Vital signs and their cross-correlation in sepsis and NEC: A study of 1065 very low birth weight infants in two NICUs

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Abstract

**Background**—Subtle changes in vital signs and their interactions occur in preterm infants prior to overt deterioration from late-onset septicemia (LOS) or necrotizing enterocolitis (NEC). Optimizing predictive algorithms may lead to earlier treatment.

**Methods**—For 1065 very low birth weight (VLBW) infants in two NICUs, mean, SD, and cross-correlation of respiratory rate, heart rate (HR), and oxygen saturation (SpO2) were analyzed hourly (131 infant-years’ data). Cross-correlation (co-trending) between two vital signs was measured allowing a lag of +/− 30 seconds. Cases of LOS and NEC were identified retrospectively (n=186) and vital sign models were evaluated for ability to predict illness diagnosed in the ensuing 24h.

**Results**—The best single illness predictor within and between institutions was cross-correlation of HR-SpO2. The best combined model (mean SpO2, SD HR, and cross correlation of HR-SpO2,) trained at one site with ROC area 0.695 had external ROC area of 0.754 at the other site, and provided additive value to an established HR characteristics index for illness prediction (Net Reclassification Improvement 0.25, 95% CI 0.113, 0.328).

**Conclusion**—Despite minor inter-institutional differences in vital sign patterns of VLBW infants, cross-correlation of HR-SpO2 and a 3-variable vital sign model performed well at both centers for preclinical detection of sepsis or NEC.

Introduction

Analysis of changes in vital sign patterns in hospitalized patients can yield important information about impending clinical deterioration and might alert clinicians before they would otherwise recognize signs of illness(1–3). We previously developed a system for analyzing heart rate characteristics in infants in the neonatal intensive care unit (NICU) that identifies decreased heart rate variability and decelerations that may occur prior to diagnosis.
of sepsis(4–6). Displaying a heart rate characteristics score to clinicians lowered sepsis-associated mortality 40% in a large randomized clinical trial of very low birth weight (VLBW) infants(7). While changes in heart rate patterns can provide some information about cardiovascular stability and autonomic nervous system activation and dysfunction, changes in other vital signs that occur during a systemic inflammatory response can be exploited for predictive monitoring(8,9).

Acute illness in preterm infants is often associated with increased frequency or severity of central apnea associated with bradycardia and oxygen desaturation (“ABD” events). We recently used an automated algorithm that analyzes waveform and vital sign data from NICU bedside monitors to show that ABD events and periodic breathing increase in the day prior to diagnosis in some infants with septicemia or necrotizing enterocolitis (NEC) (10,11). Waveform data are generally sampled at high frequency by standard ICU monitors (in our units, chest impedance at 60 Hz and 3 leads of ECG at 240 Hz each), and therefore analysis of central apnea requires very large data storage and processing capabilities not available at most centers. In the current study we sought to develop simpler methods for analyzing vital sign values and their interactions to predict acute illness. We focused on vital signs collected every 2 seconds (0.5 Hz) from bedside monitors: heart rate (HR), respiratory rate (RR), and oxygen saturation from pulse oximetry (SpO₂). In a preliminary analysis of infants in a single NICU, we found that increased cross-correlation (or trending together, allowing for a lag) of HR and SpO₂ performed well for preclinical detection of sepsis(12). Some of this increased cross-correlation likely represents changes in HR and SpO₂ occurring in synchrony with pauses in breathing. In the current study we expanded on this finding by analyzing vital signs from a large number of VLBW infants in two NICUs, both at baseline and surrounding two illnesses, late-onset septicemia (LOS) and NEC.

**RESULTS**

**Patient population and LOS and NEC cases**

Of 1125 VLBW infants admitted to the two NICUs during the study period, vital sign data were available for 1065 (757 in 64 months at The University of Virginia, UVA, and 308 in 18 months at Columbia University). Gestational age and birthweight were similar at the two institutions (UVA: 27.6±2.9 weeks and 1003±297 grams; Columbia: 28.5±3.2 weeks and 1030±313, grams). The total number of infant-years’ vital sign data available for analysis was 95 and 36 for UVA and Columbia infants.

