ORIGINAL RESEARCH

Studying sepsis in the ICU of the obstetrics department concerning the scoring system and biomarkers

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Received: 28 October, 2023 Accepted: 30 November, 2023

ABSTRACT

Background: Early initiation of treatment and early diagnosis of sepsis can help in preventing the progression of sepsis to septic shock and severe sepsis. Considering a continuous increase in the severity and rate of maternal sepsis globally and limited literature data showing the actual burden of maternal sepsis. **Aim:** The present study was designed to assess the specificity and sensitivity of different biomarkers in subjects diagnosed with sepsis and admitted to the ICU of the Obstetrics Department with the diagnosis of sepsis and compared biomarkers to clinical criteria in these subjects. **Methods:** The study assessed 104 subjects admitted to critical care of the obstetrics department with a diagnosis of sepsis and clinically assessed on SOFA and q SOFA scores and with quantitative biomarkers assessment for sepsis including procalcitonin, serum lactate, and CRP. Also, the specificity and sensitivity of both biomarkers and clinical criteria were studied. **Results:** Among biomarkers of subjects diagnosed with sepsis, a high specificity and sensitivity were seen for serum lactate and procalcitonin. A low specificity of 57.58% and a high sensitivity of 78.7% were seen with the q SOFA scores in the present study, whereas, total SOFA scores showed a high specificity of 84.78% depicting the role of total SOFA scores as confirmatory criteria and q SOFA as a screening-criteria in subjects with sepsis. **Conclusion:** The present study concludes that the most specific and sensitive predictor for prognosis in subjects with maternal sepsis is serum lactate along with procalcitonin, whereas, the least specific biomarker for maternal sepsis is CRP. Total SOFA and q SOFA scores can be used for early screening of maternal sepsis.

Keywords: CRP, maternal sepsis, procalcitonin, serum lactate, SOFA scores

INTRODUCTION

A leading cause of maternal death globally is attributed to maternal sepsis despite it being preventable. In the pre-antibiotic era, more than half of the maternal deaths were attributed to maternal sepsis. In middle-income and developing countries such as India, maternal deaths following sepsis are attributed to the scarcity of appropriate antenatal services in these countries. In developed countries, puerperal and obstetric sepsis is considered as a third major cause of maternal deaths as reported by WHO (World Health Organization). (1)

Hypertension and hemorrhage in addition to maternal sepsis contribute to maximum cases of maternal mortality and morbidity. Nearly 11% of of cases of maternal mortality in developed countries and 5% in developing countries are attributed to maternal sepsis along with 27% of ICU admissions in the obstetrics department during the pregnancy phase which leads to high maternal deaths of nearly 55% of females admitted to ICU. With the scarce accurate literature data, the actual sepsis burden globally including in India remains unknown. (2)

Following the 2017 international consensus, sepsis is defined as a 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. (3) Quick SOFA or q SOFA (quick sequential organ failure assessment) is a bedside assessment tool usually employed for the assessment of subjects with the suspicion of sepsis and is widely used. In q SOFA a

score of 1 is allotted to low blood pressure where systolic blood pressure is <100 mmHg, high respiratory rates of >22/breaths/min, and altered mental state with GCS ≤14. These items of q SOFA should alert the treating personnel to comprehensively assess the need for admission to ICU (intensive care unit) along with increased patient monitoring, escalation, or start of the therapy, and to look for any organ dysfunction. (4)

It is not appropriate to use old technologies and techniques for formulation of drugs aimed at particular infections which earlier delayed the infection diagnosis. The diagnostic modalities available currently still depend on the old parameters and are not suitable in sepsis cases described adequately. Any delay in the diagnosis of sepsis causes a delay in starting the treatment of sepsis which can cause antibiotic misuse. Hence, developing biomarkers that are sepsis-specific to evaluate host response in the detection of pathogens is needed for improved management of subjects with sepsis. In the biomarkers that are specific to sepsis, procalcitonin is reported to be the most reliable biomarker in the majority of the cases including those where conventional methods proved to be inconclusive. (5)

Timely and adequate identification of sepsis and early starting of treatment can help in the prevention of septic shock and severe sepsis progression. Considering the rapid and constant increase in the severity and rate of maternal sepsis, this study aimed to assess the impact of maternal sepsis to determine the clinical outcomes along with the role of biomarkers and clinical criteria in judging the prognosis and outcomes of maternal sepsis.

