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Comparative Evaluation of Python-based Heart Rate Variability Analysis Tools for Neonatal Sepsis Detection in Neonatal Intensive Care Units

Roshan David Jathanna[1], Dinesh Acharya Udupi[1]*, Faiza Iqbal[2], Krishnamoorthi Makkithaya[1] and Leslie Edward Simon Lewis[2]

[1]*Department of Computer Science and Engineering, Manipal Institute of Technology, Manipal Academy of Higher Education, Manipal, 576104, Karnataka, India*

[2]*Department of Pediatrics, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, 576104, Karnataka, India*

ABSTRACT

Neonatal sepsis is a severe systemic infection occurring within the first month of life and remains a significant cause of morbidity and mortality worldwide, particularly in low- and middle-income (LMICs). Despite advancements in medical care, challenges such as limited healthcare access and inadequate diagnostic capabilities persist. This study explores the impact of real-time data analytics on managing neonatal sepsis, highlighting its potential to enhance early detection, diagnosis, and treatment outcomes in neonatal intensive care units (NICUs) in LMICs. This study provides an architecture for continuously monitoring neonates using cardiopulmonary monitors and applying real-time analysis to identify sepsis onset. Data from eight infants were collected and analyzed, with each ECG signal recorded at 500 Hz, generating 36 to 126 million samples per channel. The study compared four Python packages for Heart Rate Variability (HRV) computation (NeuroKit2, HRV, HeartPy, Systole) based on features, computational efficiency, and ease of use. NeuroKit2 provided the most features but had the highest computational load, while Systole and HeartPy offered a balance of functionality and efficiency. The findings underscore the potential of real-time data analytics in improving neonatal sepsis management. Early diagnostic testing and advanced monitoring technologies can significantly enhance neonatal outcomes, particularly in resource-limited settings. These technological advancements align with Sustainable Development Goal Target 3.2 and underscore the need for continued research, policy support, and collaborative efforts to reduce neonatal mortality globally.

Keywords: Low- and middle-income countries, neonatal intensive care unit, neonatal mortality, neonatal sepsis, real-time data analytics, sustainable development goal 3.2

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E-mail addresses:
roshan.jathanna@manipal.edu (Roshan David Jathanna)
dinesh.acharya@manipal.edu (Dinesh Acharya Udupi)
faizaifra@yahoo.in (Faiza Iqbal)
k.moorthi@manipal.edu (Krishnamoorthi Makkithaya)
leslie.lewis@manipal.edu (Leslie Edward Simon Lewis)
*Corresponding author

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INTRODUCTION

Neonate refers to a baby who is younger than four weeks old. Neonatal sepsis, characterized by systemic infection occurring within the first month of life, remains a critical healthcare challenge globally, particularly in low- and middle-income countries (LMICs). Despite advancements in medical care, neonatal sepsis continues to be a leading cause of morbidity and mortality among newborns. According to the World Health Organization (WHO, 2024) report, out of the 5 million deaths that occurred in the year 2022 in children under the age of five years globally, 2.3 million are neonates. In India, a significant proportion of child deaths under the age of five occur within the initial four weeks after birth. The Sustainable Development Goal (SDG) target 3.2 aims to reduce newborn mortality to 12 per 1,000 live births by 2030 (WHO, 2024). Neonatal Intensive Care Units (NICUs) specialize in providing care for sick or premature neonates, with medical practitioners at NICUs having saved countless lives of neonates born ill or prematurely. The management of neonatal sepsis in these settings is often hindered by a myriad of factors, including limited access to healthcare facilities, shortages of skilled healthcare providers, inadequate diagnostic capabilities, and challenges in accessing and affording lifesaving interventions. However, diagnosing neonatal infection can be challenging due to the subtle clinical features and the underdeveloped immune system of newborns. Therefore, maintaining a high index of suspicion for neonatal diseases and conducting early diagnostic testing, even without apparent clinical signs, is crucial.

A newborn's immune system overreacting to an infection can result in neonatal sepsis, a potentially fatal illness that causes systemic inflammation and septic shock. This inflammatory reaction may impair the blood supply to essential organs, depriving them of the nutrition and oxygen that they require, which may result in organ failure and even death. After preterm birth and birth asphyxia, neonatal sepsis ranks third among the leading causes of newborn mortality and continues to pose a severe risk (WHO, 2024). In LMICs, where healthcare systems are often strained, and resources are limited, the management of neonatal sepsis presents unique challenges. Early identification and prompt treatment are essential for improving outcomes, yet many healthcare facilities in LMICs lack the necessary tools and infrastructure to facilitate timely diagnosis and intervention. In LMICs, where healthcare systems are often strained and resources are limited, the management of neonatal sepsis presents unique challenges (Procianoy & Silveira, 2020). Early identification and prompt treatment are essential for improving outcomes, yet many healthcare facilities in LMICs lack the tools and infrastructure to facilitate timely diagnosis and intervention. However, amidst these challenges, recent advancements in healthcare technology, particularly in the realm of data analytics, offer promising opportunities to revolutionize the management of neonatal sepsis in LMICs (Bohanon et al., 2015; Fairchild et al., 2013; Jathanna et al., 2023; Khazaei et al., 2015; McGregor et al., 2012; Mithal et al., 2016; Moorman et al., 2011; Quinten et al., 2017; Wee et al., 2020).

Clinical Risk Index for Babies (CRIB) II is a scoring system used to predict mortality risk in very low birth weight infants, combining birth weight, gestational age, and other clinical factors obtained during the first 12 hours of admission to the NICU (Parry et al., 2003). Moorman et al. (2011) studied 3003 VLBW neonates in 9 NICU. The neonates were divided into two groups. The heart rate characteristics (HRC) of only one group were displayed to the clinicians. It was observed that the mortality rate reduced from 10.2% to 8.1% in the group whose HRC was displayed. This study indicates the importance of HRC in the NICU. SNAPPE-II (Score for Neonatal Acute Physiology with Perinatal Extension-II) is used to determine the severity of disease and identify the risk of fatality in neonates admitted to NICU. The score estimates the health state of the neonate by considering both perinatal and physiological parameters. Neonates with higher SNAPPE-II scores are susceptible to sepsis due to their compromised health condition (Harsha, 2015).

Fairchild et al. (2013) developed a monitor that analyses ECG and HRC for patterns to predict sepsis at an early stage. The algorithm calculates the heart rate observations (HeRO) score using standard duration on heartbeat interval, sample asymmetry and entropy. Sample asymmetry measures the skewing of heart rate, and sample entropy measures the irregularity of heart rate. The algorithm uses logistic regression to predict the probability of sepsis in the next 24 hours. HeRO score is calculated instantaneously but displayed hourly on the monitor. The proposed system requires investing in separate hardware devices. Further, clinical decision support could be improved by using other clinical factors. Iqbal et al. (2024) used machine learning (ML) models to predict culture-positive sepsis (CPS) and clinical sepsis (CNS) in neonates using a dataset of 90 essential variables. The study concluded that Random Forest (RF) and Bagging algorithms outperformed in predicting CPS and CNS, with RF achieving an accuracy of 98.4% and ROC of 0.994. Tachycardia, bradycardia, and the presence of a central line catheter were identified as predictors of CPS.