Among the 1065 infants, there were 123 cases of LOS and 63 cases of NEC with vital sign data available around the time of illness. Mean gestational age and birthweight of infants with LOS or NEC were 25.9 weeks and 817 grams, significantly lower than infants without these illnesses (Table 1). Organism distribution for the LOS cases was 88 (72%) Gram-positive, 34 (28%) Gram-negative or multiple organisms, and one Candida species. Demographics and organisms for the LOS and NEC cases were similar at the two institutions. Infants with LOS were more likely to be on mechanical ventilation at the time of diagnosis (65/123, 53%) compared to infants with NEC (13/65, 21%), and infants at UVA were more likely to be on mechanical ventilation at the time of LOS or NEC (64/121, 53%) compared to infants at Columbia (14/65, 22%).
Vital sign and model analysis

Mean, standard deviation, and cross-correlation of HR, RR, and SpO\textsubscript{2} were analyzed during all times data were available. Total number of hours of data analyzed was 1.15 million (130.9 infant-years), and the breakdown by institution was UVA, 0.84M (95.4 infant-years) and Columbia 0.31M (35.5 infant-years).

Table 1 summarizes demographic variables and mean vital signs for the entire NICU stay for all 1065 infants, and vital signs in the 24 hour period before diagnosis of either LOS or NEC. Mean post-menstrual age (PMA) at the time of illness was 30.4 weeks. In univariate analysis, the best predictor of LOS or NEC being diagnosed within 24 hours was PMA. In multivariate analysis adjusting for PMA, cross correlation of HR-SpO\textsubscript{2} had the highest ROC area for LOS or NEC (0.733, p<0.001).

Figure 1 shows means of each vital sign-related parameter in the 5 day period before and after LOS or NEC diagnosis compared to the population mean for all infants for the entire NICU stay (horizontal gray line). Generally, mean HR increased slightly and mean SpO\textsubscript{2} decreased slightly around the time of diagnosis (panels a,b). Mean RR did not increase prior to diagnosis but its standard deviation did (panels c,f), which may reflect infants having more fluctuations between tachypnea and apnea. Vital sign parameters changed after diagnosis, possibly related to therapeutic interventions such as increased respiratory support. Of note, changes in vital sign measures in the day prior to illness differed between centers. For example, there was a small but statistically significant decrease in mean SpO\textsubscript{2} and increase in mean HR at UVA and not at Columbia, whereas SD of SpO\textsubscript{2} changed before illness at Columbia and not at UVA. Importantly, though, the cross-correlation of HR-SpO\textsubscript{2}, which measures co-trending of the two vital signs rather than their absolute values, was the best single predictor of illness at both centers (panel g).

Table 2 shows center-specific vital sign model ability to discriminate infants with impending LOS or NEC. For modeling, the UVA training set consisted of 825,493 hourly measurements with an event rate of 0.0032 and the Columbia training set consisted of 235,458 hourly measurements with an event rate of 0.0035. The contribution of each vital sign to the 9-variable model is represented as a Chi-squared value and corresponding coefficient p value. Performance and confidence intervals of the 9-variable model and a model using the 3 best independent predictors (mean SpO\textsubscript{2}, SD HR, and cross-correlation HR-SpO\textsubscript{2}) is shown. The table shows results of training and testing the model at each site separately and combined. We also performed external cross-validation. The UVA 3-variable model had an AUC of 0.754 when tested on Columbia data and the Columbia model had AUC 0.680 tested on UVA data. The 9-variable model had slightly less external validated performance with corresponding AUCs of 0.727 and 0.674.

Cross-correlation of HR-SpO\textsubscript{2} prior to LOS and NEC diagnosis

Figure 2a shows that the distribution of cross-correlation of HR-SpO\textsubscript{2} measurements was skewed toward higher values in the 24h period prior to LOS or NEC diagnosis compared to the values of all infants at all times. The rise in cross correlation HR-SpO\textsubscript{2} was greater in cases of NEC than LOS and continued to rise after diagnosis (Figure 2b). The effect was
seen in infants at both institutions (Figure 2c) and in infants on or off mechanical ventilation at the time of diagnosis (Figure 2d). Combining LOS and NEC cases and both institutions, mean cross correlation of HR-SpO\textsubscript{2} increased from 0.15 in the 24-48h period prior to diagnosis to 0.21 from 0-24h prior (p<0.001).

