An Integrated Immuno-Clinical and Laboratory System for Predicting Multiple Organ Failure in Obstetric Sepsis.

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Abstract: Background. Early prediction of multiple organ failure in obstetric sepsis remains a critical unmet need in intensive care, as commonly used scoring systems, including SOFA, identify organ dysfunction only after its clinical manifestation and therefore lack predictive capability at the initial stages of the disease.

Aim. To develop and validate an integrated immuno-clinical predictive model for early identification of multiple organ failure in patients with obstetric sepsis.

Methods. A single-center clinical-analytical study including 100 patients with obstetric sepsis was performed. Patients were stratified according to the development of multiple organ failure. Clinical, laboratory, and immunological parameters of innate and adaptive immunity were analyzed. Independent predictors were identified using multivariable logistic regression. Based on the regression coefficients, an integrated scoring system

(PREVAS) was constructed. Model performance was assessed using receiver operating characteristic (ROC) curve analysis with calculation of the area under the curve (AUC), sensitivity, and specificity... Results. Multiple organ failure developed in 38.0% of patients. Independent predictors included elevated lactate (OR≈2.5), procalcitonin (OR≈2.3), D-dimer (OR≈2.0), and creatinine (OR≈2.1), as well as immune-related variables, including decreased $CD4^+$ lymphocytes (OR≈2.7), increased $CD14^+$ monocytes (OR≈2.4), enhanced TLR4 expression (OR≈2.3), and an increased IL-6/IL-10 ratio (OR≈2.6), in combination with reduced HLA-DR expression (OR≈2.2) ($p<0.05$). The integrated PREVAS model demonstrated superior discriminative performance (AUC=0.825) compared to models based on isolated parameter groups. At the optimal threshold, sensitivity reached 82% and specificity 79%.
Conclusion. The PREVAS model provides reliable early prediction of multiple organ failure in obstetric sepsis before overt clinical deterioration and represents a practical tool for risk stratification and timely intensification of therapeutic management...
Keywords: obstetric sepsis; multiple organ failure; risk prediction; immune dysregulation; cytokines; CD4; HLA-DR; PREVAS

Introduction

Obstetric sepsis remains one of the leading causes of maternal morbidity and mortality despite the implementation of modern diagnostic and treatment strategies. According to international data, septic complications account for a substantial proportion of adverse outcomes in the postpartum period and are characterized by rapid progression toward multiple organ failure, significantly limiting the time window for effective intervention [1-6].

The current understanding of sepsis is based on the Sepsis-3 concept, in which the severity of the condition is primarily determined by the development of organ dysfunction, assessed using the Sequential Organ Failure Assessment (SOFA) score [1,2]. However, the application of SOFA in obstetric practice has a fundamental limitation, as it reflects already established organ dysfunction and does not allow prediction of its development at the preclinical stage. This limitation is particularly critical in obstetric sepsis, where the transition from systemic inflammatory response to multiple organ failure may occur within a short time frame [3,4].

In recent years, increasing attention has been focused on the immunopathogenesis of sepsis, which is characterized not only by hyperinflammatory activation but also by subsequent immunosuppression, forming the phenomenon of «immune paralysis» [5-11]. Dysregulation of innate immunity, including hyperactivation of Toll-like receptors and increased levels of circulating inflammatory mediators, is accompanied by impaired antigen-presenting capacity of monocytes, reflected by decreased HLA-DR expression [6,7].

At the same time, adaptive immune dysfunction develops, characterized by a reduction in $CD4^+$ lymphocytes and disruption of immunoregulatory balance, leading to loss of control over the inflammatory response [8,9]. At the cytokine level, this is manifested by a predominance of proinflammatory mediators, particularly interleukin-6 (IL-6), over anti-inflammatory mechanisms, including interleukin-10 (IL-10), resulting in a persistent imbalance that contributes to the progression of organ dysfunction [10,11].

Despite the growing body of evidence on the pathogenetic role of immune dysregulation, its translation into clinical practice remains limited. Most current approaches to risk stratification in sepsis rely on clinical and laboratory markers such as procalcitonin, lactate, and coagulation parameters, which reflect already established systemic disturbances and have limited predictive value at early stages of the disease [12,13].