Khazaei et al. (2015) designed and developed an Artemis framework to acquire and store physiological and clinical data for real-time analytics and visual representation. The authors use cloud services to collect and integrate data from various healthcare services. Data from various patients and devices can be concurrently streamed and analyzed using temporal analysis. The system uses variables that decide the length of stay, such as features of gestation age and probabilities of condition onset. The system has been deployed in McMaster Children's Hospital, Canada and is being used by researchers to work on various infections in neonates, including sepsis. However, the proposed system requires devices that capture physiological data to output their data for collection through an Ethernet and/or serial port. Even if the current setup has devices that can output data through required ports, the hospitals may not be willing to allow external devices to connect to the existing devices. The other limitation is that the proposed framework uses proprietary software.

Mansoor et al. (2019) proposed a Modified Sick Neonatal Score (MSNS) tailored for resource-limited settings through a study conducted in India involving 585 neonates. It assesses disease severity at admission and shows statistically significant score differences between surviving and deceased neonates, with a cutoff score of ≤10 being highly predictive of mortality. This suggests that MSNS is a viable tool for evaluating neonatal disease severity in settings lacking advanced diagnostics, potentially guiding early interventions and referrals to higher-tier care facilities. Shirwaikar et al. (2015) used supervised ML techniques for the diagnosis of neonatal diseases. They found that the ensemble technique has better predictive power than the Support Vector Machine (SVM), decision trees, and neural networks.

Lipton et al. (2016) used RNN with long short-term memory (LSTM) to identify patterns in a multivariate time series of observations obtained from the intensive care unit (ICU). For the study, an anonymized clinical time series extracted from the EHR system at Children's Hospital, LA, of 10,401 NICU visits. They trained a model to classify 128 diagnoses given 13 frequently but irregularly sampled clinical measurements. The 13 variables were diastolic and systolic blood pressure, peripheral capillary refill rate, end-tidal CO_2, fraction of inspired O_2, glascow coma scale, blood glucose, heart rate, pH, respiratory rate, blood oxygen saturation, body temperature, and urine output. Episodes vary in length from 12 hours to several months. Their results indicate that LSTM RNNs, especially with target replication, can successfully classify diagnoses of critical care patients given clinical time series data.

Mithal et al. (2016) proposed an algorithm called RALIS that uses physiological parameters to detect sepsis in neonates approximately 2.5 days prior to the blood tests. The algorithm uses heart rate, respiratory rate, body temperature and weight, desaturations (<85%) and bradycardias (<100 beats per minute) to arrive at a score between 0 to 10. Any score above 5 for 6 hours was considered critical. The algorithm could correctly identify sepsis in 28 out of 34 cases of proven sepsis. The limitation of RALIS is that it falsely identified one out of four neonates to have sepsis, which is a critical concern as it results in the overuse of antibiotics. Iqbal et al. (2023) developed an ML model to predict the mortality of neonates using non-invasive vital sign data, as well as maternal and neonatal attributes using the WEKA tool. The study reviewed 388 neonates diagnosed with neonatal sepsis over five-years. The mortality rate was 39.6% (n = 154). The study used the "OneR attribute evaluation" method for feature selection, which identified several significant attributes, including birth weight, gestational age, and mode of delivery. The model performed well using the Logistic Regression algorithm, with an accuracy of 88.4% and a ROC of 0.906.

Joshi et al. (2020). Researchers combined features derived from Heart Rate Variability (HRV), breathing patterns, and estimated infant movement in preterm infants to improve the accuracy of sepsis prediction compared to using a single measure. This suggests that monitoring changes like abnormal heart rate patterns, irregular breathing, and decreased movement, all captured through readily available physiological data, could be a valuable tool for the early detection of sepsis in newborns.

Leon et al. (2021) explored the use of HRV analysis with visibility graphs to predict LOS in premature infants. Researchers compared HRV data from infants who developed LOS (receiving antibiotics) to a control group. ML analysis incorporating visibility graph features achieved an accuracy of 87.7% (AUROC) in predicting LOS as early as 42 hours before antibiotics, suggesting its potential as a non-invasive tool for early detection and improved outcomes. However, further research with larger studies is needed to confirm these findings. Rao et al. (2024) presented a systematic literature review of predictive analytics methods for early diagnosis of neonatal sepsis, highlighting their potential to improve healthcare management. The study reviews 16 studies between 2014 and 2024, including prospective and retrospective data, and utilizing various predictive modeling techniques, such as ML and Deep Learning (DL). The study concluded that ML algorithms have high effectiveness in predicting neonatal sepsis and have the potential to improve the early diagnosis of neonatal sepsis.

McAdams et al. (2022) have used a classification stacking model to predict four main neonatal diseases: sepsis, birth asphyxia, necrotizing enterocolitis (NEC), and respiratory distress syndrome, which together account for 75% of neonatal deaths. The dataset was collected from Asella Comprehensive Hospital between 2018 and 2021. Comparisons were made with three other ML models (Xtreme Gradient Boosting, Random Forest, and SVM), and the developed stacking model demonstrated superior performance. The findings suggest that ML can significantly contribute to early detection and accurate diagnosis of neonatal diseases, particularly in resource-limited healthcare facilities. Zeigler et al. (2023) explored the efficacy of the HeRO score and neonatal sequential organ failure assessment(nSOFA) in predicting sepsis and mortality among very low birth weight infants. From 2011 to 2019 data, the study reveals that the HeRO score can serve as an early alert for late-onset sepsis, while the nSOFA score, especially when assessed 12 hours after a blood culture, accurately predicts mortality. This suggests that leveraging both HeRO and nSOFA scores could significantly improve clinical outcomes for these infants.

