential assessment of organ dysfunction during the first few days of ICU admission is a good indicator of prognosis. Both the mean and highest SOFA scores are particularly useful predictors of outcome. Independent of the initial score, an increase in SOFA score during the first 48 hours in the ICU predicts a mortality rate of at least 50%. Criticality of the patient defined on the basis of APACHE SCORE.

Statistical Analysis

All patients were divided in three groups based on their CRP at time of admission. The data for all the groups are expressed as mean ± SD. Continuous variables were compared with analysis of variance for repeated measurements. Proportions were compared using the Z test. Chi square test was done to determine the significance of association of organ failure with CRP. A p value 0.05 was considered statistically significant

Principle of the Method

Serum C-reactive protein (CRP) causes agglutination of the latex particles coated with anti-human C-reactive protein. The agglutination of the latex particles is proportional to the CRP concentration and can be measured by turbidimetry1.

4. Observations

Table 1: Distribution Of Patient In Different CRP Groups At Admission

	No of Patients	Percentage
Group 1 - <1	36	37.89%
Group 2 - 1-10	33	34.70%
Group 3 - >10	26	27.36%

Table 2: Sex By Distribution in Different Groups

Sex	Group 1 (n=36)		Group 2 (n=33)		Group 3 (n=26)	
	No.	%	No.	%	No.	%
Male	17	47.22%	15	45.45%	13	50%
Female	19	52.77%	18	54.54%	13	50%

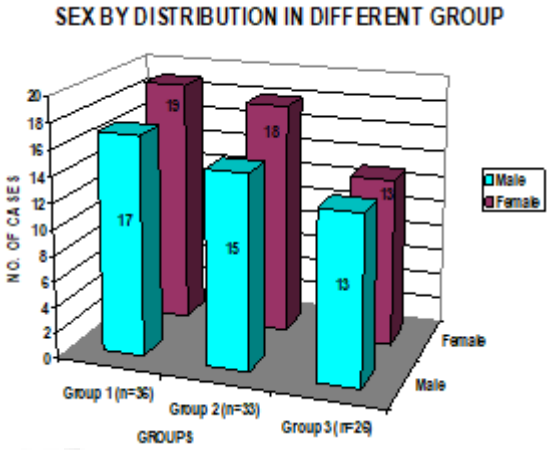


Table 3: Age by Distribution in Different Groups

Age	Group 1		Group 2		Group 3	
	No.	%	No.	%	No.	%
25-34	3	8.33	5	15.15	3	11.53
35-44	6	16.66	7	21.2	5	19.2
45-54	10	27.77	6	18.1	9	36.15
55-64	9	25	11	33.3	6	23.07
65-74	7	19.44	3	9.09	3	11.53
75-84	1	2.77	1	3.03	0	0

Major number of patient are between age 35-64 of age in all the three groups.

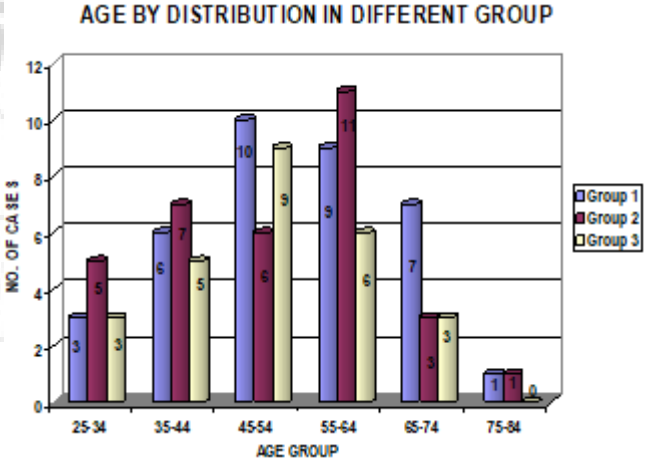


Table 4: Distribution of Death of Patient in Different CRP Groups at Admission

	No of Patients	Percentage
Group 1 - <1	5	13.88%
Group 2 - 1-10	6	18.18%
Group 3 - >10	9	34.60%!#

Group 3 have statistically significant increased mortality than group 1 & 2(p<.05).

