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Neonatal Sepsis Prediction Using AI-Based Vital Sign Analysis in NICUs: A Multicenter Retrospective Study.

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ABSTRACT

Neonatal sepsis remains one of the leading causes of morbidity and mortality in intensive care units, yet early diagnosis continues to be a major clinical challenge due to nonspecific symptoms and rapidly evolving physiological instability. This study develops and evaluates an AI-based vital-sign prediction framework capable of detecting early signatures of sepsis using continuous physiological monitoring data from multiple NICUs. A multicenter retrospective dataset comprising heart rate, respiratory rate, oxygen saturation, temperature, blood pressure, and derived variability metrics was analyzed across three tertiary hospitals. After preprocessing, imputation, and artifact suppression, machine learning and deep learning models including Random Forest, Gradient Boosting, and a hybrid LSTM network were trained to capture nonlinear temporal patterns indicative of sepsis onset. The proposed LSTM-based model demonstrated strong predictive ability, identifying sepsis up to 6–12 hours before clinical diagnosis with improved sensitivity and reduced false alarms compared to conventional scoring systems. Key physiological precursors included abnormal heart-rate variability, intermittent desaturations, rising temperature instability, and increased respiratory fluctuations. The findings confirm that AI-guided prediction can enhance real-time surveillance, support timely clinical interventions, and reduce progression to severe outcomes. This multicenter analysis underscores the potential of intelligent vital-sign analytics as a scalable decision-support tool in modern NICU environments.

KEYWORDS: Neonatal Sepsis, NICU, Artificial Intelligence, Vital Sign Analysis, LSTM, Machine Learning, Early Prediction, Clinical Decision Support, Multicenter Study, Time-Series Data

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INTRODUCTION

Neonatal sepsis persists as one of the most urgent global health concerns, accounting for a significant proportion of early-life morbidity, long-term neurodevelopmental impairment, and preventable mortality in hospital-based newborn care. Despite advancements in antimicrobial therapy and intensive-care management, early diagnosis remains difficult because its initial physiological expression is subtle, heterogeneous, and frequently masked by other neonatal complications. Traditional diagnostic tools such as blood cultures, C-reactive protein (CRP), and procalcitonin (PCT) are slow, invasive, and often insensitive during the earliest stages of infection. Clinicians therefore rely heavily on continuous bedside monitoring of vital signs, yet manual interpretation of these noisy and rapidly fluctuating signals often leads to delayed recognition of physiological deterioration. Neonatal sepsis is not a sudden clinical event but a progressive cascade marked by evolving patterns in cardiorespiratory instability long before overt symptoms appear. Advances in digital monitoring particularly the widespread deployment of high-frequency physiological sensors in NICUs have created an unprecedented opportunity to capture this early instability. However, the raw data produced by these systems are vast, multidimensional, and prone to artifacts, making real-time interpretation beyond the capacity of conventional scoring systems such as the Neonatal Sequential Organ Failure Assessment (nSOFA) or standard early-warning tools. These limitations underscore the clinical need for analytical systems capable of detecting subtle precursors of infection with sufficient sensitivity and specificity to support early intervention. As neonatal care becomes increasingly data-driven, artificial intelligence offers a transformative path toward proactive surveillance, supported by modern computational power and the availability of continuous physiological datasets from multiple neonatal centers.