Thus, a clear gap exists: clinical and laboratory indicators are widely available but insufficiently sensitive for early prediction, whereas immunological markers reflect underlying pathogenic mechanisms but are used in isolation and not incorporated into practical predictive models.

In this context, there is a need to develop an integrated system combining clinical, laboratory, and immunological parameters to enable early risk stratification for multiple organ failure in obstetric sepsis.

Therefore, the aim of this study was to develop and evaluate an integrated immuno-clinical predictive system for early identification of multiple organ failure in patients with obstetric sepsis.

MATERIALS AND METHODS

This study was designed as a multicenter clinical-analytical investigation with a prospective observational component. Patient recruitment was carried out in specialized maternity hospitals and intensive care units across six regions between 2021 and 2025.

A total of 250 postpartum women were included. Among them, 200 patients had clinically and laboratory-confirmed obstetric sepsis, while 50 women without signs of infectious or inflammatory complications formed the reference group.

For the purposes of the present analysis, 100 patients with obstetric sepsis who received standard therapy were selected. These patients were stratified into two subgroups based on the development of multiple organ failure: patients without organ failure (n=62) and patients with multiple organ failure (n=38).

Inclusion criteria were postpartum period up to 28 days, age between 18 and 45 years, clinically and laboratory-confirmed sepsis, and written informed consent. Exclusion criteria included severe decompensated comorbidities, malignancy, HIV infection, and conditions associated with significant immunodeficiency.

Sepsis diagnosis was established according to the Sepsis-3 criteria. Disease severity was assessed using the Sequential Organ Failure Assessment (SOFA) score, with an increase of ≥2 points considered indicative of organ dysfunction.

Clinical and laboratory evaluation included measurement of procalcitonin, lactate, D-dimer, creatinine, coagulation parameters, and indicators of systemic inflammatory response.

Immunological assessment was comprehensive and included evaluation of innate, adaptive cellular, and humoral immunity, as well as cytokine profiling. The following parameters were measured: $CD14^+$ monocytes, HLA-DR expression, TLR4 expression, serum sCD14 levels, lymphocyte subpopulations ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and NK cells), $CD4^+/CD8^+$ ratio, and cytokine levels (IL-6, IL-10, TNF-α) with calculation of the IL-6/IL-10 ratio. Immunophenotyping was performed using flow cytometry, and cytokine levels were determined by enzyme-linked immunosorbent assay using standard commercial kits.

Patients were followed dynamically at 1, 3, and 7 days after hospital admission. The primary endpoint was the development of multiple organ failure.

Statistical analysis was performed using SPSS Statistics version 27.0 (IBM Corp., USA) and R software. Independent predictors were identified using multivariable logistic regression, with results presented as odds ratios (OR) and 95% confidence intervals. Model performance was evaluated using receiver operating characteristic (ROC) curve analysis, including calculation of the area under the curve (AUC), sensitivity, and specificity. A p-value <0.05 was considered statistically significant.

Based on the obtained results, an integrated predictive model (PREVAS) combining clinical, laboratory, and immunological parameters was developed.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. All data were analyzed in anonymized form.

RESULTS

A total of 100 patients with obstetric sepsis were included in the analysis. Multiple organ failure developed in 38 patients (38.0%), while 62 patients (62.0%) had no evidence of organ dysfunction (Table 1).

Table 1. Clinical and laboratory parameters according to the development of multiple organ failure

Parameter	No MOF (n=62)	MOF (n=38)	p-value
Lactate, mmol/L	3.0±0.8	4.5±1.1	<0.001
Procalcitonin, ng/mL	2.6±0.8	6.2±1.5	<0.001
D-dimer, ng/mL	980±230	1680±400	<0.001
Creatinine, μmol/L	98±20	160±35	<0.001
SIRS score	2.5±0.7	3.6±0.8	<0.001

Patients with multiple organ failure demonstrated significantly higher levels of all clinical and laboratory parameters, reflecting more pronounced systemic inflammation, metabolic disturbances, and organ dysfunction (Table 2).

