Annals of Neonatology Journal

OPEN ACCESS
ISSN: 2636-3596

Original Article

Predictive Value of Heart Rate Observation (HeRO) Score for Sepsis in Preterm Neonates

Mariam J. Ibrahim* and Safaa S. Imam

DOI: 10.21608/anj.2022.176991.1060
***Correspondence**: Pediatrics department Ain Shams University, Egypt.
Email: mariam.john@med.asu.edu
Full list of author information is available at the end of the article.

Abstract

Background: Neonates admitted to neonatal intensive care units (NICU) are at an increased risk to develop sepsis, especially preterm neonates because of their immature immune systems. Early detection of sepsis, before pronounced clinical deterioration, would allow earlier administration of supportive treatments and antibiotics this will improve morbidity and lead to favorable outcomes.

Aim of work: The aim of this study was to determine the effectiveness of HeRO score to detect neonatal sepsis in preterm neonates.

Patients and methods: This prospective observational study included 170 preterm infants. All studied neonates were subjected to HeRO scores initially and throughout hospital stay. Confirmation of neonatal sepsis was done by withdrawal of positive C-reactive protein (CRP) and positive blood culture.

Results: The studied neonates were divided into initial septic group and non-septic neonates; HeRO score showed statistically significant increase in septic patients than non-septic (median (IQR) 2 (2-3) vs. 1 (0-1) respectively for day 1 of admission ($p < 0.001$) and 2(1-2) vs 0 (0-1) on day 4 of admission ($p < 0.001$) with a cut off value of > 1 in both day 1 and 4 with sensitivity and specificity 92.75% & 98.02% for day 1 and 65.22 % and 85.a5% in day 4 respectively.

Conclusions: Heart rate observation (HeRO) score can be used for early detection of neonatal sepsis in preterm neonates.

Key words: Sepsis, Preterm neonates, HeRO score, Prognosis and Outcome.

Introduction

Neonatal sepsis is the systemic affection of neonates due to bacterial, viral, or fungal agents, associated with hemodynamic changes and clinical affection that cause severe morbidity up to mortality. Early detection of sepsis, before clinical affection, would permit earlier administration of supportive therapies and antibiotics and will result in improved outcomes [1]. The difficulty in early detection of neonatal sepsis is attributed to the subtle and nonspecific clinical signs in its early phase [2].

The development of the HeRO (heart rate observation) monitor was initiated because of the accurate observation that during the early phase of sepsis, the pathological affection leads to subtle but complex alteration in heart rate characteristics. The Decrease in heart rate variability and transient repetition of heart rate decelerations, which is also seen in a fetus exposed to asphyxia, develop in neonatal sepsis. These changes can be readily seen in patients in the early phase of sepsis before overt clinical manifestations. These alterations are not visible to clinicians using standard cardiorespiratory monitoring [3].

The HeRO monitor displays a number or score, which defines the risk that a patient will have a clinical deterioration which coincides with clinical or culture-proven sepsis in the following 24 hours [4].

This study was done to evaluate the effectiveness of the HeRO score to differentiate between septic and non-septic preterm neonates. The ability to predict the development of neonatal sepsis in preterm neonates using the HeRO score was also tested. This will help in early intervention and better outcome in management of neonatal sepsis in neonates.

Aim of the Work: The aim of this study was to determine the effectiveness of HeRO score to detect neonatal sepsis in preterm neonates.

Methods

This Prospective observational study was conducted on premature infants < 37 weeks gestation who were admitted in the neonatal intensive care unit Ain Shams University hospitals. Neonates who had any major congenital or chromosomal abnormalities, congenital heart disease, grade III/IV intra-ventricular hemorrhage, Periventricular leukomalacia or hypoxic ischemic encephalopathy were excluded from the study. Patients who had a C - reactive protein (CRP) positive and positive blood culture were enrolled in the septic group. Patients with negative CRP (< 6 mg/dl) and blood culture were in the non-septic group. All preterm patients observed and subjected to HeRO score, that was assessed regularly by using HeRO duet, MPSC, United Kingdom [5]. A HeRO monitor was put on the infant till readings and curve scores were obtained. During sepsis, before the development of evident clinical signs, there is a decrease in heart rate variability and transient repetitive heart rate decelerations.

