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ORIGINAL ARTICLE

BEDSIDE PREDICTION SCORING FOR EMERGENT DIAGNOSIS OF LATE ONSET NEONATAL SEPSIS

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ABSTRACT

Background: Late Onset Neonatal Sepsis (LONS) or nosocomial sepsis has a significant mortality and morbidity that leads to overtreatment. Overtreatment happens when antibiotics are frequently started and/or shifted, eventually leading to increasing antimicrobial resistance in NICU.
Objective: To validate bedside nosocomial sepsis scoring developed by Okascharoen in 2005.
Methodology: All neonates admitted in NICU suspected of LONS were enrolled. Using Okascharoen scoring, subjects were scored based on hypotension/poor perfusion, abnormal body temperature, respiratory insufficiency, complete blood count, and length of umbilical catheter use. Growth of organisms during blood culture is considered positive outcome and is considered confirmed sepsis.
Results: Of the one-hundred-nineteen (119) subjects included in the analysis, 59 were confirmed sepsis and 60 were LONS negative. Subjects with confirmed sepsis had more events of hypotension/poor perfusion ($p<0.001$; -0.141, -0.438), thrombocytopenia (p 0.000; -0.169, -0.489), and prolonged umbilical catheter usage (p 0.014; -0.051, -0.311). The ROC curve has an AUC of 0.753 ($p <0.001$; 0.664-0.842), which means a randomly chosen neonate with LONS will have a higher predicted score than a neonate without LONS. The sensitivity of this tool was 0.92 (0.82-0.97) and specificity of this tool was 0.32 (0.21-0.46) in this setting. The positive LR= 1.35 (1.12-1.64) while the negative LR= 0.26 (0.10-0.65)
Conclusion: This scoring is a valid tool that can be used in point-of-care scoring for antibiotic stewardship in a neonate with suspected sepsis.
Recommendation: It is recommended that a score >5 be used to be predictive of late onset sepsis, and this would have a sensitivity of 83.3%, specificity of 61%, positive predictive value of 68.5% and a negative predictive value of 78.3%

KEYWORDS:
Neonatal sepsis, newborn sepsis, clinical prediction rules

INTRODUCTION

Neonatal sepsis denotes blood infection with systemic dissemination from a suspected focus, most commonly meningitis, pneumonia, pyelonephritis or gastroenteritis, in an infant less than 90 days old.[1,2,3] It is classified according to onset, either early or late onset sepsis, wherein the latter is commonly caused by hospital-acquired pathogenic organisms, developing between 3-to-90 days of life.[4] For neonates admitted in the neonatal intensive care unit (NICU), late onset sepsis is the same as nosocomial or hospital-acquired sepsis.[1,4] Statistics worldwide shows an increasing prevalence of nosocomial sepsis, with infection rates ranging from 6.24% to 33%.[1,5,6,7] This noted increase in nosocomial sepsis cases may be due to the increasing number of low birth weight (LBW) infants as well as improvement in the care of preterm infants, both of which are strong risk factors for nosocomial sepsis.[8] In the Philippine General Hospital, the largest tertiary referral center in the country, late onset neonatal sepsis (LONS) rate was noted to increase to 27.22% in 2011 from 20.54% in 2010.[9]

Early recognition of sepsis by clinicians proves challenging especially in the study age group since initial clinical signs are nonspecific, but is indicated since sepsis leads to rapid clinical deterioration if emergent management is not administered in a timely manner.[10,11] Clinicians are therefore tasked to have a high index of suspicion for sepsis, give a prompt diagnosis, and manage septic patients appropriately. Thus, it is common practice to start a broad spectrum of antibiotics from a presumptive diagnosis[2,6,12], which may pose certain disadvantages, like indiscriminate antibiotic use, risk for drug toxicity, and development of high-level multiple-drug resistant organisms.[1,13,14,15] This may also lead to increased number of hospital days and higher financial expenditure.[16,17] In this light, a clinical prediction and diagnostic tool for nosocomial sepsis can aid clinicians in accurate diagnosis and judicious use of resources.

