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RESEARCH ARTICLE

A study of sepsis in the obstetric intensive care unit with special reference to biomarkers and scoring systems

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ABSTRACT

Objectives: To study the sensitivity and specificity of various biomarkers in cases diagnosed with sepsis in the obstetric critical care unit and to compare the clinical criteria with the biomarkers in these cases. **Methods:** A total of 52 patients admitted in the obstetric critical care unit of our institution with the diagnosis of sepsis were enrolled in the study and were assessed clinically on the basis of q SOFA and total SOFA scores and the quantitative assessment of biomarkers for sepsis, namely CRP, serum lactate and procalcitonin was done. The sensitivity and specificity of both clinical criteria and biomarkers was determined. **Results:** Our study confirmed the high sensitivity and specificity of serum lactate, followed by procalcitonin (PCT) among biomarkers in subjects suspected or diagnosed with sepsis. It was also found that q SOFA score had the highest sensitivity (78.9%) but low specificity (57.60%), in contrast to high specificity (84.80%) of total SOFA score, emphasizing the role of q SOFA score as a screening tool and the total SOFA score as a confirmatory tool in cases of sepsis. **Conclusion:** Serum lactate is the most sensitive and specific predictor of prognosis in cases of maternal sepsis, followed by procalcitonin. CRP (C-reactive protein) is the least specific of the biomarkers. q SOFA may be used for initial screening followed by total SOFA scores.

Keywords: CRP, procalcitonin (PCT), q SOFA, serum lactate, SOFA score.

Maternal sepsis, despite being preventable remains the leading cause of maternal death globally. Nearly one half of all maternal deaths in the pre-antibiotic era were attributed to sepsis [1]. In LMIC (low-/middle income countries) like India, maternal mortality secondary to sepsis represents lack of good antenatal care services. According to reports of WHO, obstetric and puerperal sepsis have been stated to be the 3rd leading cause of direct maternal mortality in developing countries. Maternal sepses in conjunction with haemorrhage and hypertensive disorders are responsible for the majority of the cases of maternal morbidity and mortality. The contribution of sepsis as a cause of maternal mortality is between 4.7% in developed countries and 10.7% in developing countries [2]. Upto 27% of ICU admissions of obstetric patients result from sepsis in pregnancy and these contribute to a high mortality of around 56% [3]. The true burden of maternal sepsis however remains unknown owing to lack of accurate data.

An international consensus in 2017 defined sepsis as "life threatening organ dysfunction caused by a dysregulated host response to infection" and septic shock as "a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone" [4]. For the evaluation of cases where sepsis is suspected, a bedside assessment tool known as the quick SOFA score (q SOFA) (figure -1), has been introduced into clinical practice. These signs should prompt the physician to look carefully for organ dysfunction, start or escalate therapy, increase the level of patient monitoring, and consider transfer to an intensive care unit (ICU).

It makes no sense to use twenty-first century technology

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to develop drugs targeted at specific infections whose diagnosis is delayed by nineteenth century methods [5]. As quoted, the currently available diagnostic investigations do not suffice to accurately diagnose sepsis and we still have to depend on some outdated parameters. The delay in diagnosis leads to delay in the initiation of treatment. It may also lead to the misuse of antibiotics. Therefore, the development of biomarkers specific for sepsis to assess the host response and for pathogen detection is expected to nurture the improved clinical management of sepsis. Among the sepsis specific biomarkers, procalcitonin (PCT) has emerged as a reliable marker, even in cases where other conventional tools are inconclusive.

Timely recognition of sepsis and initiation of treatment can prevent progression to severe sepsis and septic shock. Taking into consideration the continuous increase in rate and severity of maternal sepsis worldwide and lack of data depicting the true burden of maternal sepsis, we planned this study to determine the magnitude of problem, to find out the clinical outcome of maternal sepsis and to study the role of clinical criteria and biomarkers in prognosticating the outcome in cases of maternal sepsis.

Methodology

The obstetric critical care unit of our teaching hospital is a recognized tertiary referral center for many tribal and underdeveloped rural areas around Jabalpur. This was a prospective observational study, in which 52 new subjects admitted with a diagnosis of sepsis in the obstetric ICU during a period of sixteen months (from 1st March 2018 to 31 August 2019) were enrolled for the study. The subjects included fulfilled the diagnostic criteria of sepsis and gave consent for participation in the study. Ethical approval was taken by institutional ethical committee, NSCB Medical College and Hospital, Jabalpur.

Inclusion Criteria were:

a) All patients showing 4T's (elevated temperature, tachycardia, tachypnoea, raised total counts) or any other local or systemic evidence of sepsis.
b) All patients with organ dysfunction associated with sepsis.
c) All patients admitted with some other diagnosis and later diagnosed to have sepsis in the ICU.