! p<.05 Vs Group 1
# p<.05 Vs Group 2

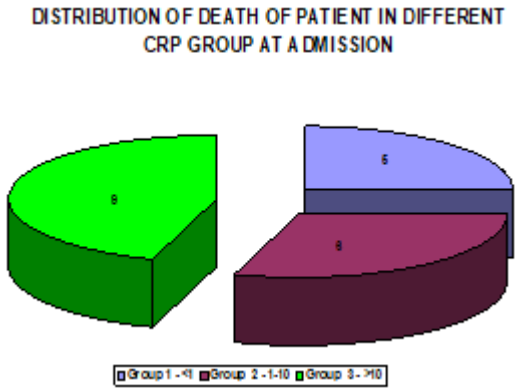
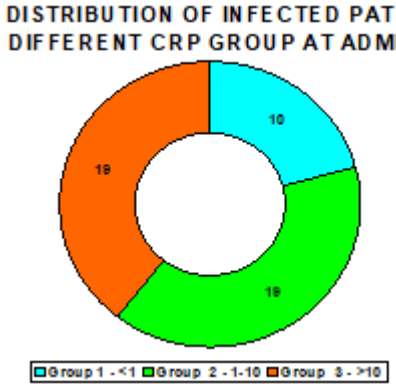


Table 5: Distribution of Infected Patient in Different CRP Groups at Admission

	No of Patients	Percentage
Group 1 - <1	10	27.77%
Group 2 - 1-10	19	57.57%!
Group 3 - >10	19	73.07% ! #

! p<.05 Vs Group 1
 # p<.05 Vs Group 2

Group 3 has statistically significant increase in infection than group 1 & 2(p<.05). Group 2 has statistically significant increased in infection than group 1(p<.05).



Variables	GP1	GP2	GP3
Age	53.4+13.36	51.6+13.18	51.5+13.6
Apache II	12.28+1.99	14.8+13.37!	18.61+2.11!#
Sofa at Admission	4.94+2.07	6.03+1.9!	6.96+2.78!
Sofa day 2	5.66+1.73	7.06+2.16!	8+1.93!
Sofa max	6.33+1.96	7.66+1.97!	9.26+1.8!
ICU stay	7.17+2.86	8.69+2.85!	12.1+3.82! #
Death	5	6	9

Data are presented as mean +_SD

! p<.05 Vs Group 1
 # p<.05 Vs Group 2

Group 3 has statistically significant increased in APACHE/SOFA /SOFA day2 & SOFA MAX / ICU stay and death rate than group 1(p<.05) and statistically significant increased APACHE, ICU stay and mortality than group 2(p<.05). Group 2 has statistically significant increased in APACHE/SOFA /SOFA day2 & SOFA MAX, ICU stay than group 1(p<.05).

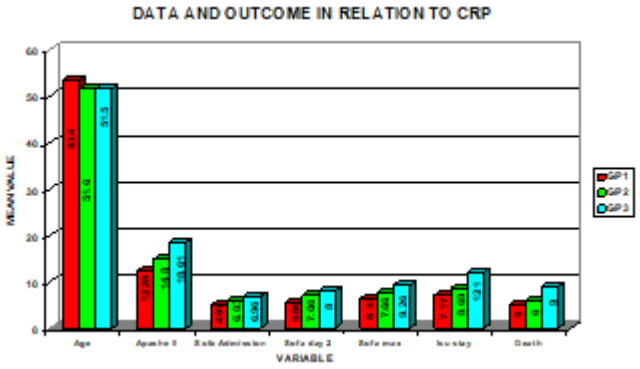


Table 7: Incidence of Organ Failure (Sofa Score 3 OR 4) on ICU admission (DAY 0) according to CRP level

Variables	Day 0	Group-I (CRP< 1 mg/dL)		Group-II (CRP 1-10 mg/dL)		Group-III (CRP > 10 mg/dL)	
		No.	%	No.	%	No.	%
CRP Measurements	0	35	33	33		26	
Respiratory	0	9	25.71	15	45.45	15	57.69!
Renal	0	1	2.85	3	9.09	6	23.07!
Coagulation	0	0	0	1	3.03	4	15.38!
Cardiovascular	0	3	8.57	4	12.12	6	23.07!
Liver	0	1	2.85	1	3.03	2	7.69
Neurological	0	6	17.14	7	21.21	7	26.9

Data are presented as no. & percentage
! p<.05 Vs Group 1
# p<.05 Vs Group 2

Cardiovascular, respiratory and renal coagulation failure statistically significant increased in group 3 than 1 at time of admission (p<.05).