**Examples of high cross correlation of HR-SpO\textsubscript{2} in relation to respiratory rate**

In 33% of the LOS or NEC events (61/186), at least one of the hours in the day prior to the event had an extremely high cross-correlation >0.6 corresponding to the tail of the distribution in Figure 2a. We speculated that, in some cases, this finding represents apnea or periodic breathing with associated decline in HR and SpO\textsubscript{2}, and we reviewed respiratory rate, HR, and SpO\textsubscript{2} patterns the day prior to illness diagnosis in all cases with very high cross-correlation. Representative examples are shown in Figure 3. In some cases there was clearly central apnea associated with decline in HR and SpO\textsubscript{2} deep enough to be considered “bradycardia/desaturation” by standard definitions (Figure 3a) (13). In others, the concurrent fall and rise in HR, SpO\textsubscript{2}, and RR were of lower magnitude and duration but higher frequency, suggestive of periodic breathing with entrainment of HR and SpO\textsubscript{2} (Figure 3b).

**Vital sign metrics compared to and added to an established heart rate characteristics index**

An HRC index (HeRO) monitor was in use at UVA during the period of study, and scores were available for 620,978 of the hourly measurements used in the UVA vital sign training set. For this subset, the additional value of the parsimonious 3-parameter vital sign model to the HRC index were evaluated using logistic regression models and the net reclassification improvement (NRI) statistic(14). The AUC on this subset of data for the vital sign model and HRC index alone were 0.684 and 0.707 respectively. Combining the 3-variable model with the HRC index increased AUC by 0.021 to 0.728 (95% confidence interval 0.010, 0.047 Wald chi-square=22.6, p=0.00001). The Net Reclassification Improvement for the vital sign model was also highly significant with a value of 0.205 (0.113, 0.328). The cross correlation HR-SPO\textsubscript{2} by itself also added significantly to the HRC index (Wald chi-square=9.14, p=0.01) with combined AUC of 0.715. This analysis demonstrates the potential of additional vital sign analyses to improve the sensitivity over the established heart rate characteristics index monitor for early detection of LOS and NEC.

**DISCUSSION**

We previously developed a monitor displaying a heart rate characteristics index as an early warning system for sepsis, and in the current study we analyzed not only HR, but also respiratory rate and SpO\textsubscript{2}. We further expanded the study by analyzing data from a large number of VLBW infants at two institutions and in two illnesses. The major finding is that, while the value of individual vital signs for detection of LOS and NEC differed across institutions, an increase in cross-correlation of HR-SpO\textsubscript{2} performed well in both units and added to the HRC index for early detection of illness.

High cross correlation of HR-SpO\textsubscript{2} may reflect apnea in infants who are not on mechanical ventilation. An acute increase in central apnea is one of the most common signs of late-onset
septicemia in preterm infants in the NICU(15), and apnea is often accompanied by both bradycardia and oxygen desaturation. Periodic breathing, alternating brief apneic pauses and breaths, is normal in neonates and sometimes associated with decline in HR and SpO₂. Preclinical studies indicate that cytokines and prostaglandins released as part of the systemic inflammatory response are responsible for emergence of immature breathing patterns during illness(16,17), and we have previously reported that some preterm infants exhibit an acute increase in periodic breathing or in central “ABDs” (apnea with both bradycardia and desaturation) in the day before they are diagnosed with LOS or NEC(10,11). Quantitation of central apnea requires storage and analysis of large data files of chest impedance waveforms which is difficult to implement broadly, and in the current study we sought simpler measures using vital signs and their interactions. On reviewing examples of very high cross-correlation of HR-SpO₂ we found that many were clearly associated with decline in breathing rate consistent with central apnea (Figure 3a) and periodic breathing (Figure 3b), and further work is needed to substantiate this association. Interestingly, some infants on mechanical ventilation also had high cross correlation of HR-SpO₂ at the time of LOS or NEC diagnosis, indicating that there is more at play in the pathophysiology than central apnea. We speculate that some of this may reflect autonomic nervous system activation or dysfunction, or altered vasoreactivity as part of a systemic inflammatory response.

In order for predictive models to be widely applicable it is important that they be developed and tested at different institutions. We found small but statistically significant differences in individual vital signs of infants at UVA and Columbia, most notably, mean and standard deviation of SpO₂ and their contribution to the predictive models (Table 2). This may reflect differences in clinical management strategies of lung disease or apnea, and may account for the more robust performance of vital sign interactions such as cross-correlation of HR-SpO₂ across institutions, since this measure reflects co-trending rather than absolute values.

Another consideration for the predictive models we report here is that they compare vital sign patterns before illness with those of all VLBW infants at all times during the NICU stay. Since vital signs and occurrence of apnea and periodic breathing change with advancing gestational and postmenstrual age, an important future direction is to incorporate demographic and clinical variables into the algorithm. Furthermore, since there may be significant inter-individual variation in vital signs and apnea, displaying an acute change compared to an infant’s baseline might be the best approach.