All the other admissions, which did not fulfill these criteria, were excluded from the study.

Subjects fulfilling the clinical criteria for diagnosis of sepsis [6], that is microbiologically confirmed or strongly suspected infection and presence of two or more of the SIRS criteria (figure - 3) or positive q sofa score (figure - 1) on admission were included in our study. The hospital course of all subjects was followed from admission to discharge. The worst physiological and laboratory measurements including biomarkers of sepsis (PCT, CRP, serum lactate), within the initial 24 hours of admission were noted and SOFA score (figure - 2) assessed. Patients were further managed as per the hospital protocol and the patient's condition. Data of the patients were collected till discharge or death and these were grouped into survivors or non survivors respectively.

Figure 1: Quick sequential organ failure assessment score

Assessment	qSOFA
Low blood pressure (SBP ≤ 100 mmHg)	1
High respiratory rate (≥ 22 breaths/min)	1
Altered mentation (GCS ≤ 14)	1

Statistical analysis: Subject case report forms were checked for its completeness and inappropriate or illogical responses were edited. Data was entered in Microsoft Excel 2007 worksheet. Qualitative (categorical) variables were numerically coded and distributed in frequency and percentage. Difference of frequency distribution in outcome variable was analyzed using chi square statistics. Fisher's exact was also applied if frequency was less than five. A receiver operating characteristic (ROC) curve plots of true positive rate (sensitivity) against the false positive (1-specificity) of binary outcome variable (death or survived) at different cut-off point of procalcitonin (PCT), CRP, serum

Figure 2: SOFA score (Sequential organ failure assessment score)

System	0	1	2	3	4
Respiratory					
PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200	<100
Coagulation					
Platelets ($\times 10^9$/L)	≥150	<150	<100	<50	<20
Liver					
Bilirubin (mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12.0
Cardiovascular					
Mean arterial pressure (mmHg)	≥70	<70	Dopamine<5 Dobutamine	Dopamine 5.1-15 Epinephrine ≤0.1 Norepinephrine≤0.1	Dopamine >15 Epinephrine >0.1 Norepinephrine>0.1
Central nervous system					
Glasgow coma score	15	13-14	10-12	6-9	<6
Renal					
Creatinine (mg/dl)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
Urine output (ml/d)				<500	<200

lactate, q SOFA score (figure -1), SIRS criteria (figure - 3) and SOFA score (figure - 2) were plotted. Correlation matrix with linear fit scatter plot was also analyzed to measure the association between PCT and SOFA score (figure - 2). The difference between areas under curve (AUC) for pair wise comparison was also analyzed for statistical significance. Critical value for statistical significance was considered at 0.05 (5% alpha). All the statistical analysis was performed using R 3.5.0 for Windows and SPSS 20.0 for Windows. Sensitivity, specificity, PPV and NPV was calculated as given below with the help of DIAGT command in STATA 8.0.

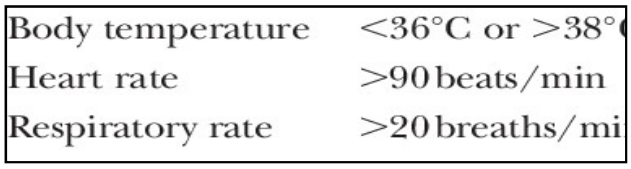

Figure 3: SIRS (Systemic inflammatory response syndrome) diagnostic criteria

Results

There were a total of 14,338 admissions in obstetrics and gynecology department at N.S.C.B MCH Jabalpur during the study period, of which 1538 were admitted in ICU. Amongst the ICU admissions, 3.5% cases were diagnosed with sepsis contributing to a mortality of 18.2%.

Table 1: Distribution of study subjects according to place of delivery

Place of delivery	Non Survivor	Survivor	p value
Home	5 (26.3%)	10 (30.3%)	0.760
Hospital	14(73.7%)	23(69.7%)	

Table 1 depicts the rate of institutional and home deliveries. It was observed that 28% (15 out of 52) of women had history of home delivery. Mortality observed in this group was 26.3%. 7% of the subjects were post-abortal and all of them were induced abortions. Most of the patients diagnosed with sepsis had multiple underlying obstetric risk factors predisposing to sepsis, such as severe anemia, pre eclampsia, eclampsia, chorioamnionitis, abortions induced with illicit over the counter medications and morbidly adherent placenta.