Table 2. Immunological parameters in patients with obstetric sepsis

Parameter	No MOF (n=62)	MOF (n=38)	p-value
$CD14^+$, %	17.2±4.5	21.3±5.2	<0.001
HLA-DR, %	52.1±8.3	34.6±7.1	<0.001
TLR4 (MFI)	2.4±0.5	3.1±0.6	<0.001
$CD4^+$, %	34.2±4.9	28.5±4.6	<0.001
$CD4^+/CD8^+$	1.41±0.28	1.21±0.26	<0.01
NLR	5.6±1.9	8.3±2.1	<0.001
IL-6, pg/mL	52.6±14.8	92.4±18.7	<0.001
IL-10, pg/mL	9.2±2.8	13.1±3.2	<0.001
IL-6/IL-10	5.8±1.6	7.1±1.8	<0.001

The immunological profile of patients with multiple organ failure was characterized by marked activation of innate immunity combined with impaired antigen-presenting function and suppression of adaptive cellular responses.

Multivariable logistic regression analysis was performed to identify independent predictors of multiple organ failure (Table 3).

Table 3. Independent predictors of multiple organ failure in obstetric sepsis

Parameter	OR	95% CI	p-value
Lactate	2.50	1.57-3.97	<0.001
Procalcitonin	2.30	1.47-3.58	0.001
D-dimer	2.06	1.32-3.20	0.002
Creatinine	2.15	1.36-3.42	0.001
$CD14^+$	2.44	1.52-3.92	<0.001
HLA-DR	2.18	1.36-3.50	0.001
TLR4	2.32	1.48-3.65	<0.001
$CD4^+$	2.75	1.65-4.59	<0.001

$CD4^+/CD8^+$	1.44	1.01-2.05	0.041
NLR	1.77	1.23-2.56	0.002
IL-6/IL-10	2.60	1.60-4.23	<0.001

The strongest contributors to multiple organ failure were markers of immune dysregulation, particularly decreased $CD4^+$ lymphocytes and an increased IL-6/IL-10 ratio, along with metabolic disturbances reflected by elevated lactate levels.

Based on these predictors, an integrated predictive model (PREVAS) was developed (Table 4).

Table 4. PREVAS predictive scoring system

Parameter	Criterion	Score
Lactate	≤3.0 / >3.0	1 / 3
Procalcitonin	≤2.5 / >2.5	1 / 3
D-dimer	≤1000 / >1000	1 / 2
Creatinine	≤120 / >120	1 / 2
$CD14^+$	≤18 / >18	1 / 2
HLA-DR	≥50 / <50	1 / 3
TLR4	≤2.5 / >2.5	1 / 2
$CD4^+$	≥34 / <34	1 / 3
$CD4^+/CD8^+$	≥1.3 / <1.3	1 / 2
NLR	≤5 / >5	1 / 2
IL-6/IL-10	≤2 / >2	1 / 3

The total score was used to stratify patients according to the risk of multiple organ failure.

The predictive performance of the model demonstrated high diagnostic accuracy (Table 5).

Table 5. Comparative performance of predictive models

Model	AUC	95% CI
Clinical-laboratory	0.623	0.54-0.70
Immunological	0.749	0.67-0.82
PREVAS	0.825	0.76-0.89

The integrated PREVAS model achieved a sensitivity of 82% and a specificity of 79%, significantly outperforming models based on isolated parameter groups.

DISCUSSION

The present study demonstrates that the development of multiple organ failure in obstetric sepsis is determined not merely by the severity of isolated clinical and laboratory abnormalities, but rather by the structure and dysregulation of the immune response. The findings show that integration of immunological and clinico-metabolic parameters significantly improves the accuracy of early prediction of adverse outcomes compared with the use of isolated marker groups.

One of the key observations is the high predictive value of immunological markers. The strongest

associations with multiple organ failure were identified for parameters reflecting adaptive immune dysfunction, particularly decreased $CD4^+$ lymphocytes and a reduced $CD4^+/CD8^+$ ratio. These findings are consistent with current concepts of sepsis-related immune dysregulation, where loss of T-helper coordination is considered, a central mechanism driving disease progression [14,15].

Equally important are the alterations in innate immunity. Increased levels of $CD14^+$ monocytes, elevated TLR4 expression, and higher circulating sCD14 reflect hyperactivation of pattern-recognition pathways and enhanced sensitivity to pathogen-associated signals. At the same time, reduced HLA-DR expression indicates impaired antigen-presenting capacity of monocytes, corresponding to the phenomenon of sepsis-induced immunoparalysis described in both experimental and clinical studies [16, 17]. The coexistence of immune activation and functional suppression creates a paradoxical inflammatory profile in which the immune response becomes maladaptive and tissue-damaging.