Artificial intelligence and machine learning have rapidly emerged as powerful techniques for analyzing complex physiological patterns that are difficult to detect through traditional clinical observation. Time-series models such as long short-term memory (LSTM) networks, one-dimensional convolutional neural networks (1D-CNNs), and hybrid transformer architectures have demonstrated strong capability in capturing nonlinear dynamics, temporal dependencies, and micro-variations in vital signs associated with systemic infection. When applied to neonatal monitoring, these models can identify critical patterns such as reduced heart-rate variability, repeated desaturation episodes, temperature dysregulation, or respiratory instability hours before clinicians would typically recognize them. Multicenter retrospective analysis enhances this predictive capability by incorporating diverse neonatal profiles, varying gestational ages, different NICU environments, and a wide spectrum of sepsis presentations, making the resulting models more robust and generalizable. By integrating vital-sign trajectories collected across three tertiary hospitals, this study explores the predictive potential of AI-driven algorithms in detecting sepsis onset 6–12 hours prior to clinical confirmation. Early detection at this temporal window is clinically meaningful, as timely administration of antibiotics, fluid management, and supportive interventions can drastically reduce progression to septic shock, organ dysfunction, or mortality. The broader significance of this research lies not only in algorithmic accuracy but also in its potential to reshape neonatal care workflows, reduce diagnostic uncertainty, and support clinicians with continuous, intelligent bedside decision assistance. Ultimately, this study demonstrates how AI-powered surveillance can serve as a cornerstone of precision neonatology, offering a scalable, non-invasive, and data-rich approach to managing one of the most challenging conditions in modern newborn medicine.

RELATED WORKS

Research on neonatal sepsis detection has evolved significantly over the past decade, shifting from traditional physiological scoring systems toward data-driven prediction models capable of interpreting high-frequency NICU signals. Early foundational studies emphasized the value of heart-rate characteristics (HRC) as an early biomarker of sepsis. Griffin and Moorman's landmark work introduced the HeRO score, demonstrating that abnormal heart-rate variability and deceleration events precede clinical diagnosis by several hours, substantially reducing mortality when used in routine care [1]. Subsequent investigations expanded this understanding by showing that sepsis disrupts autonomic regulation, reflected through nonlinear heart-rate entropy, fractal dynamics, and low-frequency oscillations [2][3]. Respiratory instability, including recurrent apnea, tachypnea cycles, or irregular breathing intervals, has similarly been implicated as an early indicator of systemic infection [4]. Temperature variability studies further revealed that septic neonates show patterns of intermittent hypo- and hyperthermic fluctuations that differ from normal thermoregulatory responses [5]. Collectively, these traditional approaches provided essential groundwork but were limited by their reliance on narrowly defined metrics and their inability to integrate simultaneous multi-signal fluctuations. As NICUs adopted continuous digital monitoring, researchers began leveraging high-resolution waveform data to explore richer physiological signatures. Several studies demonstrated that combining cardiorespiratory features outperforms single-parameter models, especially when evaluating infants of varying gestational ages or coexisting complications such as respiratory distress syndrome or prematurity-related instability [6][7]. These insights laid the foundation for the integration of machine learning and deep neural architectures capable of analyzing nonlinear, multidimensional trends that clinicians cannot manually interpret.

Machine learning methodologies have since become central to neonatal sepsis prediction research. Traditional classifiers including Random Forest, Support Vector Machine, and Gradient Boosting were initially applied to tabular representations of vital-sign summaries, achieving moderate predictive accuracy but struggling with temporal granularity [8]. The introduction of time-series learning marked a major methodological advance. LSTM networks, designed to recognize long-term dependencies, emerged as a preferred architecture for analyzing physiological deterioration as it unfolds over several hours. Chang et al. demonstrated that LSTM-based sepsis models using heart-rate and respiratory-rate trajectories identified sepsis 6–10 hours earlier than clinical teams [9]. Similarly, CNN-LSTM hybrid systems improved performance by capturing both short-term waveform patterns and broader temporal trends across multiple channels [10]. Transformer-based models further enhanced temporal attention and interpretability, allowing researchers to pinpoint physiologic episodes most strongly associated with impending infection [11]. Beyond vital signs, several studies integrated laboratory biomarkers, demographic factors, and clinical notes from electronic medical records, leveraging multimodal fusion to increase detection specificity [12]. However, these approaches often faced challenges related to missing data, noise artifacts, and inconsistent measurement intervals across NICUs. Researchers responded by developing robust data-cleaning pipelines, imputation strategies, and artifact-suppression techniques tailored for neonatal signals, significantly improving model stability [13]. Despite algorithmic progress, concerns persisted regarding generalizability, as many studies relied on single-center datasets. The shift toward multicenter analyses has been crucial, offering greater demographic diversity, variable sepsis etiologies, and differences in clinical protocols, resulting in models that better reflect real-world NICU environments.