The HeRO monitor displays a number or score, calculated inside the machine from the heart rate variability and decelerations. This score or number represents the risk that a patient will experience a clinical deterioration afterwards. A HeRO score of 1 is considered "normal" for healthy preterm infants, and a score of 5 indicates a five-fold increase in risk that sepsis diagnosis will be established in the next 24 hours to 5 days [6].

Ethical considerations

A written informed consent was obtained from parents or legal guardians of the patients before enrolment in this study. Approvals from the Pediatric Department and Ethics Committee, Faculty of medicine, Ain Shams University were obtained. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans [7].

Statistical analysis

Data were analyzed using SPSS 23. The quantitative data were presented as mean, standard deviations and ranges for parametric data and median, inter-quartile range (IQR) for non-parametric data. Also, qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. Mann-Whitney test for two independent groups with quantitative data and non-parametric distribution Kruskall-Wallis test For more than two groups regarding quantitative data and non-parametric distribution Receiver operating characteristic curve (ROC) was used to assess the best cut off point with its sensitivity, specificity, positive predictive value, negative predictive value and area under curve (AUC) of the studied marker. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was assessed as follows: P-value > 0.05 was Non-significant P-value < 0.05 was Significant.

Results

Our study was conducted on premature infants < 37 weeks gestation who were admitted to the neonatal intensive care unit, Ain Shams University hospitals, from the period of September 2020 to September 2021, it included 170 neonates. 93 (54.7%) males and 77 (45.3%) females, 74 (43.5%) born by vaginal delivery and 96 (56.5%) by cesarean section. Our studied neonates had the following diagnosis: 102 (60.0%) had respiratory distress, 90 (52.9%) had neonatal sepsis (initial sepsis and developed sepsis later during hospital stay), 69 (40.6%) had neonatal jaundice, 50 (29.4%) preterm growers, 3 (1.8%) had hemorrhagic disease of newborn and 1 (0.6%) had neonatal seizures. (table1)

HeRO scores were statistically higher in septic versus non-septic patients on day 1(D1) and 4(D4) of admission median (inter quartile range (IQR) 2(2-3) vs 1(0-1) p<0.001 for D1 respectively and 2(2-1) vs.

0(0-1) for D4 respectively. ROC curve was done and cut off point of HeRO scores for D1 and D4 were >with sensitivity and specificity 92.75% & 98.02% for day 1 and 65.22 % and 85.a5% in day 4. (Tables 2&3 and figure 1)

Patients were divided into 2 more groups those who developed sepsis after 4 days or later of admission than those who didn't. HeRO score was significantly higher in the patients that developed sepsis with median (IQR) on D4 2(1-2) vs 1(0-2) in the other group p<0.001, 2(1-3.5) vs 0(0-1) for day 7 (D7) p<0.001 and 1.5 (0-3) vs. 0 (0-1) on day 13(D13) p<0.001. cut off value >0 for D4, D7 and D13 was found to differentiate between those who developed sepsis or not with sensitivity and specificity 100% &41.61 for D4, 90%,55.56% for D7 and 72.22% & 61.11% for D13 respectively. (Tables 4&5 and figure 2)

Discussion

Sepsis is a clinical and biochemical syndrome of systemic infection with isolation of organism from blood culture only occurring in 30-60% of the cases. Sepsis can be divided according to the onset into early-onset sepsis (EONS) if within the first 72 hours of life and late-onset sepsis (LONS) if later than that. Neonates in the neonatal intensive unit (NICU) are susceptible to sepsis especially preterm neonates and low birth weight, with an incidence in the literature ranging from 1-40% which varies due to the onset [8].

The correct definition of neonatal sepsis has not yet been recognized worldwide up till now. The gold standard for diagnosis is the presence of a positive blood culture, but a negative blood culture in NICU does not exclude the presence pf sepsis, especially if there are other clinical and/or laboratory signs indicative of sepsis present. Also, blood culture results are often delayed and start of management cannot be dependent on it. So, the main issue in dealing with sepsis in neonates especially preterms is when and how to suspect the presence of sepsis before the change in laboratory biomarkers as CRP and the positivity of a

blood culture clinically evident sepsis is to suspect the diagnosis as early as possible [9].