In 1982, Tollner employed multiple laboratory and clinical parameters for prediction of nosocomial sepsis,[18] deriving the scoring system from 83 cases; the scoring system was then validated to a cohort of 54 participants. The scoring system proved to be complex and tedious because of the requisite multiple clinical parameters and laboratory examinations, [19] majority of which are not readily available nor accessible in resource-limited healthcare settings.[20] Another scoring system developed by Singh in 2003[21] was the first predictive scoring system developed for resource-limited facilities. Clinical signs were employed as parameters in the Singh scoring system. However, this system was derived from a small sample size without internal validation, with a positive predictive value of 65%. Okascharoen in 2005 developed a scoring system in Ramathibodhi Hospital, Thailand, a government-owned tertiary referral center that produced the biggest number of subject enrollment.[22] To determine the parameters for the scoring system, several clinical and laboratory variables were analyzed using Cox's proportional hazards regression model from a retrospective review of 100 neonates, followed by prospective validation on a cohort of 73 subjects (See Table 1). In 2007, the same group did an external validation of the system on McMaster Medical Center to prove its accuracy,[23] displaying approximately similar results and prediction performance as that of the original study. The scoring system employed clinical signs and simple laboratory tests available in resource-limited and point-of-care settings, and utilized risk stratification in three groups with mean probability of LONS as follows: 0.10 for low-risk (scores 0 to 3), 0.50 for intermediate-risk (scores 4 to 6), and 0.70 for high-risk (scores ≥ 7).[22]

Table 1. Bedside Nosocomial Sepsis Score*

Parameters	*Coefficient (SE)*	*Hazard Ratio (95% CI)*	*Score*
Clinical Variables			
Hypotension	4.0 (1.13)	56.4 (6.1-522.8)	4
Abnormal body temperature (fever T>38.1 C, hypothermia T< 36.5 C, or temperature instability)	2.8 (0.61)	15.8 (4.8-52.4)	3
Respiratory insufficiency (apnea, bradycardia, tachypnea, cyanosis, increased oxygen requirement or ventilator settings)	1.5 (0.60)	4.6 (1.4-15.2)	2
Laboratory Findings			
Increased neutrophil bands (band form fraction ≥ 1%)	1.7 (0.61)	5.7 (1.7-19.8)	2
Thrombocytopenia (platelet <150 x 10^3)	1.5 (0.77)	4.5 (1.0-20.5)	2
Management Variables			
Presence of umbilical venous catheters			
> 7 days	3.3 (0.78)	27.4 (6.0-125.9)	4
1-7 days	1.5 (0.77)	4.5 (1.0-20.4)	2
***with permission from Okascharoen C, Sayomporn S, Ammarin T, Dwip K, Sarayut S. A Bedside Prediction-Scoring Model for Late-Onset Neonatal Sepsis. J Perinatol. 2005:778–83**			

Our current study thus aims to validate the bedside clinical prediction rule developed by Okascharoen in our own healthcare setting using blood culture as the gold standard. We aim to determine the sensitivity, specificity, and likelihood ratios of this prediction scoring model for culture proven LONS; describe the receiver operator characteristics (ROC) curve; determine the cut-off point by which prediction of LONS can be made; and assess its applicability.

METHODS

A prospective study was conducted from August 2012 to August 2013 in the neonatal intensive care unit (NICU) of the Philippine General Hospital, enrolling suspected LONS neonates aged 2 to 90 days. Neonates with lethal conditions on palliative care, had more than one bout of culture proven nosocomial infection, and had more than one antibiotic shift were excluded from the study population. A patient database sheet containing infant and maternal profiles was used, and scoring was done based on chart entry and interview conducted by the primary clinician who was blinded to the scoring method. Routine sepsis work-up and surveillance were done following institution protocol. Positive growth of microbiologic agent in cultures done was considered a positive outcome or "confirmed LONS," while absence of growth from cultures was considered a negative outcome or "LONS negative".