A heart rate that is complicated and continually changing indicates good health. Various algorithms have been proposed to calculate the HRV from raw ECG signals. Time domain indices use variance in time intervals between consecutive heartbeats to quantify the HRV. The frequency domain uses power distribution among four bands to compute HRV. The non-linear domain appropriately describes the unpredictability of a time series (Chiera et al., 2020; Wee et al., 2020). HRV has become an easy-to-capture and dependable marker for the early identification of many diseases and abnormalities in neonates, including sepsis. Despite its promising clinical applications, HRV remains underutilized in the NICU (Chiera et al., 2020). This gap between research and practice can be attributed to a confluence of factors, impacting the implementation of this potentially valuable tool for monitoring and managing the delicate health of premature and sick neonates:

- Lack of Standardized Protocols: Variations in electrode placement, recording duration, signal processing techniques, and chosen analysis parameters significantly impact HRV measurements, making data interpretation and comparisons across studies and clinical settings challenging. Establishing reliable clinical benchmarks and translating research findings into practice necessitates the development of consensus guidelines encompassing best practices for data acquisition, analysis, and reporting (Latremouille et al., 2021).
- Lack of Normative Data: A limited amount of normative data is available for HRV parameters in neonates, particularly for preterm and sick infants. This makes it challenging to establish reference ranges and interpret HRV values accurately (Chiera et al., 2020; Kurul et al., 2022).
- Dynamic HRV Patterns in Early Life: A newborn's nervous system is still developing, especially an autonomic nervous system that controls heart rate. This ongoing maturation process causes rapid shifts in HRV patterns during the first few weeks and months. Because HRV is constantly changing, interpreting individual results and setting reference ranges becomes trickier in this early stage (Chiera et al., 2020; Patural et al., 2022).
- Influence of external factors: HRV assessment in neonates can be influenced by various external factors, such as sleep-wake cycles, feeding patterns, and environmental stimuli like loud noises or uncomfortable temperatures. Controlling these factors can be challenging, leading to potential confounding effects on HRV measurements (Chiera et al., 2020; Statello et al., 2021).
- Practical Implementation Challenges: The specialized equipment, software, personnel training, data storage, and management systems required for accurate HRV measurement and analysis can be expensive, particularly for NICU units with limited resources (Arslantas & Ozdemir, 2020; McGregor et al., 2012; Moorman et al., 2011; Ranjit & Kissoon, 2021; Statello et al., 2021).

Real-time data analytics, powered by advances in digital health platforms, electronic health records (EHRs), and mobile health technologies, enable healthcare providers to collect, analyze, and act upon clinical data in real time. By leveraging these technologies, healthcare providers can rapidly identify and respond to cases of neonatal sepsis, improve diagnostic accuracy, optimize treatment strategies, and ultimately reduce newborn morbidity and mortality rates. This paper aims to explore the transformative impact of real-time data analytics on neonatal sepsis management, shedding light on its potential to revolutionize healthcare delivery and outcomes for newborns in LMICs and beyond. Based on the literature review, it is evident that there is a need for a real-time data capture, storage, and processing system in NICU that uses the existing setup and does not require a huge investment in proprietary software or hardware.

MATERIALS AND METHODS

Study Setting

This study was conducted at the NICU of Kasturba Hospital, Manipal, Karnataka, India. Ethical approval was obtained from the Institutional Ethics Committee (IEC: 350/2018) of Kasturba Hospital. Each infant admitted to the NICU at Kasturba Hospital underwent continuous monitoring using a Philips Intellivue MP 20/30 cardiopulmonary monitor. This monitoring device employs electrodes attached to the infant to measure vital parameters, including heart activity, blood oxygen saturation (O_2 sat), blood pressure, and respiratory rate. The cardiopulmonary monitors from various beds were interconnected to a central monitoring system (M3140 Low Acuity Information Center, CPQ0A80 HP RP5700 Business System), facilitating simultaneous data display from different beds, as depicted in Figure 1. To ensure patient confidentiality, the collected data were de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) guidelines before integration into the newly proposed NICU database. Adhering to the safe harbor method outlined in the HIPAA Privacy Rule guidelines, specific identifiers that could potentially reveal an individual's identity, such as names, addresses, dates of birth,

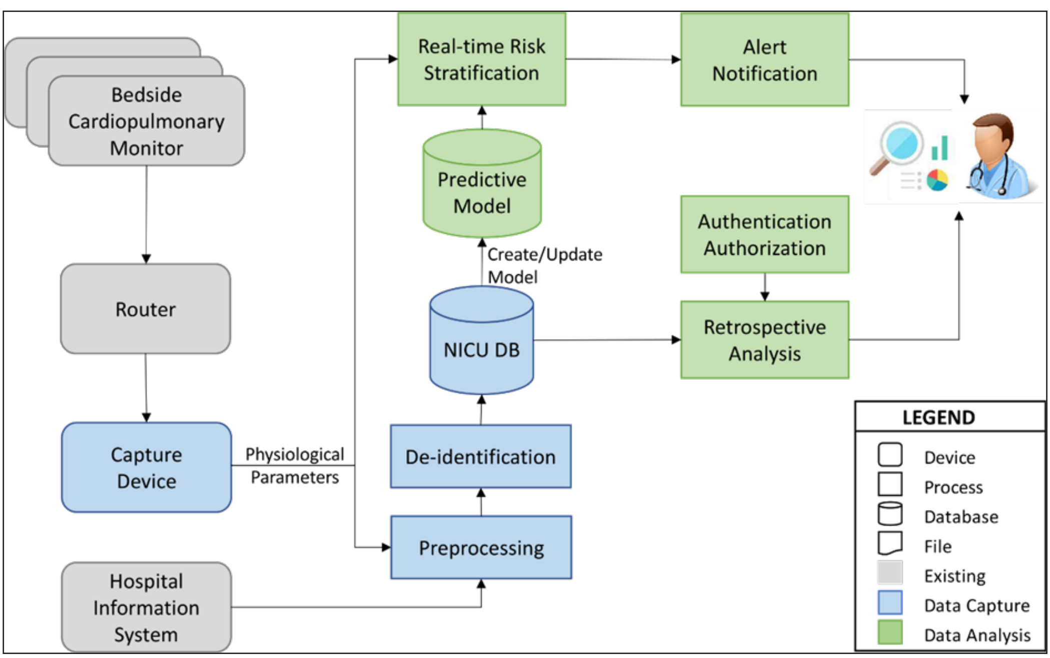

Figure 1. Overall architecture

admission dates, contact information, and unique identifiers, were removed or de-identified from the dataset. This meticulous de-identification process effectively mitigated the risk of unintentional disclosure of protected health information, safeguarding patient privacy and ensuring compliance with HIPAA regulations (Moore & Frye, 2019).

Data Capture and Decoding

Cardiopulmonary monitors from various beds connect to the central monitoring system through an ethernet switch using the LAN interface. The capture device will replace the central monitoring system. The capture device is a Windows 10 PC with a capture service, upload service, and an influxdb time-series database, as shown in Figure 2.