From a clinical point of view, the main strategy to defeat sepsis lies in prevention early diagnosis and treatment. Early diagnosis facilitates proper timely intervention and treatment. Early antibiotic administration when needed will reduce disease duration and severity. Also, along the course of management early diagnosis will help in steering the management plan as needed [8].

The aim of this Prospective observational study was to determine the effectiveness of HeRO score to differentiate between septic and aseptic patients. Our secondary aim was to follow up HeRO scores throughout hospital stay and to correlate it with the development of sepsis later. There was a statistically significant elevation of HeRO score in septic patients than aseptic patients in both days 1 and 4 of admission. A cut of value of >1 has a sensitivity of 92.75% and specificity of 98.02% to differentiate between septic and aseptic patients on day1 and, 65.22% and 85.15% on day 4 respectively (+PV & -PV 97.0% ,95.2% for day 1 and 75.0%,78.2% for day 4 respectively) . So, patients who had a high HeRO score more than 1 were suspected to be septic patients before initial biochemical assessment. Hence proper treatment can be initiated accordingly.

The decrease in the sensitivity and specificity in day 4 can be explained by the fact that patients had already started treatment and their clinical conditions started to improve with improvement of the HeRO score.

In analysis of the patients who developed sepsis there was a significant elevation in HeRO score on days 4, 7 and 13 than those who did not. These days can mark the timing at which the patients started to develop subtle changes in their heart rate characteristics that would predict the emergence of a septic episode later. A cut off value of >0 can predict the development of sepsis on days 4.7 & 13

with a sensitivity and specificity of 100% & 41.61% for day 4 and 90%&55.56% for day7 and 72.22%&61.11% for day 13 respectively (+PV & -PV 19.4%,100% for day 4, 27.3%,96.8% for day 7 and 48.1%, 81.5% for day 13 respectively). This indicates the importance of following up patients in NICU with the HeRO score as any elevation of HeRO score later can predict the development of sepsis and prompt proper timely management.

Other authors [10] confirmed the same findings, a study was done on 30 neonates with clinical signs suspicious for development of sepsis. 20 of the cases had a positive HeRO score higher than two; eight of these cases developed sepsis. Moreover, they found out that the HeRO score was able to predict sepsis from 5 to 12 hours before the development of positive biomarkers. In their study, clinicians usually waited for at least one clinical or a laboratory sign to appear before starting antibiotic therapy, even if these septic events were declared early by the HeRO score. In the literature, it is described how the early administration of antibiotics, even just an hour before, is useful in decreasing mortality from sepsis [10].

Fairchild & Aschner, [11] reported that patients who used HeRO score during hospital stay and were followed up with it, had a mean of 2.3 more days of survival alive and off respiratory support in comparison to those who did not have a HeRO score done. Importantly, mortality was 22% lower in those who had a HeRO score compared to those without (10.2% vs. 8.1%, P = 0.04). In a prespecified subgroup analysis of ELBW infants, the relative reduction in death was 26% in HeRO displayed versus HeRO nondisplaced groups (P = 0.02). This indicates that the presence of a HeRO score can alert physicians early in any expected deterioration in a patient and proper interventions can be performed [11].

The institution of HeRO score for all admitted neonates is very useful in NICU

to identify septic patients and predict the development of sepsis. Abnormal heart rate characteristics identified by the HeRO score can also be used soon after birth. The elevation in the HeRO score for such newborns has been proven to be associated with mortality and multiple morbidities in very low birth weight infants [12].

Limitations of the study

A larger sample size would help interpret our results more. Our study could be implemented on clinical septic patients versus proven septic neonates to explore the expression of the HeRO score in these situations; also, the severity of the neonatal sepsis can be correlated to the HeRO score. Furthermore, the determination of the kind of organism isolated from the blood culture and its relation to the HeRO score would be of great value.

Conclusions

Heart Rate Observation (HeRO) score is an essential tool that could permit neonatologist all over the world to differentiate between septic and non-septic neonates before the emergence of clear clinical signs and biomarkers. This facilitates early institution of targeted management which decreases morbidity and mortality of neonates especially preterms. More over HeRO score can be used to follow up the patients admitted in NICU along their hospital stay to predict early the new development of sepsis before the derangement in biochemical markers and clear clinical signs.

Acknowledgements

To all the staff members, assistant lecturers, residents and nursing team of the NICU, Ain Shams University.