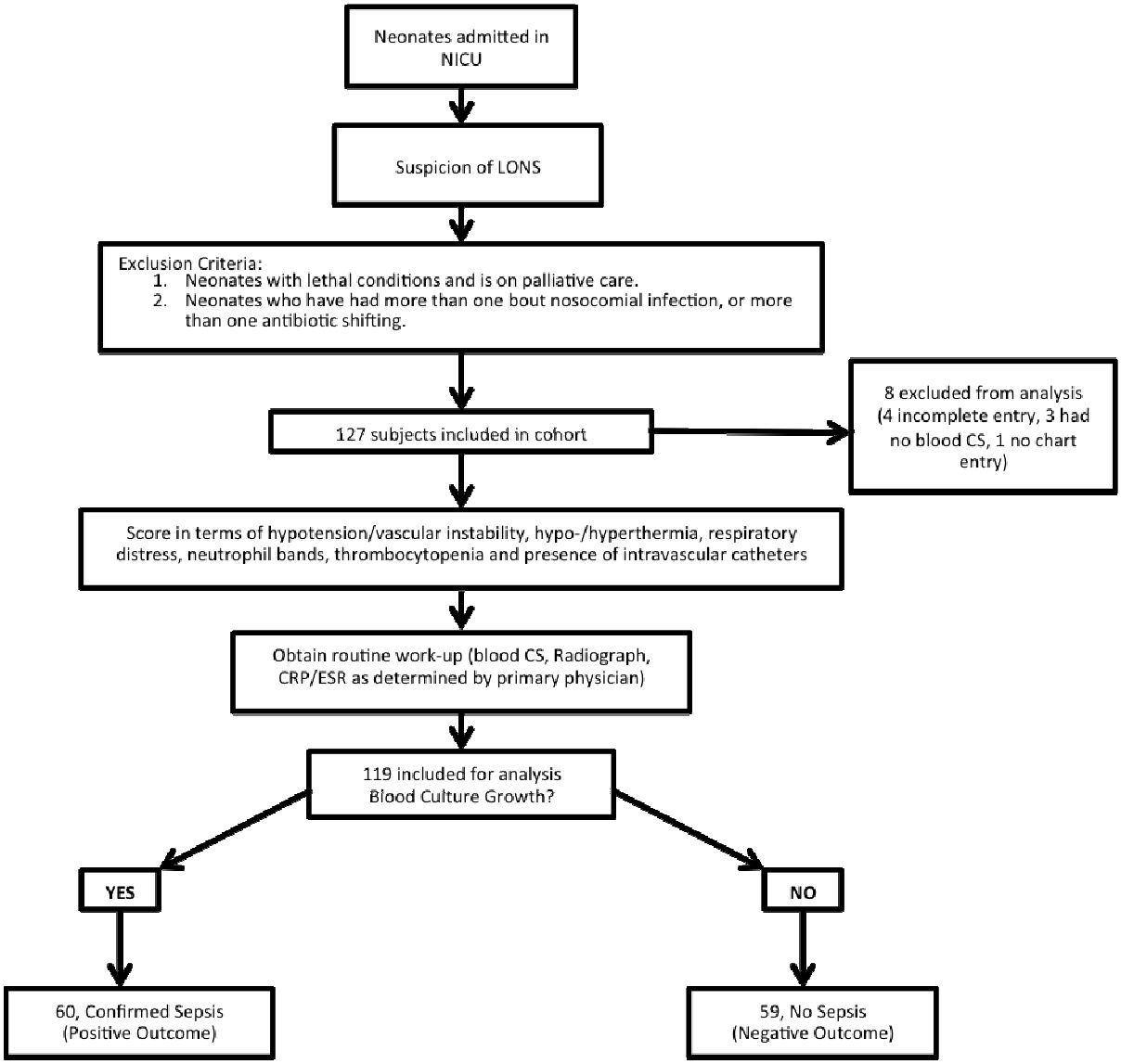

Figure 1. Enrollment of Subjects

Statistical analysis

SPSS version 21[24] was used to perform the statistical analysis. The χ^2 test and student's t-test were used for dichotomous and continuous variables, respectively, to determine statistical difference. A p value of < 0.05 was considered significant. Sensitivity and specificity were then computed for each score and were used to plot the ROC curve, which was utilized to determine the optimal cut-off point with maximal sensitivity and specificity. Diagnostic ability of the score was then assessed using Area Under the Curve (AUC) with 95% confidence interval. Sample size was computed using our institution's census for 2011 to estimate a sensitivity of 95% confidence level, assuming a sensitivity of 72% from Okascharoen study and a margin of error of 15%.