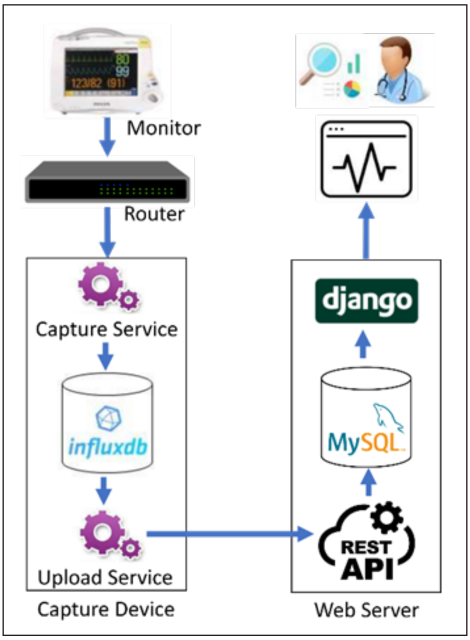

Figure 2. Data capture

The capture service is a Windows service written in C# programming language that communicates with monitors and processes and stores data in the influxdb database. The Windows service extends VSCaptureMP (Karippacheril & Ho, 2013), a high-fidelity datalogging software platform. The monitors communicate using the Universal Datagram Protocol/Internet Protocol (UDP/IP). All the monitors periodically broadcasted the connection indication messages with device information through the UDP port 24005 until a central monitoring system established a logical connection. The connection indication message also contains a UDP port (default is 24105) that the protocol will use for further communication. The capture device will receive this connection indication message and respond with the association request, as shown in Figure 3. The monitor responds with an association response indicating whether the association was successful. In the case of a successful association, the monitor sends a medical device system (MDS) message to create an event with system information and configuration. After successful association, the capture device sends poll data requests for numeric and wave data. The monitor responds with the requested data. The association release request is sent from the capture device whenever the association needs to be closed.

The capture device decodes the data received using the steps shown in Figure 4. The data received are first validated to ensure that they only contain hexadecimal characters.

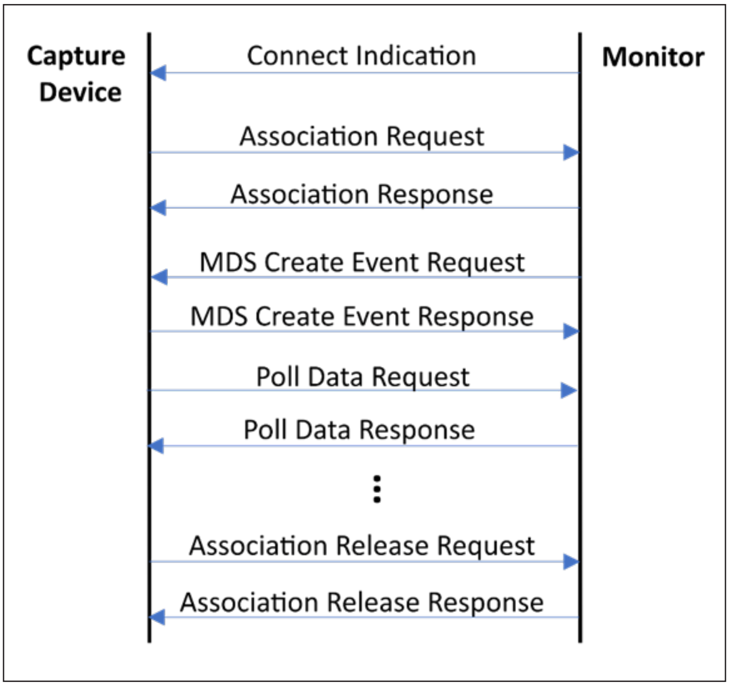

Figure 3. Protocol dialog between philips intellivue monitor and capture device

Once validated, the data is converted to an 8-bit unsigned integer. The session_id is present in the first two bytes, and if it has a fixed value of 0xE100, then the packet contains data export commands. The frame length is at the 6th and 7th bytes. The remote operation (RO) and the command types start at the 4th and 10th bytes, respectively. The packet contains physiological data if the RO type is 1 or 2 and the command type is 0. The following 14 bytes are skipped, and the rest of the packet is traversed to find either physiological numeric or wave keys. There are 932 and 47 physiological numeric and wave keys, respectively (Philips, 2015). The developed software only captures and displays the values of the physiological keys mentioned in Table 1, which are essential for detecting sepsis. The data includes the measurement state, the unit code and the value. The capture device creates a JSON object with physiological parameter values and sends it to the web server using representational state transfer (ReST) API calls. The web server receives the data and stores it in the database. For real-time monitoring, the web server features a web page designed to display the data in real time. Using JavaScript's setTimeout function, the web page periodically initiates ReST API calls to the server for continuous updates of current values. Moreover, incorporating the requestAnimationFrame method signals the browser to prepare for an animation update prior to the next repaint, optimizing the user's visual experience.