Table 2: Distribution of study subjects according to culture reports

Culture	Non survivor (19)		Survivor (33)		Total
positive	N	%	N	%	52
Blood	1	5.3	5	15.2	6
Urine	1	5.3	3	9.1	4
Tracheal aspirate	2	10.5	1	3.0	3
Vaginal swab	1	5.3	6	18.2	7
Infected wound	0	0.0	2	6.06	2
CSF	1	5.3	0	0.0	1
Sterile	7	36.84	12	36.36	19

Table 2 depicts the distribution of subjects based on culture reports. 23 out of 52 subjects had a positive culture report. Ten patients of those who were culture negative had positive viral markers. Most frequent microorganism associated with culture positive cases was E. Coli (8), followed by Klebsiella (7), non specific gram negative bacilli (4), Streptococcus, Staphylococcus, MRSA and TB Bacilli (1 each).

Table 3: Distribution of study subjects according to severity score

Variable	Non survivor	Survivor	p value
q SOFA Score			
< 2	4(21.1)	19 (57.6)	0.011
≥ 2	15 (78.9)	14 (42.4)	
SIRS Criteria			
< 2	0 (0.0)	7 (21.2)	0.031
≥ 2	19 (100)	26 (78.8)	
SOFA Score			
1-6	2 (10.5)	10 (30.3)	0.014
7-12	3 (15.8)	14 (42.4)	
13-18	9 (47.4)	6 (18.2)	
19-24	5 (26.3)	3 (9.1)	

Table 3 shows distribution of study subjects based on the clinical scoring systems and it was observed that 55.8% subjects had a positive q SOFA score (figure 1) of ≥ 2 on admission and this was associated with mortality of 78.9%. 86.5% fulfilled SIRS criteria (figure - 3) and most common criteria found, was increased in total leukocyte count followed by increase in heart rate. 32.7% subjects had a SOFA score (figure - 2) of ≥ 15 during their course of admission and this was associated with higher risk of mortality. The total SOFA score had the highest correlation with the maternal prognosis ($p< 0.001$).

Table 4: Distribution of study subjects according to biomarkers

Variable	Non survivor	Survivor	p value
Procalcitonin (ng/ml)			
< 2	2 (10.5)	8 (24.2)	0.227
≥ 2	17 (89.5)	25 (75.8)	
CRP(C- reactive protein) (mg/dl)			
< 20	7 (36.8)	9 (27.3)	
20-49.9	9 (47.4)	14 (42.4)	0.486
≥ 50	3 (15.8)	10 (30.3)	
Serum lactate (mmol/L)			
< 2	1 (5.3)	11 (33.3)	
2-3.99	2 (10.5)	8 (24.2)	0.011
≥ 4	16 (84.2)	14 (42.4)	

Table 4 shows distribution of subjects based on the biomarkers. It was noted that among non survivors 94.7% had a high serum lactate value, followed by 89.5% subjects with a high PCT value, followed by 63.2% subjects with a high CRP value.

Table 5 depicts the univariate and multivariate model for analyzing the predictable variables of mortality amongst cases of sepsis. It was observed that:

- If the value of Serum Lactate was ≥2, then the probability of death will be 9 times higher, as compared to lactate value <2. This association was found to be statistically significant (p=0.044).

If value of PCT ≥2, then probability of death will be higher by 2.7 times, as compared to PCT value <2.

As depicted in table 6, 71.2% subjects developed multi organ dysfunction syndrome (MODS) and all 19 non survivors had MODS. Among non survivors, most common organ dysfunction was respiratory (100%), followed by cerebrovascular (89.5%) and cardio vascular system (84.2%).

Table 5: Univariate and multivariate logistic regression model for analysis of death and its predictor variables

Predictor variables		Univariate Odds Ratio (95% CI)	P value	Multivariate Odds Ratio (95% CI)	P value
PCT (ng/ml)	< 2	Reference			
	≥2	2.72(0.51-14.41)	0.240		
CRP (mg/dl)	<20	Reference			
	≥20	0.55(0.16-1.87)	0.337		
S Lactate (mmol/l)	<2	Reference			
	≥2	9.0(1.06-76.48)	0.044	3.89(0.41-37.15)	0.239
SOFA score	<15	Reference			
	≥15	9.6(2.53-36.37)	0.001	7.24(1.70-30.81)	0.007
q SOFA score	<2	Reference			
	≥2	5.09(1.38-18.70)	0.014	3.87(0.88-17.12)	0.074
SIRS criteria	<2	Reference			
	≥2	1			
Culture	Neg.	Reference			
	Pos.	0.31(0.03(2.88)	0.304		

Table 6: Distribution of study subjects based on presence or absence of MODS (Multiorgan dysfunction syndrome)

MODS	Non Survivor	Survivor	p value
No	0 (0.0)	15 (45.5)	<0.0001
Yes	19 (100)	18(54.5)	

On applying the multivariate model including the predictors serum lactate, SOFA score and q SOFA score, which were found to be significant potential determining factors of death in the univariate model, the total SOFA score came out to be the only significant potential determinant of death (p=0.007). The R square for correctly explaining the multivariate model was 0.28.