Table 8: Incidence of Organ Failure (Sofa Score 3 Or 4) On Second ICU Day 2 According To Crp Level

Variables	Days	Group-I (CRP< 1 mg/dL)		Group-II (CRP 1-10 mg/dL)		Group-III (CRP > 10 mg/dL)	
		No.	%	No.	%	No.	%
CRP Measurements	2	10		40		45	
Respiratory	2	1	10	7	17.4	25	55.55!
Renal	2	0	0	1	2.5	7	15.55
Coagulation	2	0	0	2	5	5	11.11
Cardiovascular	2	3	0	2	5	16	35.55!
Liver	2	0	0	2	5	2	4.44
Neurological	2	1	10	6	15	15	33.33

Data are presented as no. & percentage
! p<.05 Vs Group 1
# p<.05 Vs Group 2

Significant cardiovascular, respiratory failure in group 3 than group 1 after 48 hour(p<.05).

5. Results

The study carried out in emergency medical ward Hamidia between April to November 2011 total 95 patient included in study. Patient divided in 3 groups based on CRP at time of admission. In group 1 CRP<1mg/dl group2 1-10mg/dl & group 3 >10mg/dl.data are presented in observation tables 1 to 7. Patients with high CRP levels had significantly higher

SOFA scores, infection, mortality rates, and ICU stays than reported patients with normal CRP levels.

Age: The max no. of patient between 35-64[gp1 68% group 2 72% group 78%] the mean age almost same in each group[gp153.4±13.36 gp 2 51.6±13.18 gp3 51.5±13.6.p>.05]

Infection: The incidence of infection was directly related to the CRP level on ICU admission [gp1 27.77% vs gp2 57.57% vs gp3 73.07% p<.05]

Organ failure its correlation with CRP: The number of organs failing during the ICU stay increased with increasing CRP concentrations, both at ICU admission and at 48 h.

Coagulation failure: The incidence of coagulation failure was directly proportional to ICU admission CRP levels. Coagulation failure was not in patients with ICU admission CRP concentrations >1 mg/dL; it was 3.03% for patient CRP levels in the range of 1 to 10 mg/dL, and 15.38% for patient ICU for admission CRP values > 10 mg/dL[p<.05] .

Respiratory and cardiovascular dysfunction: At admission, CRP levels>10 mg/dL were associated with a significantly higher incidence of respiratory cardiovascular and renal dysfunction than CRP levels < 1 mg/dL (Table 7)

Duration of ICU Stay and Mortality:
Duration of ICU admission increased with increase in CRP it is Mortality and its correlation with APACHE score & SOFA score: The overall mortality rate was 21.5%. Nonsurvivors had significantly higher CRP levels than survivors at ICU admission (9.6±6.54 mg/dL vs 5.9±5.13 mg/dL, p < 0.05) and at day 2(15.55±5.36 mg/dL vs 9.91±5.17 mg/dL, p <0.05) . Patients with CRP concentrations between 1 mg/dL and 10 mg/dL on ICU admission, in whom the serum CRP concentration was unchanged or decreased after 48 h (n = 9), had similar APACHE II scores (14.23±2.04 vs 14.75±1.69, not significant, NS] but lower SOFA ICU admission (5.48±2.1 vs 6.81±1.95, p <0.05) and , and a significant lower mortality rate (6.07% vs 18.1%; , than those whose CRP levels increased on day 2 (n = 24). Patients with CRP concentrations >10 mg/dL on ICU admission in whom the serum concentration decreased after 48 h (<10 mg/dL) had no differences in APACHE II score (17.6±2.35 vs 17.92 ±2.29, NS), SOFA ICU admission (6.35±1.96 vs 7.65±2.1, NS) score, or maximum SOFA (7.81±2.43 vs 9.9±2.56, NS) scores, but had a lower mortality rate (11.11% [1 of 9 patients] vs 47.05% [8 out of 17 patients]) compared with those whose CRP levels increased on day 2(> 10mg/dL) [p< 0.05].