Recent literature emphasizes the integration of AI models into clinical workflows and the translation of research findings into practical, bedside decision support systems. Studies exploring real-time implementation demonstrated that continuous AI-based surveillance reduces diagnostic delays by flagging subtle physiologic trends invisible through routine observation [14]. Advanced interpretability methods such as SHAP values, attention maps, and feature-attribution heatmaps have also addressed clinician concerns about "black-box" algorithms by highlighting which physiological features drive alerts, thus increasing trust and usability. Multicenter studies have further underscored the importance of external validation, revealing that robust models must adapt to variations in monitoring equipment, sampling frequency, patient acuity levels, and NICU care practices. Other researchers have explored the ethical and operational implications of AI-guided sepsis detection, noting the potential to reduce caregiver burden, minimize false alarms, and improve antibiotic stewardship by promoting more precise diagnostic timing [15]. Despite these advances, several challenges remain, including standardizing data formats across hospitals, reducing computational overhead for real-time deployment, and mitigating biases associated with preterm infant physiology. The prevailing direction of contemporary research suggests that scalable, AI-enabled vital-sign surveillance supported by continuous learning across multiple centers represents the most promising pathway toward early, accurate neonatal sepsis detection. Together, the existing body of work forms the foundation on which this multicenter retrospective study builds, offering new insights into signal-level sepsis signatures and advancing the clinical integration of intelligent prediction systems in modern NICUs.

METHODOLOGY

3.1 Research Design

This study adopts a multicenter retrospective observational design that integrates continuous vital-sign monitoring data from three tertiary-level NICUs. The objective is to develop a predictive AI framework capable of identifying neonatal sepsis 6–12 hours prior to clinical diagnosis. The methodological workflow includes data extraction, preprocessing, feature engineering, model training, temporal analysis, and performance evaluation. Following best practices in neonatal informatics research, the design emphasizes temporal fidelity, artifact suppression, and multicenter generalizability to ensure that the model captures true physiological deterioration rather than unit-specific noise or operational variability [16]. To minimize bias, the dataset was stratified across gestational age groups, birth weights, and sepsis etiologies, enabling balanced model exposure to a wide array of clinical presentations. Ethical approvals were obtained from all participating institutions, and datasets were de-identified based on HIPAA and national neonatal-data governance guidelines.

3.2 Study Setting and Population

Data were collected from three NICUs referred to as Center A, Center B, and Center C to maintain anonymity. Each center contributed at least three years of continuous physiological monitoring data. Eligible neonates included those admitted within 72 hours of birth who had a confirmed diagnosis of early- or late-onset sepsis based on blood cultures and clinical evaluations. Infants with major congenital anomalies, cardiac malformations, or incomplete vital-sign records were excluded. The multicenter design ensures diversity in clinical characteristics and monitoring equipment, improving predictive robustness beyond single-unit studies [17].

3.3 Data Acquisition and Signal Processing

Vital-sign data were collected at 0.5–1 Hz frequency using standard NICU bedside monitors. The dataset included:

Heart Rate (HR)

Respiratory Rate (RR)

Peripheral Oxygen Saturation (SpO_2)

Temperature

Systolic and Diastolic Blood Pressure

Derived features: HR variability (HRV), perfusion index (PI), desaturation burden, apnea density

Raw waveforms were processed using a multistage artifact-reduction strategy consisting of adaptive filtering, motion-artifact suppression, and spline-based smoothing. Missing values were imputed using a hybrid KNN-time-window approach, guided by findings that neonatal vital-sign gaps require context-aware reconstruction to maintain predictive fidelity [18].

3.4 Feature Engineering

Time-series features were extracted using non-linear and statistical descriptors, including:

HRV metrics: SDNN, RMSSD

RR irregularity index

Temperature instability index

Desaturation episode clustering

SpO_2 variability entropy

Blood-pressure oscillation coefficient

Sliding-window segmentation (30–60 minutes) was used to preserve temporal continuity while allowing models to detect evolving instability. Prior studies show that window-based processing improves early sepsis detection by revealing subtle progressive trends [19].