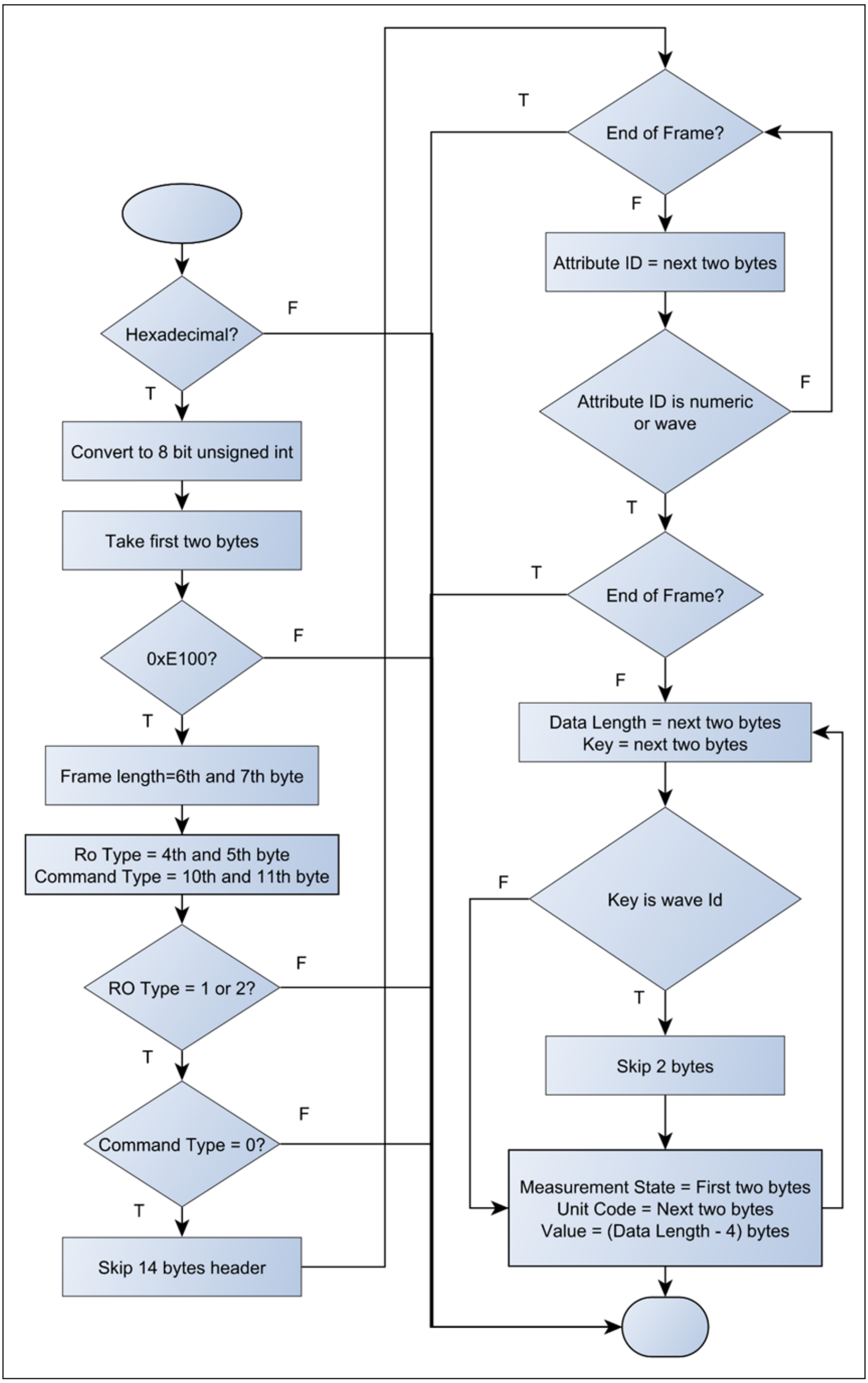

Figure 4. Data decoding

The upload service is a Windows service written in the C# programming language to periodically retrieve data from the influxdb database and upload it to the web server using the representational state transfer (ReST) API calls. The ReST API uses the Django framework and saves the physiological data in the MySQL database.

Table 1
Physiological ID with units

Physiological Id	**Description**	**Units**
0X4BB8	Arterial Oxygen Saturation (SpO_2)	Percentage
0X4822	Pulse rate	Beats per minute
0X4182	Heart rate	Beats per minute
0X500A	Respiration rate	Respiration per minute
0x0102	ECG Lead II	Milli-volt

Data Mapping

Other necessary information on neonates, such as maternal data, radiographic findings, and laboratory data from the current hospital information system, is pre-processed, de-identified, and mapped to bedside data before being integrated into the NICU database. A website with two web pages was developed to ease the mapping. The first webpage shows the list of bedside monitors from which data were not received for 30 minutes, indicating that the baby on the bed may have changed. A waiting time of 30 minutes is proposed to rule out device errors.

The mapping is performed by clicking the 'map' button, which opens the web page shown in Figure 5. Details such as the reason for not receiving data and the new patient ID must be entered. The reason for not receiving data can be a device error, a shift because of

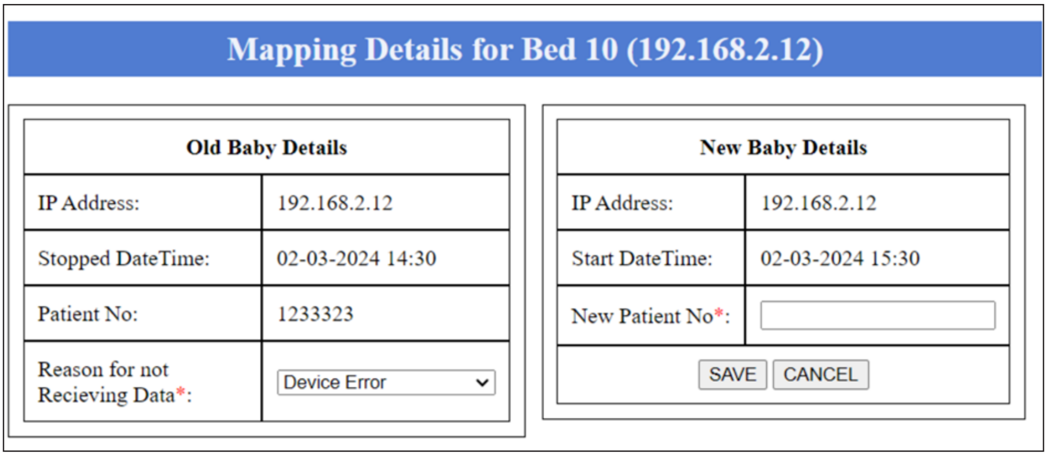

Figure 5. Webpage to map bed to baby

sepsis, a shift to another bed or discharge from the NICU. The stakeholders can view real-time physiological data of all neonates using the responsive website, which was developed using the Django framework. Historical physiological data and various neonatal scores of the selected neonates are displayed after they click the cell for a particular bed.

The major challenge in storing data from monitors in the NICU is the generation of high-frequency ECG data for each neonate. The ECG data can be stored as they are or can be compressed (Jha & Kolekar, 2022). In this study, ECG data were stored without compression. We compared and evaluated four popular Python packages used for computing HRVs from ECG signals, such as Neurokit2 (Makowski et al., 2021), HRV (Bartels & Peçanha, 2020), HeartPy (van Gent et al., 2019) and Systole (Legrand & Allen, 2022). The comparison focused on assessing the performance, dependencies, memory consumption, and ease of use of packages. The goal was to provide insights into the strengths and limitations of each package, enabling researchers and developers to make informed choices when selecting the appropriate tool for their HRV analysis needs.

Real-time Risk Stratification

The physiological data from the capturing device is analyzed in real time using predictive models to detect the onset of complications. Neonates will be scored using various scoring schemes, such as CRIB II (Parry et al., 2003), SIRS (Poggi et al., 2023), SNAPPE-II (Harsha, 2015), MSNS (Mansoor et al., 2019) and nSOFA (Berka et al., 2022). If the score crosses the permissible limit, appropriate stakeholders will be notified through an alert notification system.

Authentication and Authorization

All the data in the NICU database can only be accessed with proper credentials. Authentication determines whether a user can access the data. The authorization will control what part of the information the user can access.

Retrospective Analysis

Researchers can use the data collected in the NICU database for retrospective analysis with proper consent from Kasturba Hospital's ethical committee. With the committee's approval, credentials with appropriate permission will be created.

RESULTS AND DISCUSSION

Data from eight infants depicted in Table 2 was collected using a single-channel electrocardiogram (ECG) signal from a 3-lead ECG setup on bedside patient monitors (Gee et al., 2017; Goldberger et al., 2000). Each ECG signal was recorded at a sampling rate of 500 Hz, resulting in 500 data points per second. The recording durations ranged from approximately 20 to 70 hours per infant, resulting in a data volume of 36 million to 126 million samples per channel. A 10-minute segment of each ECG recording (600 seconds) was extracted, resulting in 300,000 data points per baby used for HRV computation. The study assessed computational efficiency by measuring the average time taken and the average number of function calls during the HRV calculation process on the 10-minute data samples.