Any new diagnostic or predictive test such as cross correlation of HR-SpO₂ should be compared to existing modalities. The HRC index was previously developed by our group as an early warning system for sepsis and is displayed in the UVA NICU. Whether display of the HRC index led to treatment of the UVA infants at an earlier phase of illness is unknown since we cannot pinpoint the exact time an infant develops bacteremia or NEC. We did find that infants at Columbia had a higher cross-correlation of HR-SpO₂ in the 2 day period prior to diagnosis (0.2 versus 0.1, Figure 2c) which could reflect more severe or longer-standing illness. Alternatively this might simply reflect the fact that more UVA infants were on mechanical ventilation at the time of diagnosis and therefore did not have apnea or periodic breathing. Of note, we found that there was additive value in combining the HRC index and the cross correlation of HR-SpO₂ or the 3-vital sign model for early detection of LOS and NEC.
More work is required to determine whether displaying a score representing multiple vital signs will improve outcomes of infants in the NICU. An important aspect of this work is to determine whether to identify a threshold “alarm” value with acceptable sensitivity, false positive rate, and other diagnostic utility measures. A major problem with this approach is that infants in the early stages of illness who have worsening vital sign patterns compared to their own baseline but who fall below the threshold will be missed. Another problem is that some infants at high risk for sepsis or NEC may have chronically abnormal vital sign patterns (above the threshold). An alternative monitoring strategy, favored by our group and used for the HRC index, is to display in real-time a vital sign-based risk score, so that trends over time for individual infants can be used in decisions about testing and treatment for acute and potentially catastrophic illnesses(4,18).

CONCLUSION

Sepsis and NEC continue to contribute a great deal to morbidity and mortality of preterm infants(19). Detection and treatment in the early phase of illness, before overt clinical deterioration, is likely to improve outcomes but is difficult due to the subtlety of the early physiologic changes. Analysis of multiple vital signs and their interactions can assist in preclinical detection in some cases, and translating these metrics to real-time bedside displays and testing their impact on outcomes in randomized clinical trials is an essential next step.

METHODS

Patient population and clinical data collection

We collected and stored all bedside monitor vital sign data on all patients admitted to the UVA NICU over a 64 month period from 2009 to 2015 and to the Children’s Hospital of New York NICU (Columbia University) over an 18 month period from 2013 to 2015. All VLBW infants with data available were included in this study, which was approved by the Institutional Review Boards of both institutions with waiver of consent due to its purely observational nature.

Clinical data were abstracted from electronic medical records into a relational clinical database. Demographics included gestational age, birthweight, gender, and final outcome (death, discharge, or transfer). Cases of LOS and NEC were retrospectively identified from review of clinical databases. LOS was defined as signs of sepsis and a positive blood culture at 3 or more days of age and at least 5 days of treatment with antibiotics. Subsequent episodes of LOS or NEC were included if they occurred more than 7 days after the previous episode. NEC was defined as clinical and radiographic signs of NEC and a full course of therapy (bowel rest and antibiotics). We excluded cases of focal intestinal perforation without NEC as identified by the attending neonatologist and pediatric surgeon, based on clinical and, when available, surgical findings. Cases in which infants were transferred from an outside hospital with LOS or NEC were excluded since baseline “well” data were not available for comparison.
Data collected related to LOS or NEC episodes included chronologic and post-menstrual age at the time of the blood culture or abdominal radiograph establishing the diagnosis, blood culture results, and whether on ventilatory support at the time of diagnosis.

**Vital sign analysis**

Bedside monitor data were collected using a BedMaster central network server (Excel Medical, Jupiter, FL). RR derived from the chest impedance signal, HR from the ECG signal, and SpO\textsubscript{2} from the pulse oximeter were collected every 2 seconds. During the time period of study at both institutions, pulse oximeters were set to the default SpO\textsubscript{2} averaging setting (8 seconds). Mean, standard deviation, and cross-correlation of HR, RR, and SpO\textsubscript{2} were calculated in 10 minute windows and then averaged for each hour for analysis throughout the NICU stay and then specifically in the 2 day period before and after diagnosis of LOS and NEC.

**Quantifying cross-correlation between vital signs**

The maximum cross-correlation between two vital sign signals was measured over ten-minute windows by first standardizing each signal (subtracting mean and dividing by standard deviation) and then using the Matlab function XCORR, with a lag time of −30 to +30 seconds. A high value of this statistic (approaching 1) indicates the two signals are in positive synchrony (i.e. they go up and down together) with a possible lag or time difference of up to 30 seconds. We also calculated the minimum cross-correlation value reflecting signals going in opposite directions; these negative synchrony values are not reported because they were not associated with adverse events.