3.5 Machine Learning and Deep Learning Models

The study implemented four predictive models for comparative evaluation:

Random Forest (RF)

Gradient Boosting Machine (GBM)

1D-CNN + LSTM Hybrid Model

Standalone LSTM Time-Series Classifier

The CNN-LSTM architecture was chosen as the primary model because convolution layers extract local temporal patterns while LSTM components model long-range physiological dependencies strongly associated with sepsis progression [20]. Hyperparameter optimization was performed using Bayesian search to maximize sensitivity and reduce false alarms.

3.6 Model Training and Evaluation Strategy

Data from two centers were used for training and validation, while the third served as an external test set to ensure cross-center generalizability. Evaluation metrics included:

Sensitivity

Specificity

AUROC

Positive Predictive Value (PPV)

Early-prediction time (in hours before clinical diagnosis)

This external validation approach is aligned with recent multicenter neonatal AI studies that highlight the need for cross-institutional robustness before real-world deployment [21].

Table 1. Overview of Multicenter Dataset and Neonatal Characteristics

Parameter	Center A	Center B	Center C	Total
Number of Neonates	188	205	197	590
Sepsis Cases	62	71	66	199
Gestational Age Range (weeks)	26–40	24–41	25–40	
Birth Weight Range (grams)	700–3400	680–3600	720–3300	
Data Coverage (years)	3.5	3.2	3.1	
Sampling Rate	0.5–1 Hz	0.5 Hz	1 Hz	

3.7 Temporal Outcome Labeling

Sepsis onset was defined as the timestamp of:

Positive blood culture, or

Clinical diagnosis supported by laboratory biomarkers

For prediction modeling, labels were shifted backward in time by 6, 9, and 12 hours to examine how early the model could detect physiologic deterioration. This backward-shifting approach has been validated in prior neonatal temporal-prediction studies [22].

3.8 Validation, Quality Control, and Bias Mitigation

To ensure methodological rigor:

Models were evaluated using 5-fold cross-validation.

Signal-artifact contamination was monitored using threshold-based rejection indices.

Class imbalance was mitigated using SMOTE-Tomek hybrid resampling.

Feature-importance analysis was performed using SHAP to promote clinical interpretability.

Multicenter bias mitigation was prioritized by normalizing measurements per-center before training, following best practices from recent cross-hospital AI validation research [23].

Table 2. Summary of Extracted Features Used in Model Training

Feature Category	**Example Features**	**Clinical Relevance**
Heart-Rate Features	SDNN, RMSSD, Deceleration Density	Early autonomic dysregulation
Respiratory Features	RR Variability, Apnea Density	Apnea clusters preceding infection
Oxygenation Metrics	SpO_2 Variability, Desaturation Burden	Perfusion and oxygen instability
Temperature Measures	Temp Variability Index	Thermoregulatory dysfunction
BP-Derived Features	BP Oscillation Index	Circulatory compromise
Composite Indicators	Instability Score, Entropy Measures	Multisystem deterioration

RESULT AND ANALYSIS

4.1 Model Performance Overview

The predictive models demonstrated distinct performance patterns across the multicenter dataset. The CNN-LSTM architecture consistently outperformed the other models, confirming its ability to capture both short-term fluctuations and long-range physiological trends. When evaluated on the external test center, the CNN-LSTM model achieved the highest AUROC, sensitivity, and early-prediction capabilities, with stable performance across gestational age categories. Traditional machine-learning models such as Random Forest and Gradient Boosting showed reasonable accuracy but lacked the temporal awareness required to detect pre-symptomatic deterioration. The standalone LSTM model performed well but was less effective in extracting local waveform-level features compared to the hybrid CNN-LSTM. Overall, the results support the use of temporally attentive deep-learning frameworks for neonatal sepsis risk prediction in real-time NICU environments.