6. Discussion

Recently, CRP has been seen not only as a biochemical marker of inflammation but also as an active modulator of the inflammatory response. In this context. The correlation of CRP levels with organ failure and early mortality after ICU admission has been evaluated in a heterogeneous group of ICU patients. This is found that increased CRP concentrations were associated with organ failure, prolonged ICU stay, and high infection and mortality rates. Particularly CRP concentrations >10 mg/dL on ICU admission were associated with a high mortality. Increasing or persistently high levels suggesting ongoing inflammatory activity, indicated a poor prognosis, while decreasing values were associated with a more favorable prognosis.

Due to the fast rise in CRP concentrations, critically ill patients will often already have raised CRP levels on ICU admission. The relatively short half-life of approximately 19 h makes. it a useful monitor for follow-up of inflammatory response, infection, and antibiotic treatment. In addition, laboratory tests for CRP are easily available and less costly than cytokine tests
Infection : The incidence of infection was directly related to the CRP level on ICU admission. [gp1 27.77% vs gp3 73.07% p<.05]

Póvoa P, Coelho L, et al[12]Concluded that CRP was a better marker of infection than temperature.this is in accordance to my study that number of infected patient increase as crp level increase [gp1 27.77% vs gp3 73.07% p<.05]
Lisboa T, Seligman R,[155] similarly conclude C-reactive protein is a useful biochemical surrogate of bacterial burden in patients with ventilator-associated pneumonia. Follow-up measurements of serum C-reactive protein anticipate the appropriateness of antibiotic therapy

Almeida E, Moreira P, Fernandes A[12], .Found a plasma CRP of 50 mg/l or more was highly suggestive of sepsis .

Gian P Castelli[[162] CRP levels are related to the severity of organ dysfunction.

Seller-Pérez G[163], at al also found CRP level on admission is an useful marker for early infection

Parnaby RM, Eaton SE, Shafi MS, Bell D[164]. assess the value of routine serum C-reactive protein (CRP) measurement in the early diagnosis of infection in ICU patients. Neither absolute CRP levels nor rates of change in CRP were found to relate significantly to proved infection.

Lobo SM[165], C-reactive protein levels correlate with mortality and organ failure in critically ill patients

W de Werra CRP levels may be useful together with full clinical assessment including signs of sepsis, bacteriological data, and organ function evaluation.

Mortality and multiorgan dysfunction the number of organs failing during the ICU stay increased with increasing CRP concentrations, both at ICU admission and at 48 h.

Coagulation failure: The incidence of coagulation failure was directly proportional to ICU admission CRP levels(Table 7). Coagulation failure was not found in patients with ICU admission CRP concentrations <1 mg/dL. It was 3.03% for patient CRP levels in the range of 1 to 10 mg/dL, and 15.38% for patient ICU for admission CRP values > 10 mg/dL similar result obtained by suzana et al coagulation failure increased as CRP increase.

Respiratory and cardiovascular dysfunction :on admission CRP levels > 10 mg/dL were associated with a significantly higher incidence of respiratory and cardiovascular dysfunction than CRP levels <1 mg/dL (Table 7). Similar finding got by Mradul Kumar Daga[158] et al in their study in pneumonia patient.

Mendall MA, Strudy achan DP, Butland BK, et al.[166] also got similar result increase C-reactive protein: associated with increased cardiovascular mortality .

Liver failure not significantly associated with increased CRP level in different group this according to existing literature as Silvestre JP[167] et al also got similar finding in their study on liver failure patient.