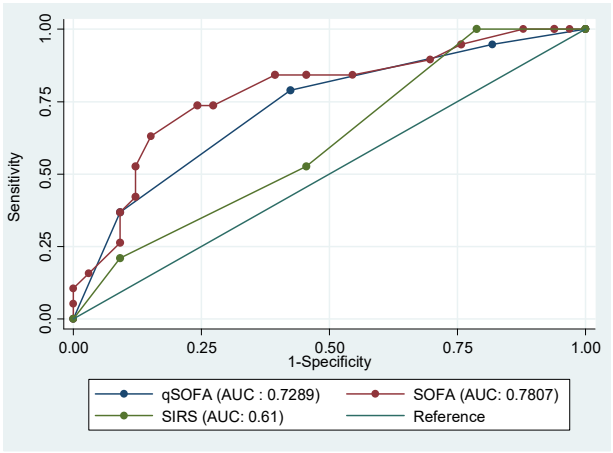

Figure 4: Receiver operating curve (ROC) analysis comparing SIRS, q SOFA and SOFA SCORE in predicting mortality in cases of maternal sepsis

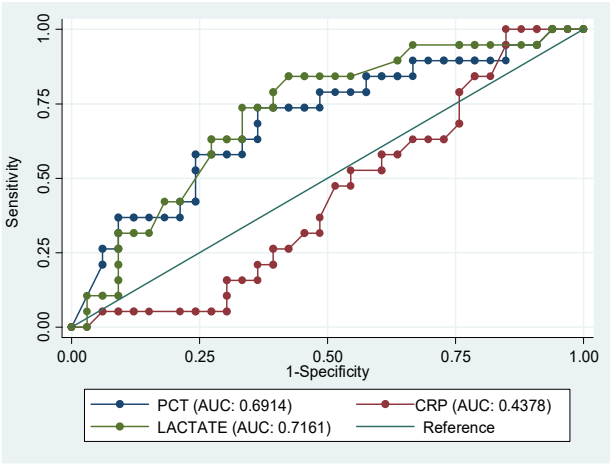

Figure 5: Receiver operating curve (ROC) analysis comparing procalcitonin, CRP and serum lactate levels in predicting mortality in cases of maternal sepsis

The receiver operating curve for SIRS criteria, q SOFA and SOFA scores showed maximum area under the ROC curve for total SOFA scores (figure 4). Area under curve of ROC analysis showed that SIRS criteria was able to accurately predict mortality in 61% cases, q SOFA in 73% cases and SOFA score in 78% cases, suggesting that total SOFA score was the best predictor of mortality in the patients admitted to the ICU.

In the ROC curve for the biomarkers, serum lactate levels were the most accurate predictors of mortality, closely followed by procalcitonin levels. Serum Lactate accurately

predicted mortality in almost 71% cases and PCT in 69% cases whereas CRP alone was able to accurately predict mortality in only 43% cases.

Discussion

Sepsis is a life threatening condition characterized by dysregulated immune response to bacterial, viral or fungal infection. The continuum of sepsis care comprises primarily of timely detection and diagnosis followed by early treatment initiation. The biomarkers used for sepsis hold enormous potential for facilitating early diagnosis and treatment. They however, should facilitate detection of infection before clinical signs and organ damage becomes apparent.

In the current study, most subjects were young primiparas. Majority of subjects (26.9%) were illiterate, strengthening the fact that lower levels of maternal education are associated with low awareness about antenatal care as is shown by the fact that only 11.5% subjects were booked at any health care facility. Apart from unbooked status, unsupervised delivery is an important risk factor for the development of maternal sepsis. Delay in referral to tertiary care level was observed in most of the patients and this reflects upon the fact that most of the patients initially present to the primary care general practitioners or emergency medical team who may be less aware of the signs and symptoms of sepsis or even the rapidity of progression of sepsis.