MATERIALS AND METHODS

The present clinical study was designed to assess the specificity and sensitivity of different biomarkers in subjects diagnosed with sepsis and admitted to the ICU of the Obstetrics Department with the diagnosis of sepsis and compared biomarkers to clinical criteria in these subjects. The study was done at Department of Obstetrics and Gynecology, JNU Institute of Medical Science and Research Center, Jaipur, Rajasthan from January 2022 to July 2023, after the concerned institutional Ethical committee allowed proceeding with the study. The study population was selected from the Department of Obstetrics and Gynecology of the institute. Written and verbal informed consent were collected from all the participants before participation. The study included 104 female subjects admitted to the intensive care unit of the obstetrics department with a confirmed diagnosis of sepsis in the defined study period and fulfilled the diagnostic parameters of sepsis.

The inclusion criteria for the study were subjects having organ dysfunction that was associated with the sepsis, subjects presenting the 4 Ts including the raised total counts, tachypnoea, tachycardia, and elevated temperature or any other systemic or local sepsis evidence, and subjects admitted with other conditions and were later diagnosis as having sepsis in the ICU. The exclusion criteria for the study were subjects who did not fit the inclusion criteria for the study as described and the subjects who were not willing to participate in the study.

After the final inclusion, a detailed history recording and examination were done. The criteria for sepsis were considered as defined by Gul F et al (6) in 2017 which is based on strongly suspected or microbiologically confirmed infection along with positive q SOFA scores (7) or a minimum of two or more SIRS criteria while subjects were included in the present study. The SIRS (systemic inflammatory response syndrome) is considered with a body temperature of either <36ºC or >38ºC, heart rate of >90 beats/ min, and respiratory rate of >20 breaths/ min.

After including all the eligible participants, they were carefully assessed from admission till their discharge following their hospital stay duration completely. Worst laboratory and physiological parameters were assessed within the first 24 hours of admission including the biomarkers of sepsis such as serum lactate, CRP (C reactive protein), and PCT (procalcitonin), and the SOFA scores. All the subjects were then managed based on their condition and following the standard protocols. The study data for all the subjects were gathered until their discharge or death, whichever was earlier. After data collection, these subjects were listed as survivors for discharge and nonsurvivors for death respectively.

After collection, the data were checked for it being appropriateness and completeness, and the illogical and inappropriate responses were edited. The data gathered were entered into the Microsoft Excel worksheet. Categorial and qualitative variables were entered numerically and were expressed in percentage and frequency. The Chi-square test was used to assess the outcome variables for the differences in a frequency distribution. For data with a frequency of less than 5, Fisher's exact test was used. All the statistical tests were performed using the SPSS (Statistical Package for the Social Sciences) software version 21.0 (IBM Corp., Armonk, NY, USA). The statistical significance was kept at $p<0.05$.

RESULTS

During the study duration, 7169 females were admitted to the Department of Obstetrics and Gynecology of the Institute. Among these 7169 females, only 10.72% (n=769) subjects were admitted to ICU, and in these subjects admitted to ICU, 13.52% (n=104) subjects had sepsis. The mortality rate among subjects with sepsis was 36.53% (n=38) subjects.

On assessing the various cultures in the study subjects, it was seen that the culture was sterile in 36.36% (n=24) survivors 36.84% (n=14) non-survivors, and a total of 38 subjects. The CSF culture was positive in 26% (n=2) non-survivor subjects.

Infected wound was seen in 6.06% (n=4) survivors. Vaginal swab culture was positive in 18.1% (n=12) and 5.26% (n=2) survivor and non-survivor subjects respectively. The tracheal aspirate was positive in 3.03% (n=2) and 10.52% 9 (n=6) survivors and non-survivors respectively. Urine culture was positive in 9.09% (n=6) survivors and 5.26% (n=2) non-survivors. Blood culture was positive in 15.1% (n=10) survivors and 5.26% (n=12) non-survivors respectively as shown in Table 1. Among 22 culture-negative subjects, the viral markers were positive. The commonly isolated microorganisms were TB bacilli, MRSA, staphylococcus, and streptococcus in culture-negative cases, whereas, E. coli and Klebsiella were the most commonly seen microorganisms.