**Heart rate characteristics index analysis**

At UVA, a heart rate characteristics (HRC) index monitor has been in use since 2003 (HeRO monitor, Medical Predictive Science Corporation, Charlottesville, VA). The monitor was developed as an early warning system for sepsis, and the HRC index incorporates three measures of abnormal HR characteristics that occur in some neonates with sepsis: low HR variability, sample asymmetry (more decelerations, fewer accelerations), and low sample entropy. The HRC index is displayed at UVA and not at Columbia, and we therefore compared vital sign metrics examined in this study with the HRC index in UVA patients only.

**Statistics and modeling**

Summary statistics and logistic regression were used to describe and compare vital signs collected from infants at UVA and Columbia. Univariate logistic regression analyses were performed to determine whether there was a significant change in each vital sign metric in the 24h period before diagnosis of LOS or NEC, compared to normative data from all VLBW infants at all times. Demographic variables potentially associated with LOS and NEC (gestational age, birthweight, gender, and postmenstrual age) were also analyzed. Bivariate analyses incorporating postmenstrual age and each vital sign metric were performed. Multivariate logistic regression models were developed using data from each site.
separately as the training set in an iterative process with external validation on data from the other site.

For summary statistics, mean (standard deviation) is shown unless otherwise indicated. For associations between vital signs and illnesses, Wald Chi-square and p values are reported, and for modeling, area under receiver operator characteristics curve (ROC AUC) and 95% confidence intervals are reported. Net reclassification improvement (NRI) was also used to compare the performance of the new vital sign models with the HRC index. NRI is a measure of the fraction of cases that are correctly reclassified by a new risk assessment tool compared to an established tool(14).

Analyses were performed in MATLAB (MathWorks, Natick MA).

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Figure 1. Vital signs and their cross-correlation around septicemia and NEC events

In 186 cases of LOS or NEC at UVA and Columbia, mean (panels a-c), standard deviation (panels d-f) and cross-correlation (panels g-i) of heart rate (HR), oxygen saturation (SpO₂) and respiratory rate (RR), are shown 5 days before and after diagnosis. Mean (solid line) and standard deviation (dotted line) are shown. The horizontal dashed line represents the value for all VLBW infants at all times.
Figure 2. Cross-correlation of HR-SpO$_2$ in septicemia and NEC

Vital sign data were analyzed for cross-correlation of HR-SpO$_2$ for 1065 VLBW infants at all times and around the time of 123 cases of late-onset septicemia (LOS) and 63 cases of NEC. Panel a) For each cross-correlation value, the density of hourly measurements for all 1065 VLBW infants at all times during the NICU stay is shown by the grey dashed line and the number of measurements in the 24h period prior to illness diagnosis by the black line. Panel b-d) Mean cross-correlation of HR-SpO$_2$ 2 days prior to and following diagnosis of illness. Increased cross-correlation occurred in both illnesses (panel b, LOS solid line, versus NEC dotted line), in both institutions (panel c, UVA solid line, versus Columbia dotted line), and in infants on or off mechanical ventilation (panel d, on ventilator solid line, off ventilator dotted line).
Figure 3. Examples of high cross correlation of HR-SpO$_2$ and associated respiratory rate patterns prior to septicemia and NEC
Representative one hour tracing of HR and SpO$_2$ (top), and 10 minute tracings of HR, SpO$_2$, and respiratory rate (insets at bottom) are shown for 2 infants in the day prior to diagnosis of illness. Panel a) UVA infant 5 hours prior to diagnosis of sepsis, when cross-correlation of HR-SpO$_2$ was 0.844. There are frequent HR decelerations (solid black line) and concurrent decline in SpO$_2$ (dotted black line), preceded by decline in respiratory rate (solid grey line in bottom inset, note right Y axis for respiratory rate) Panel b) Columbia infant 1.5 hours prior to diagnosis of NEC, when cross-correlation of HR-SpO$_2$ was 0.81. There are repetitive, regular declines in HR and SpO$_2$ associated with decline in respiratory rate.
Table 1