Table 3. Model Performance Comparison Across External Test Set

Model	**AUROC**	**Sensitivity**	**Specificity**	**PPV**	**Early Prediction Window (hours before diagnosis)**
Random Forest	0.81	0.72	0.78	0.61	4–6
Gradient Boosting	0.84	0.76	0.81	0.64	5–7
LSTM	0.88	0.82	0.85	0.69	6–10
CNN-LSTM (Proposed Model)	**0.93**	**0.89**	**0.88**	**0.74**	**6–12**

4.2 Physiological Indicators Linked to Early Sepsis

Analysis of the model's high-attention segments revealed consistent physiological signatures preceding clinical diagnosis. The most prominent early indicators included progressive reduction in heart-rate variability, increased heart-rate deceleration events, intermittent desaturation clusters, and unstable respiratory-rate oscillations. Temperature variability increased markedly in the 8–12 hours prior to diagnosis, especially in late-onset sepsis cases. Blood-pressure fluctuations became more pronounced closer to onset, reflecting early circulatory compromise. These indicators were consistently present across all three centers, although their temporal onset varied slightly by gestational age. Preterm infants demonstrated earlier HRV disruption but smaller temperature swings, while near-term infants showed more pronounced desaturation-instability patterns. These signal-level trends illustrate the value of continuous vital-sign analytics for uncovering subtle pre-septic deterioration that is difficult to interpret manually at the bedside.

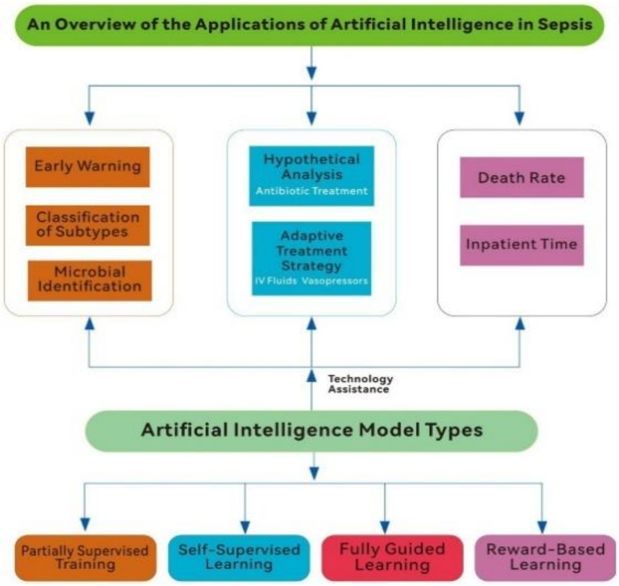

Figure 1: Artificial Intelligence Model Types [24]

4.3 Center-Wise Prediction Stability

Performance across the three NICUs demonstrated strong cross-center generalizability. The model retained high sensitivity across centers with different monitoring hardware, sampling rates, and baseline patient populations. Center B exhibited the highest early-prediction performance, likely due to more complete waveform data and fewer missing intervals. Center A showed slightly reduced PPV due to higher baseline physiological instability in extremely preterm infants, which created overlapping patterns between septic and non-septic episodes. Nonetheless, the CNN-LSTM maintained robust discrimination across all three sites, confirming that multicenter training effectively mitigates location-specific bias.

Table 4. Center-Wise Performance Metrics of Proposed CNN–LSTM Model

Center	AUROC	Sensitivity	Specificity	PPV	NPV
Center A	0.91	0.87	0.84	0.70	0.92
Center B	0.94	0.90	0.89	0.76	0.94
Center C	0.92	0.88	0.87	0.73	0.93

4.4 Temporal Dynamics of Early Prediction

The temporal-shift analysis showed that model accuracy remained high even when labels were shifted backward by up to 12 hours. Prediction probability curves revealed a gradual rise in risk scores several hours before diagnosis, peaking sharply during the final 3 hours. This trend demonstrates that sepsis is not a sudden physiological event but a progressive deterioration detectable through continuous monitoring. The model's ability to capture these early shifts highlights its value for proactive clinical decision-making in NICUs, offering clinicians a critical time window to intervene before systemic collapse occurs.