Table 2
Summary of dataset

Subject	Weight (kg)	Postconceptional Age (weeks)
Infant 1	1.76	30.71
Infant 2	1.71	30.71
Infant 3	0.84	30.14
Infant 4	1.14	30.14
Infant 5	1.11	30.14
Infant 6	2.10	32.43
Infant 7	1.23	30.57
Infant 8	1.90	34.29

The computational efficiency of various Python packages for HRV calculation was evaluated by comparing the number of features each package offers, as illustrated in Figure 6(a). NeuroKit2 stands out with the highest number of features, offering a total of 89 features. This extensive functionality makes it a comprehensive tool for HRV analysis but may also contribute to longer processing times and higher computational demands. In contrast, the HRV package offers the fewest features, with only 7, suggesting that it may be suitable for simpler HRV analysis tasks where computational efficiency is prioritized over the range of available features. HeartPy provides a moderate number of features, with 23 indicating that it can deliver efficient performance while still offering a reasonable range of HRV analysis capabilities. Similarly, Systole provides 32 features, balancing computational efficiency and the breadth of HRV analysis functionalities.

Further analysis of the packages included the number of function calls and primitive calls, as shown in Figures 6(b) and 6(c). NeuroKit2 again showed the highest computational load, with 5,952,381 function calls and 5,754,083 primitive calls. The HRV package showed significantly fewer function calls at 2,400,222 and 2,400,218 primitive calls. HeartPy demonstrated much lower values, with 60,740 function calls and 60,651 primitive calls, reflecting its more efficient performance. Systole also showed superior computational efficiency, with 35,208 function calls and 34,803 primitive calls.

NeuroKit2 is the most popular package, with 862 stars, reflecting its extensive community support and usage. HeartPy follows with 689 stars, indicating significant popularity. The HRV package has 160 stars, and Systole has 55 stars, showing relatively lower popularity, as depicted in Figure 6(d). The number of required packages for each tool varies, with NeuroKit2 requiring the most dependencies (862), HeartPy (689), HRV (160), and Systole (55), as seen in Figure 6(e). This indicates the complexity and potential setup effort needed for each package. The time taken for HRV computation was also measured, with NeuroKit2 taking the longest at 4.94 seconds. The HRV package took 2.28 seconds, HeartPy took 0.8 seconds, and Systole was the fastest, taking only 0.6 seconds as seen in Figure 6(f). This highlights the differences in computational efficiency among the packages, with Systole and HeartPy being the most efficient, followed by HRV. Then, NeuroKit2 is the least efficient in terms of time taken. In summary, NeuroKit2, despite its comprehensive functionality and popularity, requires a significant number of dependencies, potentially complicating its setup and use. HeartPy and Systole offer a balance of popularity and manageable dependency requirements, making them more accessible. The HRV package, while less popular, has the least number of dependencies, simplifying its installation and use. This evaluation helps in selecting the most suitable Python package for HRV calculation based on the specific needs and constraints of the study.

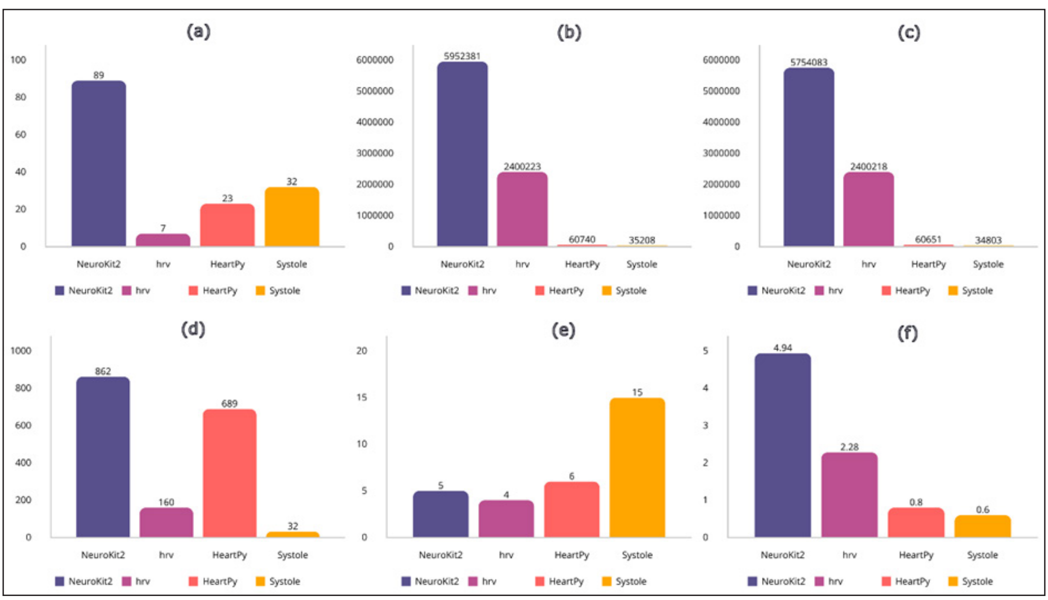

Figure 6. Comparison of various python packages (a) Number of features (b) Function calls (c) Primitive calls (d) Stars in GitHub (e) Required packages (f) Time Taken (in milliseconds)

CONCLUSION

Based on the findings of this study, neonatal mortality, mainly due to conditions such as neonatal sepsis, remains a significant global health challenge. As we navigate through the complexities of neonatal care, particularly in the context of India, where a substantial proportion of child deaths under five occur within the first month of life, the indispensable role of NICUs and advanced technological interventions comes to the forefront. In conclusion, this study sheds light on the critical challenges faced in reducing neonatal mortality and highlights promising pathways forged by technological and clinical advancements. Integrating real-time data analysis, predictive modeling, and comprehensive physiological monitoring presents hope for enhancing neonatal outcomes, particularly in LMICs. These innovations must be embraced and scaled up as we move forward, paving the way for a future where neonatal mortality is significantly reduced. In alignment with Sustainable Development Goal target 3.2, which aims to end preventable deaths of newborns and children under five years. Through collaborative efforts, continued research, and policy support, we can ensure that the most vulnerable populations receive the care and protection they need during the most critical phase of life.

Limitations of the Study

The primary limitation of this study lies in the inconsistency across the NICU infrastructures, which can affect the adaptability of systems in other settings. Variability in monitoring equipment, regulatory requirements, and IT resources across regions could also impede seamless integration, especially in under-resourced NICUs. Furthermore, the storage of high-frequency, uncompressed ECG data demands substantial computational and storage resources, limiting scalability. Reliance on specific hardware (e.g., Philips monitors) and software configurations also constrains generalizability, potentially requiring additional compatibility adjustments for broader implementation.

Future Directions and Recommendations

Future work could enhance the predictive accuracy of the system by adding various clinical parameters, such as maternal health data and laboratory biomarkers, to allow personalized risk assessments. Exploring other data compression techniques can also improve storage and affirm efficiency in data-intensive settings. Further research could evaluate emerging HRV analysis tools and ML methods for anomaly detection, broadening analytical capabilities. Finally, multi-site validation studies would help standardize protocols across diverse NICUs, facilitating larger-scale adoption and improving generalizability.