Author's contributions

Safaa Imam contributed in designing the study, follow up and choice of patients included, data analysis and interpretation Conceived and designed the analysis and revision of the paper. Mariam John Amin Ibrahim contributed in suggesting the idea of the study, designing the study, follow up and choice of patients included, data analysis and interpretation writing, revising and following up the publishing of the paper

Conflict of interest

The authors declare that there were no conflicts of interest.

Funding

There was no funding for the study from any source

Author's details

Pediatrics department Ain Shams University, Egypt.

Date received: 4th November 2022, accepted 15th December 2022

References

1. Raynor L, Saucerman J, Akinola MO: Cytokine screening identifies NICU patients with Gram-negative bacteremia. Pediatr Res. 2012; 71:261–266.
2. Sullivan B, Grice S, Lake D, Moorman J and Fairchild K: Infection and other clinical correlates of abnormal heart rate characteristics in preterm infants. J Pediatr. 2014; 164:775–80.
3. Griffin M, Lake D and Bissonette E: Heart rate characteristics: novel physiomarkers to predict neonatal infection and death. Pediatrics, 2005; 115:1070–1074.
4. Fairchild K and O'Shea T.: Heart rate characteristics: physiomarkers for detection of late-onset neonatal sepsis. Clin Perinatol. 2010; 37:581–598.
5. Gang Y and Malik M: Heart rate variability in critical care medicine. Curr Opin Crit Care, 2002; 8:371-75.
6. Seely A, Green G and Bravi A.: Continuous multiorgan variability monitoring in critically ill patients – complexity science at the bedside. Conf Proc IEEE Eng Med Biol Soc, 2011; 5503–5506.
7. World Medical Association: Wma declaration of Helsinki – ethical principles for medical research involving human subjects.2013 © 2022 World Medical Association accessed online 12,2022, [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/}
8. Wynn, J. L., Wong, H. R., Shanley, T. P., Bizzarro, M. J., Saiman, L., & Polin, R. A.: Time for a Neonatal-Specific Consensus Definition for Sepsis. Pediatric Critical Care Medicine, 2014, 15(6), 523–528. https://doi.org/10.1097/PCC.0000000000000157.
9. Goldstein B, Giroir B, and Randolph A.: International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med, 2005, 6(1):2-8.

10. Tarricone, F., Brunetti, A., Buongiorno, D., Altini, N., Bevilacqua, V., Del Vecchio, A etal.: Intelligent Neonatal Sepsis Early Diagnosis System for Very Low Birth Weight Infants. Applied Sciences, 2021, 11(1), 404. https://doi.org/10.3390/app11010404

11. Fairchild K & Aschner J: HeRO monitoring to reduce mortality in NICU patients. Res Rep Neonatol. 2012, 2. 65-76. 10.2147/RRN.S32570.

12. Sullivan B, McClure C, Hicks J, Lake D, Moorman R and Fairchild K: Early heart rate characteristics predict death and morbidities in preterm infants, J Pediatr. 2016; 174: 57–62. doi: 10.1016/j.jpeds.2016.03.042.

Table (1): Demographic data and diagnosis of the studied patients

Total no. = 170		**No. (%)**	**Range**	**Mean ± SD**	**Median (IQR)**
***GA (weeks)**			28 – 36	34.20 ± 1.87	
Weight (kg)			0.8 – 3.6	2.17 ± 0.46	
Age on admission (days)			1 – 22		1 (1 – 4)
Total Hospital stay (days)			3 – 20		10 (7-13)
Sex	Male	93 (54.7%)			
	Female	77 (45.3%)			
Mode of Delivery	Vaginal	74 (43.5%)			
	*C. S	96 (56.5%)			
Diagnosis	*R. D	102 (60.0%)			
	Sepsis	90 (52.9%)			
	*N. J	69 (40.6%)			
	Preterm growers	50 (29.4%)			
	*HDN	3 (1.8%)			
	*N. Seizures	1 (0.6%)			
Feeding	Breast feeding	114 (69.5%)			
	Artificial feeding	50 (30.5%)			
Inotrope	*1st line	11 (26.2%)			
	*2nd line	31 (73.8%)			
Antibiotics	*1st line	135 (79.4%)			
	*2nd line	20 (11.8%)			
	*3rd line	5 (2.9%)			
Ventilation	No	70 (41.2%)			
	Yes	100 (58.2%)			
Complications	No	77 (45.3%)			
	Yes	93 (54.7%)			
Outcome	Survived	162 (95.3%)			
	Died	8 (4.7%)			

*Number& percent for sex, mode of delivery, type of feeding, type of inotrope, type of antibiotics, ventilation, diagnosis, complications, total hospital stay and outcome.