We evaluated and compared performance of clinical scoring systems, SIRS criteria, q SOFA score and total SOFA score in obstetric sepsis patients and the AUROC cutoff of SIRS criteria, q SOFA and SOFA score in predicting mortality in subjects was found to be 0.61, 0.73 and 0.78 respectively. q SOFA was more accurate than SIRS criteria; however, SOFA score demonstrated significantly greater discrimination for in-hospital mortality. The present study, confirmed the high sensitivity and low specificity of the q SOFA score, compared to SOFA score, thereby emphasizing the role of q SOFA score as a screening tool for sepsis. q SOFA is a more specific test to identify patients requiring critical care input or at risk of death. The lack of specificity of SIRS criteria makes it a much less effective tool for severe sepsis.

The total SOFA score is a very good prognostic indicator for mortality. As the total SOFA is based on a number of parameters based on six vital organ systems, it is obviously more detailed and accurate for prognostication of the patient in the ICU. The q SOFA has its value as a quick bedside prompt for deciding the eligibility of the patient for ICU admission whereas the total SOFA is valuable for evaluation of the condition of the patient.

We also evaluated the diagnostic usefulness of PCT, comparing it with CRP and serum lactate in obstetric sepsis patients. Area under curve of ROC analysis showed that PCT alone was able to accurately predict mortality in 69% cases, CRP alone in only 43% cases whereas, serum lactate alone was most efficient among biomarkers to predict mortality in up to 71% cases. These findings were consistent with those of a study by L Simon et al in 2005 [7] and Muller et al in 2008 [8] who reported PCT to be the most reliable marker in diagnosing sepsis. PCT measurement may help with the decision to initiate antibiotic therapy in low risk acuity of infection. Serial PCT measurement rather than a single measurement is advisable in most situations.

C-reactive protein (CRP) is a clinical marker frequently used to assess the presence of sepsis. CRP is an acute-phase protein released by the liver after the onset of inflammation or tissue damage. CRP rises slowly and peaks 36 hours after an infection. Levels ≥ 20mg/dl usually represent moderate degree of sepsis. Plasma concentrations of CRP may remain elevated for up to several days, even after elimination of infection [9]. CRP thus has a low specificity as a biomarker of sepsis, its main clinical use being for screening of the early onset of sepsis due to its high sensitivity.

PCT, the precursor of the hormone calcitonin, has been used as a biomarker to aid in diagnosis of sepsis. Its production is normally confined to the thyroid C-cells and to a lesser extent other neuroendocrine cells. Production is, however, activated in all parenchymal tissues in response to bacterial infection. PCT is detectable 3 to 4 hours following an infection, peaks at 6 to 12 hours and has a half-life of about 24 hours [10]. This favorable kinetic profile, and its specificity and sensitivity for bacterial infection make it the most promising biomarker for diagnosis of sepsis and disease progression monitoring. Levels of PCT ≥ 2ng/ml denote systemic bacteremia.

Increase in serum lactate levels usually occur secondary to anaerobic metabolism induced by tissue hypo perfusion and hypoxia or by epinephrine mediated pathway (in absence of hypoxia) associated with aerobic glycolysis [11]. Serum levels ≥2mmol/l indicate tissue hypoxia and levels ≥4mmol/l are associated with severe tissue hypoxia. Elevated serum lactate in pregnancy is associated with adverse maternal outcomes from presumed sepsis. Univariate as well as multivariate analysis in our study has shown that among

biomarkers, Serum lactate is most predictive of mortality in cases of maternal sepsis. These findings were consistent with study conducted by Albright CM et al[12] and R Agarwal et al[13].

We investigated the role of biomarkers along with clinical scoring systems in an obstetric population in a low-income setting. Our study demonstrated reasonable specificity of serum lactate and procalcitonin for maternal sepsis. It was found that serum lactate was more specific as a predictor of prognosis, followed by procalcitonin. These markers proved to be useful in critically ill patients in conjunction with newer bedside tools like q SOFA score for complementing the diagnosis. Among the clinical scoring systems, q SOFA score was found to be superior to SIRS criteria in terms of specificity for predicting severity of the disease. A positive q SOFA score should prompt the calculation of SOFA score to confirm the diagnosis of sepsis. Therefore, we recommend use of a simple bedside tool i.e. q SOFA score as a screening tool in cases of maternal sepsis. If these biomarkers are elevated, microbial identification and prompt antibiotic administration should be considered.

Conclusion

Maternal sepsis is one of the important causes of mortality. Out of the clinical criteria, SIRS criteria are not as specific as compared to the q SOFA and total SOFA scores. Among the biomarkers, CRP lacks specificity in comparison to lactate and procalcitonin levels. In a patient suspected to have sepsis, quick assessment should be done with q SOFA. Procalcitonin is as excellent marker to diagnose bacterial infection. Total SOFA scores and serum lactate levels both are very good prognostic indicators in a patient admitted in the ICU.

Conflict of interest: None. **Disclaimer:** Nil.

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