Concerning the place of delivery, it was done in a hospital in 69.6% (n=46) of survivors and 73.6% (n=28) of non-survivors. Delivery was done at home in 30.3% (n=20) survivors and 26.3% (n=10) non-survivor subjects. The difference was statistically non-significant with p=0.74. SOFA scores of 13-18 and 19-24 were significantly higher in the non-survivor study subjects compared to the survivors with p=0.01. Significantly higher mortality rates were seen in subjects with SIRS criteria of ≥2 which was seen in all 100% (n=38) non-survivor subjects with p=0.02. Similarly, significantly higher mortality rates were seen in subjects with q SOFA scores of ≥2 seen in 42.4% (n=28) survivors and 78.94% (n=30) non-survivor subjects with p=0.01.

In Biomarkers, serum lactate levels of ≥4 mmol/L were significantly higher in non-survivor subjects with 84.21% (n=32) compared to 42.4% (n=28) survivor subjects showing significantly higher mortality rates with p=0.01. CRP levels showed a non-significant difference in survivor and non-survivor sepsis subjects with p=0.46. A similar non-significant impact was seen of procalcitonin on the mortality rates in the study subjects with p=0.24 as depicted in Table 2.

On multivariate and univariate logistic regression analysis of death and its predictors in study subjects, the results are summarized in Table 3. Significant results were seen for serum lactate levels and SOFA scores. It was seen that a 9 times higher probability of death was seen in subjects having serum lactate levels of ≥2 mmol/L compared to the subjects having serum lactate levels of <2 mmol/L with p=0.03. A higher probability of death was also seen in subjects with higher SOFA and q SOFA scores with p=0.001 and 0.01 respectively. Univariate and multivariate analysis showed that a high probability of death by 2.7 times was seen in subjects with PCT ≥2 compared to subjects with PCT <2 ng/ml.

The study results showed that for the presence of multiorgan dysfunction syndrome in study subjects, it was seen that multiorgan dysfunction syndrome was seen in all 100% (n=38) non-survivor subjects and 54.5% (n=36) survivor subjects. In the non-survivor group, the most common organ dysfunction was respiratory, cerebrovascular, and cardiovascular seen in 100% (n=38), 89.47% (n=34), and 84.21% (n=32) study subjects respectively as depicted in Table 4.

Table 1: Grouping of study subjects depending on the culture reports

S. No	Positive culture	Survivors		Non-survivors		Total (n=104)
		n=66	%	n=38	%	
1.	**Sterile**	24	36.36	14	36.84	38
2.	**CSF**	0	0	2	5.26	2
3.	**Infected wound**	4	6.06	0	0	4
4.	**Vaginal swab**	12	18.1	2	5.26	14
5.	**Tracheal aspirate**	2	3.03	4	10.52	6
6.	**Urine**	6	9.09	2	5.26	8
7.	**Blood**	10	15.1	2	5.26	12

Table 2: Distribution of study subjects based on delivery place, severity score, and biomarkers

S. No	Positive culture	Survivors		Non-survivors		Total (n=104)
		n=66	%	n=38	%	
1.	**Delivery place**					
a)	Hospital	46	69.6	28	73.6	0.74
b)	Home	20	30.3	10	26.3	
2.	**SOFA score**					
a)	1-6	20	30.3	4	10.52	**0.01**
b)	7-12	28	42.4	6	15.78	
c)	13-18	12	18.1	18	47.36	
d)	19-24	6	9.09	10	26.31	
3.	**SIRS criteria**					
a)	<2	14	21.1	0	0	**0.02**
b)	≥2	52	78.7	38	100	
4.	**q SOFA score**					

a)	<2	38	57.5	8	21.05	**0.01**
b)	≥2	28	42.4	30	78.94	
5.	**Serum lactate (mmol/L)**					
a)	<2	22	33.3	2	5.26	**0.01**
b)	2-3.99	16	24.2	4	10.52	
c)	≥4	28	42.4	32	84.21	
6.	**CRP (mg/dl)**					
a)	<20	18	27.2	14	36.84	0.46
b)	20-49.9	28	42.4	18	47.36	
c)	≥50	20	30.3	6	15.78	
7.	**Procalcitonin (ng/ml)**					
a)	<2	16	24.2	4	10.52	0.24
b)	≥2	50	75.7	34	89.47	