RESULTS

One hundred twenty seven (127) infants satisfied the criteria but only 119 were included in the study cohort; eight were excluded due to poor reporting and incomplete data recording (Figure 1). Baseline characteristics between groups were statistically similar (Table 2). There was slight male predominance in the LONS negative group. Lower mean birth weight was noted in the LONS negative group as compared to the confirmed LONS group (1624 g ± 942 vs 1905 g ± 887). Mean maturity aging was comparable in both groups with almost equal distribution of preterms.

Table 2. Baseline characteristics of neonates enrolled in the study

Parameters	Confirmed Sepsis (n=60)	No Sepsis (n=59)	P value	95% CI
Male, n (%)	32 (53)	38 (64)	0.298	-0.065, 0.277
Maturity Aging, wks, mean (SD)	34.08 ± 3.8	33.93 ± 3.9	0.283	-0.638, 2.160
Prematurity, n (%)	41 (68)	44 (75)	0.582	-0.099, 0.219
Birth weight, g, mean (SD)	1905 ± 887	1624 ± 942	0.098	-52.3, 612.8
Low Birth Weight, n (%)	43 (72)	50 (85)	0.132	-0.019, 0.274
Congenital Anomalies, n	10	12	0.779	-0.104, 0.177
Operative Delivery, n (%)	45 (75)	35 (59)	0.104	-0.314, 0.012
Age of LONS Mean, days Median, days	8.2 ± 8.91 5	11.7 ± 11.53 7	0.069 -	-7.226, 0.27 -
Medical Device/ Indwelling Catheters, n (%)	32 (53)	27 (46)	0.521	-0.246, 0.101

Table 3. Pathogens Isolated from patients with LONS

	Frequency (n=60)	Percentage (%)
Gram positive Organism		
CONS	9	15%
Staphylococcus aureus	2	3%
Gram negative Organism		
Klebsiella species	37	62%
Enterobacter	7	12%
Achromobacter species	3	5%
Escherichia coli	1	2%
Sensitivity Patterns		
ESBLs	10	17%
MDRO	5	8%
MRSEs	9	15%

CONS, coagulase-negative Staphylococcus; ESBLs, extended-spectrum beta-lactamases gram negative bacilli; MDRO, multiple drug resistant organisms; MRSE, methicillin-resistant Staphylococcus epidermidis

Table 4. Presenting signs for suspicion of sepsis

Parameters	Confirmed Sepsis, N=60	No sepsis, N=59	P value	95% CI
Respiratory distress n (%)	17 (28)	33 (56)	0.004	0.099, 0.431
Bleeding (of any sites), n (%)	11 (18)	8 (14)	0.645	-0.181, 0.087
Poor activity, n (%)	11 (18)	3 (5)	0.050	-0.253, -0.015
Sclerema, n (%)	7 (12)	3 (5)	0.335	-0.176, 0.040
Abdominal distention and intolerance of feeding, n (%)	5 (8)	4 (7)	0.979	-0.121, 0.090