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REFERENCES

Arslantas, M. K., & Ozdemir, H. (2020). Sepsis management in resource-limited settings. *Anesthesia & Analgesia*, *130*(2), Article e37. https://doi.org/10.1213/ANE.0000000000004536

Bartels, R., & Peçanha, T. (2020). HRV: A pythonic package for heart rate variability analysis. *Journal of Open Source Software*, *5*(51), Article 1867. https://doi.org/10.21105/joss.01867

Berka, I., Korček, P., Janota, J., & Straňák, Z. (2022). Neonatal sequential organ failure assessment (nSOFA) score within 72 hours after birth reliably predicts mortality and serious morbidity in very preterm infants. *Diagnostics*, *12*(6), Article 1342. https://doi.org/10.3390/diagnostics12061342

Bohanon, F. J., Mrazek, A. A., Shabana, M. T., Mims, S., Radhakrishnan, G. L., Kramer, G. C., & Radhakrishnan, R. S. (2015). Heart rate variability analysis is more sensitive at identifying neonatal sepsis than conventional vital signs. *The American Journal of Surgery*, *210*(4), 661–667. https://doi.org/10.1016/j.amjsurg.2015.06.002

Chiera, M., Cerritelli, F., Casini, A., Barsotti, N., Boschiero, D., Cavigioli, F., Corti, C. G., & Manzotti, A. (2020). Heart rate variability in the perinatal period: A critical and conceptual review. *Frontiers in Neuroscience*, *14*, 1–23. https://doi.org/10.3389/fnins.2020.561186

Fairchild, K. D., Schelonka, R. L., Kaufman, D. A., Carlo, W. A., Kattwinkel, J., Porcelli, P. J., Navarrete, C. T., Bancalari, E., Aschner, J. L., Walker, M. W., Perez, J. A., Palmer, C., Lake, D. E., O'Shea, T. M., & Moorman, J. R. (2013). Septicemia mortality reduction in neonates in a heart rate characteristics monitoring trial. *Pediatric Research*, *74*(5), 570–575. https://doi.org/10.1038/pr.2013.136

Gee, A. H., Barbieri, R., Paydarfar, D., & Indic, P. (2017). Predicting bradycardia in preterm infants using point process analysis of heart rate. *IEEE Transactions on Biomedical Engineering*, *64*(9), 2300–2308. https://doi.org/10.1109/TBME.2016.2632746

Goldberger, A. L., Amaral, L. A. N., Glass, L., Hausdorff, J. M., Ivanov, P. Ch., Mark, R. G., Mietus, J. E., Moody, G. B., Peng, C. K., & Stanley, H. E. (2000). PhysioBank, PhysioToolkit, and PhysioNet: Components of a new research resource for complex physiologic signals. *Circulation, 101*(23), e215-e220. https://doi.org/10.1161/01.CIR.101.23.e215

Harsha, S. S. (2015). SNAPPE-II (score for neonatal acute physiology with perinatal extension-II) in predicting mortality and morbidity in NICU. *Journal of Clinical and Diagnostic Research*, *9*(10), SC10–SC12. https://doi.org/10.7860/JCDR/2015/14848.6677

Iqbal, F., Chandra, P., Khan, A. A., Lewis, L. E. S., Acharya, D., Vandana, K. E., Jayashree, P., & Shenoy, P. A. (2023). Prediction of mortality among neonates with sepsis in the neonatal intensive care unit: A machine learning approach: Prediction of Mortality in neonates. *Clinical Epidemiology and Global Health*, *24*, Article 101414. https://doi.org/10.1016/j.cegh.2023.101414

Iqbal, F., Chandra, P., Lewis, L. E. S., Acharya, D., Purkayastha, J., Shenoy, P. A., & Patil, A. K. (2024). Application of artificial intelligence to predict the sepsis in neonates admitted in neonatal intensive care unit. *Journal of Neonatal Nursing*, *30*(2), 141-147. https://doi.org/10.1016/j.jnn.2023.07.016

Jathanna, R. D., Acharya, D., Lewis, L. E. S., & Makkithaya, K. (2023). Early detection of late onset neonatal sepsis using machine learning algorithms. *Engineered Science*, *26*, Article 976. https://doi.org/10.30919/es976

Jha, C. K., & Kolekar, M. H. (2022). Electrocardiogram data compression techniques for cardiac healthcare systems: A methodological review. *IRBM*, *43*(3), 217–228. https://doi.org/10.1016/j.irbm.2021.06.007

Joshi, R., Kommers, D., Oosterwijk, L., Feijs, L., van Pul, C., & Andriessen, P. (2020). Predicting neonatal sepsis using features of heart rate variability, respiratory characteristics, and ECG-derived estimates of infant motion. *IEEE Journal of Biomedical and Health Informatics*, *24*(3), 681–692. https://doi.org/10.1109/JBHI.2019.2927463

Karippacheril, J., & Ho, T. (2013). Data acquisition from S/5 GE Datex anesthesia monitor using VSCapture: An open source.NET/Mono tool. *Journal of Anaesthesiology Clinical Pharmacology*, *29*(3), 423-424. https://doi.org/10.4103/0970-9185.117096

Khazaei, H., Mench-Bressan, N., McGregor, C., & Pugh, J. E. (2015). Health informatics for neonatal intensive care units: An analytical modeling perspective. *IEEE Journal of Translational Engineering in Health and Medicine*, *3*, 1–9. https://doi.org/10.1109/JTEHM.2015.2485268

Kurul, Ş., van Ackeren, N., Goos, T. G., Ramakers, C. R. B., Been, J. V., Kornelisse, R. F., Reiss, I. K. M., Simons, S. H. P., & Taal, H. R. (2022). Introducing heart rate variability monitoring combined with biomarker screening into a level IV NICU: A prospective implementation study. *European Journal of Pediatrics, 181*(9), 3331-3338. https://doi.org/10.1007/s00431-022-04534-4

Latremouille, S., Lam, J., Shalish, W., & Sant'Anna, G. (2021). Neonatal heart rate variability: A contemporary scoping review of analysis methods and clinical applications. *BMJ Open*, *11*(12), 1–18. https://doi.org/10.1136/bmjopen-2021-055209

Legrand, N., & Allen, M. (2022). Systole: A python package for cardiac signal synchrony and analysis. *Journal of Open Source Software*, *7*(69), Article 3832. https://doi.org/10.21105/joss.03832

Leon, C., Carrault, G., Pladys, P., & Beuchee, A. (2021). Early detection of late onset sepsis in premature infants using visibility graph analysis of heart rate variability. *IEEE Journal of Biomedical and Health Informatics*, *25*(4), 1006–1017. https://doi.org/10.1109/JBHI.2020.3021662