Table 3: Multivariate and univariate logistic regression analysis of death and its predictors in study subjects

S. No	Variables	Multivariate Odds ratio	p-value	Univariate Odds ratio	p-value
1.	**Culture**				
a)	Positive			0.33 (0.02-2.86)	0.306
b)	Negative			Reference	
2.	**SIRS criteria**				
a)	<2			Reference	
b)	≥2			1	
3.	**q SOFA score**				
a)	<2	3.85 (0.86-17.14)	0.09	Reference	**0.01**
b)	≥2			5.07 (1.36-18.72)	
4.	**SOFA score**				
a)	<15	7.22 (1.72-30.83)	**0.006**	Reference	**0.001**
b)	≥15			9.4 (2.51-36.3)	
5.	**Serum lactate (mmol/L)**	3.87 (0.43-37.13)	0.21		
a)	<2	3.87 (0.43-37.13)	0.21	Reference	**0.03**
b)	≥2			9.2 (1.04-76.46)	
6.	**CRP (mg/dl)**				
a)	<20			Reference	0.31
b)	≥20			0.53 (0.14-1.85)	
7.	**PCT (ng/ml)**				
a)	<2			Reference	0.22
b)	≥2			2.74 (0.53-14.43)	

Table 4: Presence of multiorgan dysfunction syndrome in study subjects

S. No	Multiorgan dysfunction syndrome	Survivors		Non-survivors		p-value
		n	%	n	%	
1.	**Yes**	36	54.5	38	100	**<0.0001**
2.	**No**	30	45.5	0	0	

DISCUSSION

Sepsis is a life-threatening condition showing a higher number of cases in developing nations including India. It is usually seen secondary to dysregulation in the immune response to fungal, viral, or bacterial infections. The ideal care for the subjects with sepsis mainly constitutes early identification. Early diagnosis, and prompt start of the management therapy. However, it is advisable to allow identification of infection before the appearance of clinical symptoms and signs before any organ damage is evident as suggested by Gary T (8) in 2016 and Albright CM et al (9) in 2015.

The present study included young females who were primipara. The majority of the study subjects were illiterate with 26.92% (n=28) subjects. This was in agreement with Shamanewadi AN et al (10) in 2020 who reported that mothers with low education are less aware concerning antenatal care which is also supported by the fact that healthcare facilities during pregnancy were only availed by 10.57% (n=11) subjects. As the majority of the subjects did not avail of health care facilities, they underwent unsupervised

delivery which proved a vital risk factor for maternal sepsis as also reported by Foeller ME et al (11) in 2020. In the majority of the study subjects with sepsis, referral delay was seen which depicts that primary physicians are less aware of symptoms and signs associated with sepsis and with the rapid disease progression.

The present study also compared the efficacy of clinical scoring systems including the total SOFA scores, q SOFA scores, and SIRS criteria in subjects admitted to the ICU Of the Department of Obstetrics to predict the mortality in sepsis subjects. SOFA scores of 13-18 and 19-24 were significantly higher in the non-survivor study subjects compared to the survivors with p=0.01. Significantly higher mortality rates were seen in subjects with SIRS criteria of ≥2 which was seen in all 100% (n=38) non-survivor subjects with p=0.02. Similarly, significantly higher mortality rates were seen in subjects with q SOFA scores of ≥2 seen in 42.4% (n=28) survivors and 78.94% (n=30) non-survivor subjects with p=0.01. These results were comparable to the studies of Agarwal M et al (12) in 2022 and Guwlani P et al (13) in 2023 where the authors reported. SOFA scores of 13-18 and 19-24 were significantly higher in the non-survivor study subjects compared to the survivors and significantly higher mortality rates in subjects with q SOFA scores of ≥2.