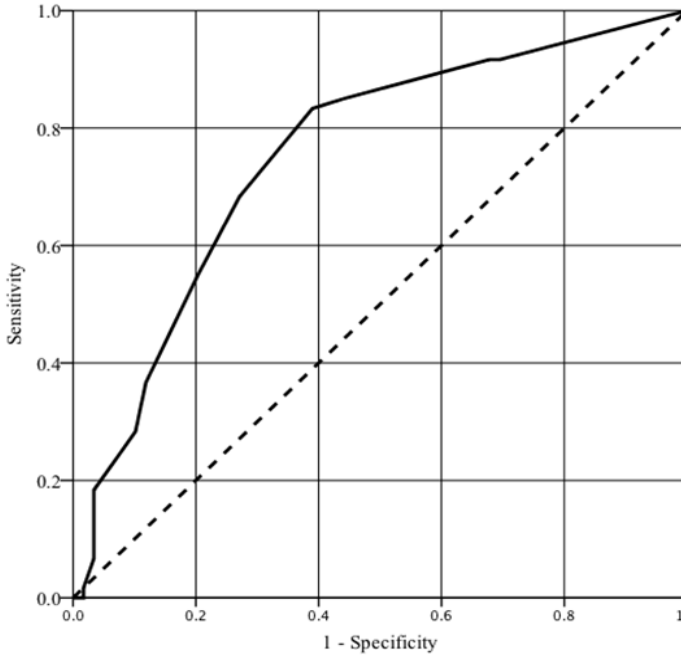

Figure 2. Receiver Operating Characteristics Curve

The ROC curve (Figure 2) revealed an AUC of 0.753 (p <0.001; 0.664, 0.842). Univariate analysis of the scoring system showed an odds ratio of 1.35 (p <0.001; 1.177, 1.556). The scoring system performance is presented in Table 6 along with the comparison of this study to the derivation group.

Table 5. Performance of different scoring parameters

Parameters	Confirmed Sepsis N=60	No sepsis N=59	P-value	95% CI
Clinical Variables				
Hypotension	25	7	0.001	-0.438, -0.141
Abnormal body temperature (fever T>38.1 C, hypothermia T < 36.5 C, or temperature instability)	22	11	0.046	-0.019, 0.329
Respiratory insufficiency (apnea, bradycardia, tachypnea, cyanosis, increased oxygen requirement or ventilator settings)	44	45	0.874	-0.126, 0.182
Laboratory Findings				
Increased neutrophil bands (band form fraction ≥ 1%)	12	14	0.787	-0.111, 0.185
Thrombocytopenia (platelet < 150 x 10^3)	47	26	0.000	-0.489, -0.169
Management Variables				
Presence of umbilical venous catheters	32	25		
1-7 days	17	21	0.514	0.093, 0.234
> 7 days	15	4	0.014	-0.311, -0.051

Table 6. Comparison of derivation study (Okascharoen 2005) from validation study

Comparison Parameters	Derivation Study		Validation Study	
	Confirmed Sepsis	No sepsis	Confirmed Sepsis	No sepsis
Sample Size	35	70	60	59
Patient Characteristics				
Gestational age	28.5 ± 0.5	28.5 ± 0.4	34.08 ± 3.8	33.93 ± 3.9
Birth weight	1396 ± 119	1149.3 ± 66	1905 ± 887	1624 ± 942
Gender (male)	60.0%	64.3%		
Age at LONS suspicion	12	15	5	7
Utilization of Central Catheters	17	26	32	25
Incidence of LONS	0.35		0.50	
Score Performance	At ≤ 3		At ≤ 3	
AUC (95% CI)	0.80 (0.59, 0.90)		0.75 (0.66, 0.84)	
Sensitivity	0.92 (0.71, 0.98)		0.92 (0.82; 0.97)	
Specificity	0.56 (0.43, 0.73)		0.32 (0.21; 0.46)	
Positive predictive values	0.56 (0.40, 0.71)		0.58 (0.47; 0.68)	
Negative predictive values	0.90 (0.73, 0.98)		0.79 (0.58; 0.93)	
Likelihood ratio positive	2.10 (1.50, 2.90)		1.35 (1.12; 1.64)	
Likelihood ratio negative	0.10 (0.03, 0.5)		0.26 (0.10, 0.65)	

The most common pathogens isolated in the cultures done were *Klebsiella* species, followed by coagulase-negative *Staphylococcus* and Enterobacter (Table 3); 40% of which were commonly ESBLs (extended-spectrum beta-lactamases positive gram-negative bacilli).