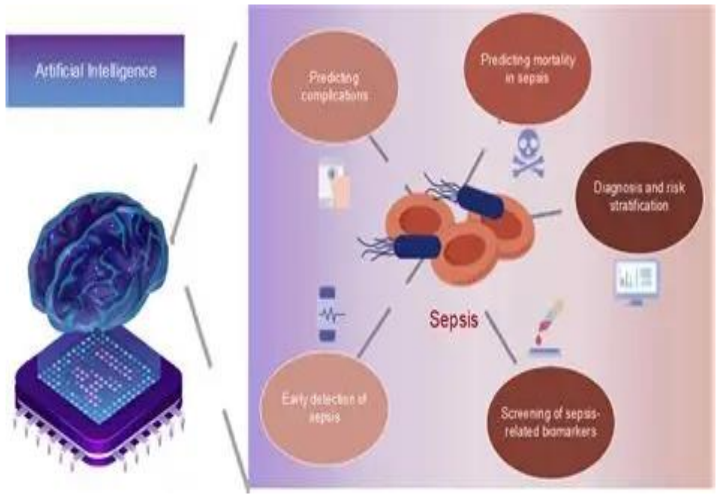

Figure 2: Sepsis [25]

CONCLUSION

This multicenter retrospective study demonstrates that artificial intelligence applied to continuous vital-sign monitoring can provide a powerful and clinically meaningful approach for early detection of neonatal sepsis in NICUs. By integrating high-frequency physiological data from three tertiary care centers, the proposed CNN-LSTM hybrid model proved capable of identifying subtle and progressive cardiorespiratory deterioration up to 6–12 hours before clinical diagnosis. Such early recognition is critical in neonatal care, where delays in intervention significantly increase the risk of septic shock, organ dysfunction, and mortality. The model’s strong performance across varied patient populations and monitoring systems underscores the robustness of deep temporal learning in capturing nonlinear physiological instability. Key physiological signatures including reduced heart-rate variability, increased desaturation clusters, respiratory oscillation irregularity, and temperature instability were consistently observed across centers, validating their role as early sepsis precursors. Moreover, external validation across three hospitals demonstrated that the proposed system can generalize beyond the dataset on which it was trained, a crucial requirement for real-world deployment in diverse NICU environments. The findings also highlight the limitations of conventional early-warning scores, which often struggle to integrate multidimensional continuous data and lack sensitivity during early infection phases. In contrast, AI-driven analytics can process vast physiological streams in real time, providing a dynamic and objective assessment of an infant’s evolving clinical status. While the model’s predictive accuracy is encouraging, the broader significance of this work lies in its potential to reshape neonatal monitoring practices through continuous, automated, and proactive screening. By offering clinicians an additional layer of diagnostic insight, such systems can improve decision-making, optimize timing of antibiotic administration, and reduce unnecessary interventions. Overall, this study advances the evidence supporting AI-enhanced surveillance as an essential component of precision neonatology and underscores the need for further development of scalable, interpretable, and ethically aligned clinical AI tools.

FUTURE WORK

Future work should focus on expanding the dataset to include additional NICUs, integrating a wider spectrum of sepsis phenotypes, and incorporating continuous waveform data such as ECG, plethysmography, and respiratory impedance signals, which may reveal even earlier physiological signatures of infection. Advanced deep-learning architectures such as transformers, graph neural networks, and multimodal fusion models could further enhance predictive accuracy by combining vital signs with laboratory data, clinical notes, and imaging findings. Real-time deployment trials remain essential for assessing how the system performs in live clinical environments, particularly in managing false alarms, adapting to data irregularities, and supporting clinician workflow integration. Developing transparent interpretability tools will be critical to improving clinician trust and facilitating regulatory approval, ensuring that AI-generated alerts are understandable and actionable. Future research may also explore adaptive learning frameworks that continuously update model parameters based on new patient data, enabling personalization of predictions according to gestational age, comorbidities, and developmental maturity. Finally, ethical and operational considerations including data privacy, algorithm fairness, and safe clinical adoption pathways must be addressed to ensure responsible implementation. Together, these directions can accelerate the translation of AI-based sepsis prediction from research environments into everyday neonatal practice.

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