Lipton, Z. C., Kale, D. C., Elkan, C., & Wetzel, R. (2016). *Learning to Diagnose with LSTM Recurrent Neural Networks*. ArXiv Preprint. https://doi.org/10.48550/arXiv.1511.03677

Makowski, D., Pham, T., Lau, Z. J., Brammer, J. C., Lespinasse, F., Pham, H., Schölzel, C., & Chen, S. H. A. (2021). NeuroKit2: A python toolbox for neurophysiological signal processing. *Behavior Research Methods*, *53*(4), 1689–1696. https://doi.org/10.3758/s13428-020-01516-y

Mansoor, K. P., Ravikiran, S. R., Kulkarni, V., Baliga, K., Rao, S., Bhat, K. G., Baliga, B. S., & Kamath, N. (2019). Modified sick neonatal score (MSNS): A novel neonatal disease severity scoring system for resource-limited settings. *Critical Care Research and Practice*, *2019*, 1–6. https://doi.org/10.1155/2019/9059073

McAdams, R. M., Kaur, R., Sun, Y., Bindra, H., Cho, S. J., & Singh, H. (2022). Predicting clinical outcomes using artificial intelligence and machine learning in neonatal intensive care units: A systematic review. *Journal of Perinatology*, *42*(12), 1561–1575. https://doi.org/10.1038/s41372-022-01392-8

McGregor, C., Catley, C., & James, A. (2012). Variability analysis with analytics applied to physiological data streams from the neonatal intensive care unit. In *2012 25th IEEE International Symposium on Computer-Based Medical Systems (CBMS)* (pp. 1-5). IEEE Publishing. https://doi.org/10.1109/CBMS.2012.6266385

Mithal, L. B., Yogev, R., Palac, H., Gur, I., & Mestan, K. K. (2016). Computerized vital signs analysis and late onset infections in extremely low gestational age infants. *Journal of Perinatal Medicine*, *44*(5), 491-497. https://doi.org/10.1515/jpm-2015-0362

Moore, W., & Frye, S. (2019). Review of HIPAA, part 1: History, protected health information, and privacy and security rules. *Journal of Nuclear Medicine Technology*, *47*(4), 269–272. https://doi.org/10.2967/jnmt.119.227819

Moorman, J. R., Carlo, W. A., Kattwinkel, J., Schelonka, R. L., Porcelli, P. J., Navarrete, C. T., Bancalari, E., Aschner, J. L., Walker, M. W., Perez, J. A., Palmer, C., Stukenborg, G. J., Lake, D. E., & O'Shea, T. M. (2011). Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: A randomized trial. *Journal of Pediatrics*, *159*(6), 900–906. https://doi.org/10.1016/j.jpeds.2011.06.044

Parry, G., Tucker, J., & Tarnow-Mordi, W. (2003). CRIB II: An update of the clinical risk index for babies score. *The Lancet*, *361*(9371), 1789–1791. https://doi.org/10.1016/S0140-6736(03)13397-1

Patural, H., Franco, P., Pichot, V., & Giraud, A. (2022). Heart rate variability analysis to evaluate autonomic nervous system maturation in neonates: An expert opinion. *Frontiers in Pediatrics, 10*, Article 860145. https://doi.org/10.3389/fped.2022.860145

Philips. (2015). *Data Export Interface Programming Guide - Intellivue Patient Monitor & Avalon Fetal Monitor*. http://incenter.medical.philips.com/doclib/GetDoc.aspx?func=ll&objId=11407611&objAction=Open&AppLibId=1.DAD

Poggi, C., Ciarcià, M., Miselli, F., & Dani, C. (2023). Prognostic accuracy of Neonatal SOFA score versus SIRS criteria in preterm infants with late-onset sepsis. *European Journal of Pediatrics*, *182*(10), 4731–4739. https://doi.org/10.1007/s00431-023-05143-5

Procianoy, R. S., & Silveira, R. C. (2020). The challenges of neonatal sepsis management. *Jornal de Pediatria*, *96*, 80–86. https://doi.org/10.1016/j.jped.2019.10.004

Quinten, V. M., van Meurs, M., Renes, M. H., Ligtenberg, J. J. M., & ter Maaten, J. C. (2017). Protocol of the sepsivit study: A prospective observational study to determine whether continuous heart rate variability measurement during the first 48 hours of hospitalisation provides an early warning for deterioration in patients presenting with infection or sepsis to the emergency department of a Dutch academic teaching hospital. *BMJ Open*, *7*(11), Article e018259. https://doi.org/10.1136/bmjopen-2017-018259

Ranjit, S., & Kissoon, N. (2021). Challenges and solutions in translating sepsis guidelines into practice in resource-limited settings. *Translational Pediatrics*, *10*(10), 2646–2665. https://doi.org/10.21037/tp-20-310

Rao, K. V. K. L. N., Dadabada, P. K., & Jaipuria, S. (2024). A systematic literature review of predictive analytics methods for early diagnosis of neonatal sepsis. *Discover Public Health*, *21*, Article 96. https://doi.org/10.1186/s12982-024-00219-5

Shirwaikar, R. D., Acharya, U. D., Makkithaya, K., Surulivelr, M., & Lewis, L. E. S. (2015). Machine learning techniques for neonatal apnea prediction. *Journal of Artificial Intelligence*, *9*(1–3), 33–38. https://doi.org/10.3923/jai.2016.33.38

Statello, R., Carnevali, L., Sgoifo, A., Miragoli, M., & Pisani, F. (2021). Heart rate variability in neonatal seizures: Investigation and implications for management. *Neurophysiologie Clinique*, *51*(6), 483–492. https://doi.org/10.1016/j.neucli.2021.10.002

van Gent, P., Farah, H., van Nes, N., & van Arem, B. (2019). HeartPy: A novel heart rate algorithm for the analysis of noisy signals. *Transportation Research Part F: Traffic Psychology and Behaviour*, *66*, 368–378. https://doi.org/10.1016/j.trf.2019.09.015

Wee, B. Y. H., Lee, J. H., Mok, Y. H., & Chong, S. L. (2020). A narrative review of heart rate and variability in sepsis. *Annals of Translational Medicine*, *8*(12), 768–768. https://doi.org/10.21037/atm-20-148

WHO. (2024). *End preventable deaths of newborns and children under 5 years of age*. World Health Organization. https://www.who.int/data/gho/data/themes/topics/sdg-target-3_2-newborn-and-child-mortality

Zeigler, A. C., Ainsworth, J. E., Fairchild, K. D., Wynn, J. L., & Sullivan, B. A. (2023). Sepsis and mortality prediction in very low birth weight infants: Analysis of HeRO and nSOFA. *American journal of perinatology, 40*(04), 407-414. https://doi.org/10.1055/s-0041-1728829