The most common presenting sign in both the confirmed LONs and LONS negative groups was respiratory distress/insufficiency, with higher incidence in the LONS negative group (56% vs 28%, p 0.004). Bleeding diathesis, poor activity, and sclerema were more frequently observed in the confirmed LONS group (see Table 4). With regard to the scoring parameters, hypotension/poor perfusion, thrombocytopenia, and one week use of central venous catheters were statistically more frequent among the confirmed sepsis group (Table 5).

DISCUSSION

Early detection and intervention are of utmost importance for the prevention of infectious morbidities and mortalities in neonatal sepsis. An accurate prediction tool is thus essential in guiding clinicians in the recognition of sepsis in neonates.[20,25] Our study validates the use of the bedside prediction scoring system in our setting. An ROC curve describes the performance of a clinical prediction rule by plotting true-positive against false-positive rates.[26,27] This study produces a curve that lies above the line of no-discrimination, illustrating a more accurate prediction. It has an AUC of 0.753 (p <0.001; 0.664, 0.842), meaning the probability of a random neonate suspected of LONS to be confirmed of sepsis is 0.753. Furthermore, we compare the predictive values of derivation group to our study and observed an increased

positive predictive value and a better negative predictive value (Table 6). Although the disparity in predictive value may be due to higher prevalence rate of confirmed sepsis in this study, two main factors, namely the microbiologic epidemiology and patient factors, may be regarded as influential to the results in this study. Our study cohort had positive cultures revealing growth ofgram-negative bacilli in comparison to gram-positive organisms observed in the derivation study. Clinical manifestations vary depending on infectious etiology; gram-negative sepsis has been noted to predispose patients to a more morbid clinical course, ultimately posing a higher risk for mortality, in contrast to usual clinical course in gram-positive sepsis.[3,28,29,30] Differences in admission rates and patient case-mix are additional factors that may have affected the predictive accuracy noted in this study. The derivation study was done in a university hospital (32-bed capacity for special care nursery and 6-bed capacity for intensive care) with 7000 live births per annum and a cesarean rate of 32-40%.[22] Our study was likewise done in a university government referral center (50-70 bed capacity for intensive care), with 5000 live births per annum and a cesarean rate of 40-50% (cesarean rate is a surrogate measure on high-risk deliveries). It can thus be inferred that our NICU admits more high-risk infants. Such differences may provide some bias, affecting the predictive acuity.

This scoring system may have exhibited better prediction if the diagnosis of clinically compatible but culture-negative sepsis was included as a positive outcome. More "ill" appearing neonates often score high in the clinical prediction rule, which leads to the diagnosis of clinical nosocomial sepsis. Clinical nosocomial sepsis is a term which implies absent growth in blood culture but has clinical features of LONS.[10,11] We deviated from the validation study, as we excluded culture-negative sepsis from the positive outcome. The major drawback

Table 7. Performance of prediction score at cut-off Score of Five.

Test Results Score)	Confirmed sepsis	LONS negative	Total
Positive (>5.0)	50	23	73
Negative (≤ 5.0)	10	36	46
Total	60	59	119
ROC Characteristics			
Sensitivity	50/60 = 83.3% (71.5; 91.7)		
Specificity	36/59 = 61.0% (47.4; 73.5)		
Positive predictive value	50/73 = 68.5% (56.6; 78.9)		
Negative predictive value	36/46 = 78.3% (63.6; 89.1)		
Prevalence of LONS after positive test			
Pre-test prevalence of LONs	60/119 = 50.4%		
Pre-test odds of LONS	Prevalence/(1 – Prevalence) = 0.504/(1 – 0.504) = 1.02		
Likelihood ratio positive	Sensitivity/(1 – Specificity) = 0.833/(1 – 0.610) = 2.14		
Post-test odds of LONS	Pre-test odds x LR+ = 1.02 x 2.14 = 2.18		
Post-test prevalence of LONS	Post-test odds/(Post-test odds +1) = 2.18/(2.18 + 1) = 68.6%		
Prevalence of LONS after negative test			
Likelihood ratio negative	(1 – Sensitivity)/Specificity = (1 – 0.833)/0.610 = 0.274		
Post-test odds of LONS	Pre-test odds x LR- = 1.02 x 0.274 = 0.279		
Post-test prevalence of LONS	Post-test odds/(Post-test odds +1) = 0.279/(0.279+1) = 21.8%		