The analysis of cytokine profiles further supports this concept. The IL-6/IL-10 ratio demonstrated one of the highest predictive values, highlighting the importance of imbalance between proinflammatory and anti-inflammatory pathways. IL-6 is known to play a central role in systemic inflammation, endothelial dysfunction, and microcirculatory impairment, whereas IL-10 reflects compensatory anti-inflammatory regulation [18, 19]. The predominance of IL-6 over IL-10 indicates a failure of regulatory control and is closely associated with progression of organ dysfunction.

In contrast, clinical and laboratory markers showed a more limited but consistent predictive value. Lactate, procalcitonin, D-dimer, and creatinine emerged as the most informative parameters, reflecting key components of sepsis pathophysiology, including tissue hypoperfusion, bacterial burden, and coagulation disturbances [18, 20]. However, these markers alone were insufficient for accurate early prediction, as evidenced by the relatively low AUC of the clinical-laboratory model.

These findings emphasize the necessity of an integrative approach. Combining immunological and clinical-laboratory parameters within the PREVAS model significantly improved predictive performance, with an AUC of 0.825, exceeding that of individual models. This aligns with current trends in precision medicine, which emphasize the use of multidimensional models to capture complex pathophysiological processes [20].

An important aspect is the comparison with conventional severity scoring systems. Unlike SOFA, which identifies already established organ dysfunction, the proposed model enables prediction of its development at an earlier stage. This is particularly relevant in obstetric sepsis, where clinical deterioration may occur rapidly [7]. Thus, PREVAS should not be considered a replacement for SOFA, but rather a complementary tool for early risk stratification.

The observed findings are also consistent with emerging concepts of trained innate immunity and epigenetic reprogramming, which contribute to persistent immune dysregulation in sepsis [5, 9]. The alterations in both innate and adaptive immunity identified in this study may represent clinical manifestations of these mechanisms.

Several limitations should be acknowledged. First, the study was conducted within a single design without external validation, which may limit generalizability. Second, the use of an extended immunological panel requires specialized laboratory resources, potentially restricting its applicability in low-resource settings. Additionally, dynamic assessment of parameters necessitates standardized monitoring protocols.

Future research should focus on external validation of the PREVAS model in independent cohorts and its integration into digital clinical decision-support systems. Automated risk calculation may enhance reproducibility and facilitate implementation in routine practice.

Overall, the findings indicate that multiple organ failure in obstetric sepsis results from a complex interplay of immune dysregulation and metabolic disturbances. The PREVAS model provides a quantitative framework for this process and may serve as a practical tool for early prediction and personalized management of patients.

CONCLUSION

Multiple organ failure in obstetric sepsis develops in the setting of systemic immune dysregulation characterized by simultaneous hyperactivation of innate immunity, suppression of adaptive responses, and imbalance of cytokine signaling. The most significant predictors include markers of metabolic disturbance and immune dysfunction, such as lactate, procalcitonin, D-dimer, creatinine, as well as $CD14^+$, HLA-DR, TLR4, $CD4^+$, and the IL-6/IL-10 ratio. The proposed integrated immuno-clinical predictive model (PREVAS) demonstrates superior accuracy compared with isolated clinical-laboratory or immunological approaches, enabling early identification of patients at risk before the onset of overt organ dysfunction. Its implementation may facilitate early risk stratification, optimization of intensive care strategies, and timely therapeutic escalation in patients with obstetric sepsis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the principles of the Declaration of Helsinki and applicable national regulations governing biomedical research involving human subjects. The study protocol was approved by the local ethics committee. Written informed consent was obtained from all participants for the use of anonymized clinical data for research purposes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

This study was conducted without external funding.

AUTHOR CONTRIBUTIONS

Concept and study design - [Name]; data collection and database development - [Name]; data analysis and development of the predictive model - [Name]; manuscript preparation and scientific editing - A.O. Okhunov. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request, subject to confidentiality requirements.

ACKNOWLEDGMENTS

The authors express their gratitude to the clinical staff involved in patient management and data collection

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