The study also assessed the efficacy of procalcitonin as a diagnostic aid in subjects with sepsis admitted to the ICU of the obstetrics department and a comparison was made with serum lactate and CRP. The study results showed that serum lactate levels of ≥4 mmol/L were significantly higher in non-survivor subjects with 84.21% (n=32) compared to 42.4% (n=28) survivor subjects showing significantly higher mortality rates with p=0.01. CRP levels showed a non-significant difference in survivor and non-survivor sepsis subjects with p=0.46. A similar non-significant impact was seen of procalcitonin on the mortality rates in the study subjects with p=0.24. These results were consistent with the results of Muller B et al (14) in 2008 and Simon L et al (15) in 2005 where authors suggested that the most reliable biomarker in sepsis subjects for diagnosis is procalcitonin which is also helpful in deciding the antibiotic therapying subjects with low-risk acuity of infection. The authors also advised that in the majority of cases, serial assessment of PCT should be done rather than a single assessment.

Another commonly used biomarker in the assessment of sepsis is CRP which is an acute-phase protein produced by the liver as a consequence of tissue damage and the onset of inflammation. The concentration of CRP increases slowly and reaches its peak at 36 hours following infection. A moderate degree of sepsis is usually indicated by CRP levels of ≥ 20mg/dl as reported by Jeon JH et al (16) in 2014CRP shows a bio specificity when taken as a sepsis biomarker. The main clinical use of CRP is screening for early sepsis onset as it has a high sensitivity. In plasma, CRP concentrations can remain high for several days after the infection has subsided as reported by Tschaikowsky K et al (17) in 2011.

Procalcitonin is widely used in the assessment of subjects with sepsis and is present in thyroid C-cells and in small quantities in neuroendocrine cells. The production of procalcitonin is activated in parenchymal tissues following bacterial infection. Within 3-4 hours of infection, procalcitonin is detectable reaching its highest concentration at 6-12 hours and half-life at 24 hours. With its high sensitivity, specificity, and kinetic profile, PCT is considered as most promising biomarker for disease progression and diagnosis of sepsis. Systemic bacteremia is suggested by PCT levels of ≥ 2 ng/ml as reported by Vijayan AL et al (18) in 2017 and Meisner M et al (19) in 2014.

In Biomarkers, serum lactate levels of ≥4 mmol/L were significantly higher in non-survivor subjects with 84.21% (n=32) compared to 42.4% (n=28) survivor subjects showing significantly higher mortality rates with p=0.01. Serum lactate levels are usually increased in anaerobic metabolism secondary to aerobic glycolysis, tissue hypoxia, and hypoperfusion. Severe tissue hypoxia and tissue hypoxia are respectively denoted by serum lactate levels of ≥2 mmol/L and ≥ 4 mmol/L. Increased levels of serum lactate in pregnancy might result in sepsis and other adverse maternal outcomes. In the present study, multivariate and univariate analysis depicts that among biomarkers, the most reliable predictor of mortality in subjects with maternal sepsis is serum lactate. These results were in line with the findings of Agarwal R et al (20) in 2018 and Albright CM et al (21) in 2016.

The present study assessed the role of clinical scoring systems and biomarkers in assessing the obstetric subjects with sepsis in an Indian scenario. The study results showed that procalcitonin and serum lactate are reliable biomarkers in subjects with maternal sepsis. These markers helped assess subjects with sepsis in critically ill subjects along with various clinical scoring systems including the q SOFA scores. In subjects with high q SOFA scores SOFA scores should be assessed for confirmatory diagnosis. Also, q SOFA is a bedside and simple scoring system. In cases with positive clinical profiles and biomarkers, immediate microbial identification should be done and appropriate antibiotics should be started.

CONCLUSION

One of the most common causes of maternal mortality in Indian subjects is maternal sepsis. SOFA scores and q SOFA scores are the most reliable clinical scoring systems in subjects with maternal sepsis. Also, procalcitonin is a reliable biomarker in subjects with maternal sepsis. The study also concludes that the most specific and sensitive predictor for prognosis in subjects with maternal sepsis is serum lactate along

with procalcitonin, whereas, the least specific biomarker for maternal sepsis is CRP. Total SOFA and q SOFA scores can be used for early screening of maternal sepsis.

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