in this methodology was the exclusion of neonates with manifestations of systemic inflammatory response syndrome (SIRS). Our NICU admits a large number of tertiary-level cases requiring multidisciplinary management, however significant limitation in resources and technology to rule out rare disease entities (e.g. inborn error of metabolism) poses diagnostic disadvantages which limited the ability for complete evaluation of a "sickly" neonate, and consequently lead to over diagnosis of sepsis. The validation of the scoring system in culture-proven sepsis can diminish wrongful diagnosis of infection, especially when the clinical manifestations may be from another disease entity. Lastly, there had been no clear diagnostic criteria for neonatal sepsis, and experts have presented varying opinions with regards to this issue, particularly in diagnosing culture-negative sepsis.[5,10,11,18,29] Meanwhile, blood culture has been accepted as an "imperfect" gold standard for the diagnosis of sepsis.[12,31] It served as a reference standard of many researches on diagnostic tests for infection, including studies testing acute phase reactants, cytokines, chemokines and other markers of infection use culture studies as their gold standard.[18,32,33] Since this prediction score is aimed in screening confirmed LONS, it needs to be compared to a universally accepted gold standard for its validity to be established.[34]

For the clinical application of this score, we propose a modification on classifying suspected neonates. A two-group stratification simplifies the clinical decision-making between two distinct management strategy:[35,36] the initiation of broad-spectrum antibiotics and antibiotic use based on laboratory test results prior to. We selected a cut-off score of five for providing the highest sensitivity which is important in a setting with high prevalence rate, with high specificity (Table 7). It has sensitivity and specificity of 83% and 61%, respectively. Neonates with scores of >5 are at higher risk of LONS than those with scores of ≤ 5 (68.49% vs. 21.74%, $p<0.001$). We therefore suggest that for scores of >5, broad spectrum antibiotics should be immediately started. An initial presentation of bleeding, sclerema and poor activity, with clinical findings of hypotension/ poor perfusion, thrombocytopenia or more-than-a-week's use of umbilical catheters is highly correlated with nosocomial infection. They may also be classified as high-risk and can also be managed accordingly. Scores of ≤ 5 are considered low-risk group, and initiation of antibiotics can be decided upon after the result of sepsis work-up.

We emphasize further that this scoring system cannot be used in ruling out nosocomial sepsis. If any, it helps delineates the neonate who needs immediate therapy from those who require further tests prior to antibiotic use.[11,37] Infection is ruled out based on the results of confirmatory exams (i.e. cultures and serologic markers for infection).[11]

Although the scoring method is already valid for application, a locally derived score is highly suggested to factor in the institutional differences already mentioned. Another subject that may also be of interest is the use of acute phase reactants and other markers of infection. Aside from adding accuracy in predicting diagnosis, the use of these markers should also factor in the availability and cost-effectiveness of laboratory tests prior to institutionalization. Finally, an impact analysis of this scoring system is proposed to determine the change in clinician practices and neonatal outcomes by having a systematic approach in LONS.

CONCLUSION

There has been an increasing trend in diagnosing culture-negative clinical sepsis in the NICU. Meanwhile, clinical parameters and

management practices are widely varied. In resource-poor settings, a combination of standardized definition of historical risk factors, high-risk signs for infection, and cost-effective laboratory testing is being advocated in the bedside diagnosis of late onset neonatal sepsis. However, this has to be tailored to the local epidemiologic and availability of diagnostic exams in the institution where the scoring will be applied.

This score is a valid clinical tool that can be used for the prediction of late-onset neonatal sepsis. A locally derived predictive scoring model is highly advised with consideration of local epidemiology.

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