*Median (IQR) for non-parametric data.

*Mean (SD) for parametric data.

*Abbreviations: *GA: Gestational age. *CS: Cesarean section*RD: Respiratory Distress. *N. J: Neonatal jaundice.*HDN: Hemorrhagic disease of newborn.*N. seizures: Neonatal seizures. 1st line of inotrope: Dopamine. *2nd line of inotrope: Dopamine + Dobutamine. *1st line of antibiotics: Ampicillin+ Gentamicin. *2nd line of antibiotics: Meropenem + Vancomycin. *3rd line of antibiotics: Amikacin, Cefotaxime, clindamycin, cefoperazone, fluconazole, Amoxicillin/clavulanic acid, Azithromycin, Ciprofluxacin, Teicoplanin.

Table (2): Comparison of HeRO score in patients with initial sepsis than non-septic patients

Item		Non-septic patients	Initial septic patients	Test value≠	P-value
		n= 101	n= 69		
HeRO score D1	**Median (IQR)** **Range**	1 (0 – 1) 0 – 4	2 (2 – 3) 1 – 5	-10.755	<0.001
HeRO score D4	**Median (IQR)** **Range**	0 (0 – 1) 0 – 5	2 (1 – 2) 0 – 5	-6.687	<0.001

HeRO: Heart Rate Observation, P-value > 0.05: Non -significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant ≠: Mann-Whitney test

Table (3): Cut off point, AUC, sensitivity, and specificity for HeRO score for D1 and D4

Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
HeRO Score D1	>1	0.969	92.75	98.02	97.0	95.2
HeRO Score D4	>1	0.789	65.22	85.15	75.0	78.2

HeRO: Heart Rate Observation, AUC: area under curve, PV: predictive value

Table (4): Comparison of HeRO score for development of sepsis

Item		Groups Did not develop sepsis	 Developed sepsis	Test value≠	P-value
		n = 149	**n = 21**		
HeRO scoreD4	**Median (IQR)** **Range**	1 (0 – 2) 0 – 5	2 (1 – 2) 1 – 5	-3.577≠	<0.001
HeRO scoreD7	**Median (IQR)** **Range**	0 (0 – 1) 0 – 5	2 (1 – 3.5) 0 – 4	-4.079≠	<0.001
HeRO scoreD13	**Median (IQR)** **Range**	0 (0 – 1) 0 – 5	1.5 (0 – 3) 0 – 5	-2.618≠	0.009

HeRO: Heart Rate Observation, P-value > 0.05: Non -significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant ≠: Mann-Whitney test,

Table (5): cut off point, AUC, sensitivity, and specificity for HeRO score for D4, D7 and D13 for the development of sepsis

Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
HeRO Score D4	>0	0.731	100.00	41.61	19.4	100.0
HeRO Score D7	>0	0.768	90.00	55.56	27.3	96.8
HeRO Score D13	>0	0.704	72.22	61.11	48.1	81.5