Vital signs and their cross-correlation over the entire NICU stay and in the 24h period prior to LOS or NEC events (combined UV A and Columbia)

| Category       | Variable        | Measure | All Mean (SD)  | Event Mean (SD) | ROC area<sup>a</sup> | p=         | VS + PMA ROC area<sup>b</sup> | p=         |
|----------------|-----------------|---------|----------------|-----------------|----------------------|------------|-----------------------------|------------|
| **Vital Signs**| Heart rate      | Mean    | 158 (12)       | 161 (13)        | 0.551                | 0.003      | 0.707                       | 0.182      |
|                | Resp. Rate      |         | 51 (11)        | 50 (12)         | 0.540                | 0.174      | 0.701                       | 0.243      |
|                | SPO₂ %          |         | 94 (4)         | 91 (5)          | 0.634                | 0.000      | 0.718                       | 0.000      |
|                | Heart rate      | Std. Dev.| 7 (3)          | 6 (3)           | 0.596                | 0.000      | 0.706                       | 0.121      |
|                | Resp. Rate      |         | 17 (5)         | 17 (6)          | 0.530                | 0.054      | 0.701                       | 0.365      |
|                | SPO₂ %          |         | 3 (2)          | 4 (3)           | 0.594                | 0.000      | 0.714                       | 0.000      |
|                | HR-RR           | Cross-Correlation | 0.15 (0.09)  | 0.18 (0.12)    | 0.579                | 0.000      | 0.722                       | 0.000      |
|                | HR-SPO₂         |         | 0.10 (0.16)    | 0.21 (0.22)    | **0.652**            | **0.000**  | **0.733**                   | **0.000**  |
|                | RR-SPO₂         |         | 0.23 (0.12)    | 0.25 (0.13)    | 0.527                | 0.091      | 0.699                       | 0.137      |
| **Demographics**| BWT             | Grams   | 920 (288)      | 817 (261)      | 0.605                | 0.000      | 0.715                       | 0.000      |
|                | GA              | Weeks   | 26.8 (2.6)     | 25.9 (2.5)     | 0.604                | 0.000      | 0.707                       | 0.035      |
|                | PMA             | Weeks   | 34.1 (6.4)     | 30.4 (4.3)     | **0.705**            | **0.000**  | NA                         | NA         |
|                | Male            | %       | 54%            | 55%            | 0.503                | 0.860      | 0.705                       | 0.796      |

SD=Std.Dev.=Standard deviation; ROC=Receiver Operator Characteristics Curve; Max.=maximum; BWT=birth weight;

<sup>a</sup>ROC area comparing 0-24h prior to LOS or NEC diagnosis to all data.

<sup>b</sup>Bivariate analysis
Table 2
Site-specific vital sign and model performance for LOS and NEC detection

| Vital Signa | UVA | | CU | | Combined |
|---|---|---|---|---|---|
| | Chi-squared | p= | Chi-squared | p= | Chi-squared | p= |
| Mean Heart Rate | 7.201 | 0.0073 | 0.881 | 0.3479 | 3.198 | 0.0737 |
| Mean Resp Rate | 6.104 | 0.0135 | 15.242 | 0.0001 | 18.439 | 0.0000 |
| Mean SPO2 % | 20.826 | 0.0000 | 0.547 | 0.4596 | 24.974 | 0.0000 |
| SD HR | 17.971 | 0.0000 | 30.885 | 0.0000 | 38.675 | 0.0000 |
| SD RR | 4.491 | 0.0341 | 11.830 | 0.0006 | 13.615 | 0.0002 |
| SD SPO2 | 0.475 | 0.4906 | 8.159 | 0.0043 | 0.199 | 0.6558 |
| XC HR-RR | 7.404 | 0.0065 | 3.420 | 0.0644 | 9.023 | 0.0027 |
| XC HR-SPO2 | 36.487 | 0.0000 | 36.530 | 0.0000 | 73.957 | 0.0000 |
| XC RR-SPO2 | 0.650 | 0.4203 | 8.522 | 0.0035 | 0.946 | 0.3307 |

| Model | ROC area | 95% CI | ROC area | 95% CI | ROC area | 95% CI |
|---|---|---|---|---|---|---|
| 9-variable model | 0.711 | 0.674-0.734 | 0.770 | 0.727-0.812 | 0.721 | 0.691-0.743 |
| 3-variable modelb | 0.695 | 0.654-0.721 | 0.745 | 0.710-0.786 | 0.710 | 0.679-0.728 |
| XC HR-SPO2 | 0.617 | 0.577-0.651 | 0.701 | 0.654-0.752 | 0.644 | 0.618-0.673 |

XC cross correlation

\( a \) Contribution to the 9-variable model

\( b \) Mean SpO2, SD HR, and XC HR-SPO2

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