Patients with high CRP levels had significantly higher SOFA scores, mortality rates[13.88%in crp <1 18.18% in crp 1-10 &34.6% in crp >10], and ICU stays [8.89±2.85 Vs 12.1±3.82 in gp2 crp 1-10 Vs gp3 crp >10 respectively]than reported patients with normal CRP levels[7.17 ±2.86 in gp1 crp <1] The number of organs failing during the ICU stay increased with increasing CRP concentrations, both at admission[4.94±2.07 in crp gp1 <1 Vs 6.96±2.78 gp3 crp >10 p <0.05] and at48 h[5.66±1.73 in gp1crp <1 Vs Vs 8±1.93 gp3 crp >10 p < 0.05] .These finding in similarity with *Suzana M. A. Lobo, MD; Francisco R. M. Lobo[165] who reported that,* patients with high CRP levels at ICU admission had more severe organ dysfunction (higher sequential organ failure assessment scores, days of longer ICU stays, and higher mortality rates than patients with normal ICU admission CRP levels. CRP concentrations were correlated with the presence and number of organ failures. , Presterl et al[15] demonstrated a correlation between the plasma levels of CRP, IL-6 and tumor necrosis factor-sR, and the APACHE III and mortality probability model II scores. Both scoring systems, as well as CRP levels, were significantly higher in the non survivors compared with the survivors.

Non survivors had significantly higher CRP levels. Findings on the relation between the peak concentrations of CRP and the number of organs failing indicate that both these parameters are useful indicators of severity and prognosis. ICU admission serum CRP levels > 10 mg/dL were associated with a significantly morbidity and mortality

The incidence of coagulation failure was directly proportional to ICU emergence CRP levels. Coagulation failure was not in patients with ICU admission CRP concentrations <1 mg/dL ; it was 3.03% for patient CRP levels in the range of 1 to 10 mg/dL, and 15.38% for patient ICU for admission CRP values > 10 mg/dL . At 48 h, CRP levels > 10 mg/dL were associated with a significantly higher incidence of respiratory[10% in crp gp1 <1 Vs 55.55% gp3 crp >10 p < 0.05]. This is accordance with *Suzana M. A. Lobo, MD; Francisco R. M. Lobo* at al[165] they also have reported higher incidence of respiratory failures and with higher mortality rates than CRP levels < 1 mg/dL. In patients with CRP concentrations > 10 mg/dL on ICU admission, Nonsurvivors had significantly higher CRP levels than survivors at ICU admission [9.6±6.54 mg/dL vs 5.9±5.13 mg/dL, p < 0.05] (15.55±5.36 mg/dL vs 9.91±5.17 mg/dl)

Reny JL, Vuagnat A, Ract C, Benoit MO, Safar M, Fagon JY[153].evaluate diagnostic and prognostic values of C-reactive protein (CRP) dosage in critically ill patienCRP in combination with SIRS was useful to diagnose infection in ICU patients; a CRP decrease > or = 50 mg/L between admission and day 4 was the best predictor of recoveryts.

Silvestre J, Póvoa P, Coelho L, Almeida E, Moreira P, Fernandes A, Mealha R, Sabino H[168].evaluate CRP as marker of prognosis outcome in septic patients and to assess the correlation of CRP with severity of sepsis.n septic patients, CRP of the day of sepsis diagnosis is not a good marker of prognosis.

7. Summary & Conclusion

CRP is a marker of inflammation that has been used to monitor the course of infection and inflammation CRP has been seen not only as a biochemical marker of inflammation but also as an active modulator of the inflammatory response. In this context, we have evaluated the correlation of CRP levels with organ failure and early mortality after ICU admission in a heterogeneous group of ICU patients with different disease.

1) It is found that increased CRP concentrations were associated with organ failure, prolonged ICU stay, and high mortality rates.
2) CRP concentrations > 10 mg/dL on ICU admission were associated with a particularly high mortality.
3) Increasing or persistently high levels, suggesting ongoing inflammatory activity, indicated a poor prognosis,
4) Declining values, suggesting a decreasing inflammatory reaction, were associated with a more favorable prognosis.
5) Hence, trends of CRP concentrations during the first 48 h of ICU admission can be important in predicting the outcome and perhaps timely modifying the therapeutic interventions. However, further studies are needed in this subject.

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