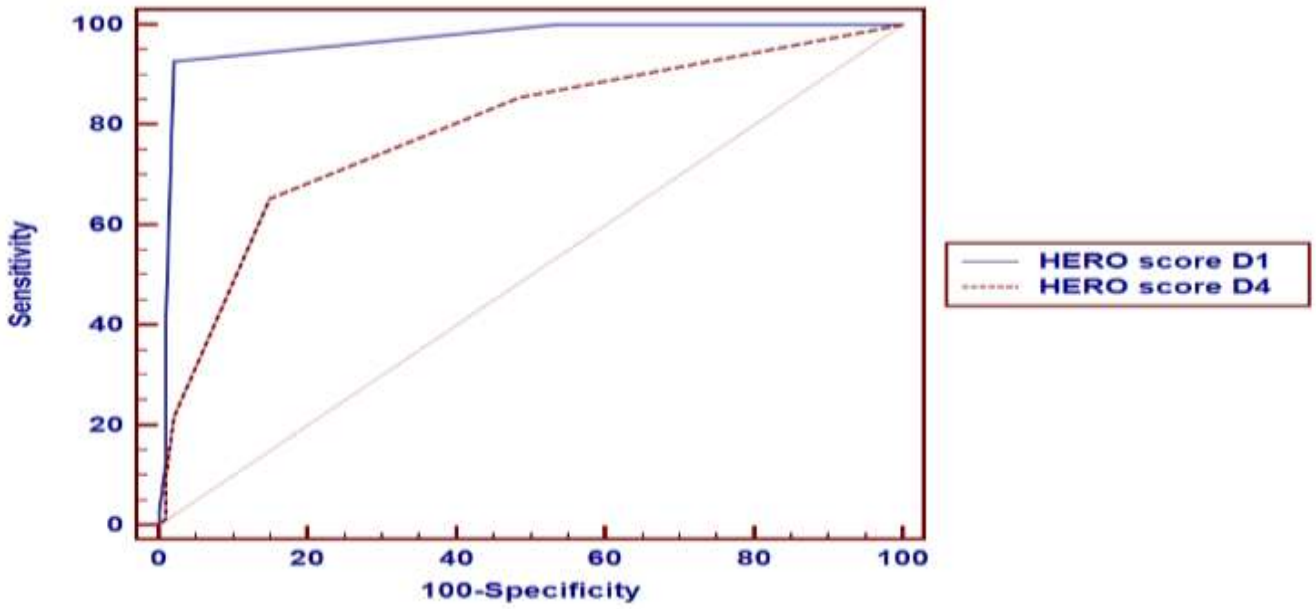

Figure (1): Receiver operating characteristic curve (ROC) curve for HeRO score to predict initial sepsis

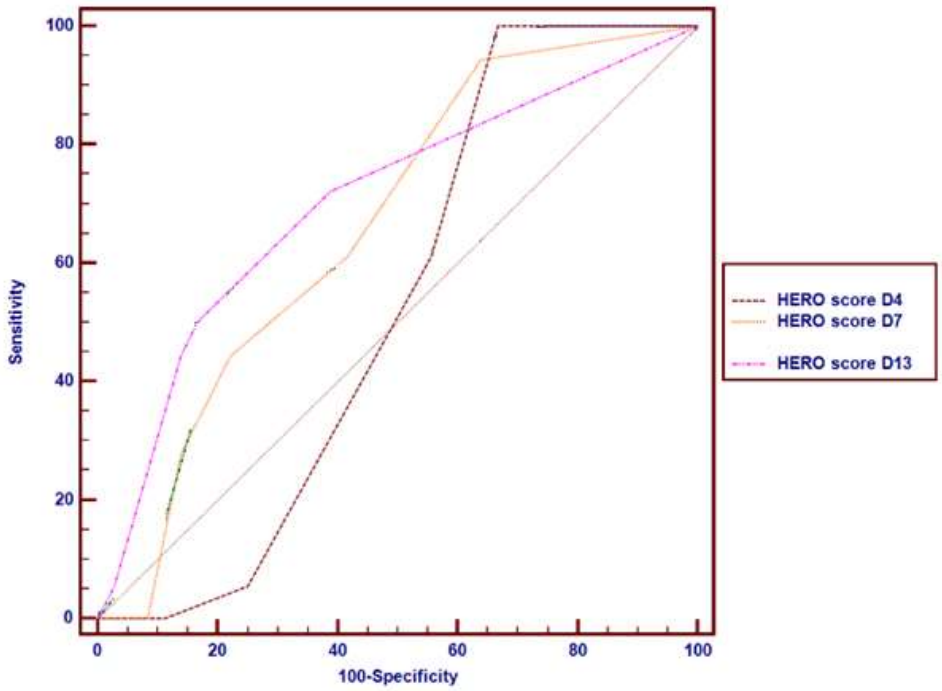

Figure (2): Receiver operating characteristic curve (ROC) curve for development of sepsis

Citation: Mariam J. Ibrahim; Safaa S. Imam. "Predictive Value of Heart Rate Observation (HeRO) Score for Sepsis in Preterm Neonates". *Annals of Neonatology Journal*, 2023; 5(1): 28-41 doi: 10.21608/anj.2022.176991.1060