The Risk of Mortality for Patients with Persistently Elevated HeRO Scores

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Background

The HRC index, or HeRO Score, was developed to predict imminent infection among premature infants by detecting abnormal heart rate variability (HRV)[1] that is associated with pro-inflammatory cytokines.[2] Elevated HeRO Scores have been linked with a number of adverse events in neonates, including death.[3] The clinical utility of HeRO monitoring was assessed in a pragmatic randomized controlled trial of 3,003 very low birthweight (VLBW; birth weight < 1500g) patients, the largest ever conducted among premature infants. Randomization to have HeRO Scores displayed to clinicians was associated with an all-cause mortality reduction of 22%,[4] and a reduction in mortality after infection of 40%.[5]

As more neonatal ICUs around the world adopt HeRO monitoring in their units, clinicians have observed patients with persistently elevated HeRO Scores. That is, a HeRO Score that stays at the maximum value that HeRO will display, 7.00, for several days at a time. In this analysis, we sought to use the control patients (i.e., those randomized to HeRO non-display) from the RCT dataset to discern the implications of persistently elevated HeRO Scores on mortality.

Methods

For each hourly HeRO Score generated by control patients (those randomized to have HeRO Scores masked from clinicians) in the RCT dataset, we calculated the median HeRO Score of the previous 7-day period whenever there was at least 75% data coverage (that is, at least 168 x 75% = 126 hourly HeRO Scores were available in the previous seven days). For each patient, we took the maximum value of each of these 7-day medians, and called it the maximum 7-day median HeRO Score.

We defined a patient as having had a persistently elevated HeRO Score when the maximum 7-day median HeRO Score was 7.0 (the highest possible). It is important to note that the patient must have survived at least 126 hours in order to have a maximum 7-day median HeRO Score.

Patients without a complete pertinent demographic record or without a maximum 7-day median HeRO Score were excluded from subsequent analysis. We compared the rate of mortality among those patients with a persistently elevated HeRO Score to those without.

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Figure 1. A patient with a persistently elevated HeRO Score. The plot is showing a 5-day trend of the hourly HeRO Score on the left as well as the most recent hourly HeRO Score on the right

Further, we calculated the performance of the maximum 7-day median HeRO Score as a predictor of death using standard metrics (Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), Risk Ratio, and area under the Receiver Operating Characteristic (ROC) curve) at a variety of thresholds besides 7.0.

We used a logistic regression model to evaluate the performance of available demographics variables that were collected during the RCT to predict mortality, and compared it to a logistic regression model using the same demographic variables *plus* maximum 7-day median HeRO Score.

Finally, we repeated all analyses using the *mean* 7-day HeRO rather than the median.

All calculations were performed in R.[6] We assessed significance at $p<0.05$.

Results

Of the 1488 control patients in the RCT, 1266 patients had complete demographics records and enough HeRO Scores to be included in this analysis. The overall mortality was 7.5% in this cohort. Table 1 shows the demographic characteristics of those patients with and without a persistently elevated HeRO Score (maximum 7-day median HeRO Score = 7.0). 7.4% of patients had a persistently elevated HeRO Score, and their mortality was 7x those without (37.2% versus 5.1%, respectively, $p<0.0001$).

Table 2 shows metrics of the maximum 7-day median HeRO Score to predict death for a number of thresholds. ROC was 0.865 (95% CI: 0.832 to 0.898).

In developing a logistic regression model to predict death based on demographic variables, we noted high correlation between gestational age and birth weight, and elected to keep birth weight because it was an inclusion criterion (the RCT was conducted on VLBW patients). We sequentially removed the least significant

Table 1. Patient Demographics. Continuous variables were evaluated with a t-test, categorical variables were evaluated with a test of proportions.

	No Persistently Elevated HeRO Score	Persistently Elevated HeRO Score	p
N (% of total)	1172 (92.6%)	94 (7.4%)	
Gestational Age (sd)	28.3 (2.7)	25.2 (1.5)	< 0.0001
Birth Weight (sd)	1018 (282)	724 (184)	< 0.0001
Male Sex (%)	601 (51.3%)	47 (50%)	0.895
Apgar 1 (sd)	5.2 (2.5)	3.2 (2.2)	< 0.0001
Apgar 2 (sd)	7.2 (1.8)	5.7 (2.0)	< 0.0001
Died (%)	60 (5.1%)	35 (37.2%)	< 0.0001

Table 2. Metrics of various thresholds of maximum 7-day median HeRO Score to predict death.

HeRO Threshold	Percentile	Sensitivity	Specificity	PPV	NPV	Risk Ratio
1.0	35.4th	98.9%	38.3%	11.5%	99.8%	51.7x
2.0	58.8th	93.7%	63.1%	17.1%	99.2%	21.2x
5.0	85.0th	62.1%	88.8%	31.1%	96.7%	9.3x
7.0	92.6th	36.8%	95.0%	37.2%	94.9%	7.3x

variable one at a time while there were any non-significant predictor variables until all predictor variables were significant. The resulting model included two predictor variables: birth weight and Apgar2, and had an ROC area for predicting death of 0.825 (95% CI: 0.789 to 0.861).

When we re-trained the logistic regression model using the same demographics variables, plus maximum 7-day median HeRO Score, all variables were significant with maximum 7-day median HeRO Score having $p < 0.0001$. The ROC of this combined demographics plus HeRO model was 0.876 (95% CI: 0.848 to 0.905). Figure 2 shows the predictiveness curve of the combined demographics plus maximum 7-day median HeRO Score model to predict death.

Performance using maximum 7-day *mean* HeRO Score was slightly improved relative to the median. ROC of the maximum 7-day mean HeRO Score was 0.871 (95% CI: 0.840 to 0.903) versus 0.865 for the median. Remarkably, the risk ratio of death for those above the 50th percentile versus below the 50th percentile of the demographics plus maximum 7-day mean HeRO Score model was 92x, versus 46x for same model using the median.

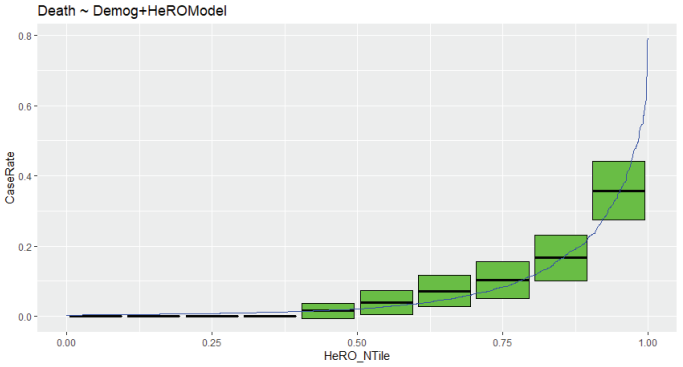

Figure 2. Predictiveness curve of the combined demographics plus maximum 7-day median HeRO Score model to predict death. The x-axis represents the percentile of model's predictions, the y-axis represents the rate of death. The smooth blue line is the model's predicted risk of death. The black bars represent the observed rate of death for each decile, boxed by 95% confidence intervals in green.

Discussion

The randomized controlled trial of HeRO monitoring was a pragmatic design. That is, clinicians were not instructed to perform specific clinical actions at set thresholds of HeRO Score. Instead, they were educated on how the HeRO Score was developed and left to incorporate HeRO into their clinical practice as they saw fit.

An advantage of this pragmatic design is that the profoundly positive results of the RCT should be reproducible in clinical practice outside the rigors of an RCT protocol. Nevertheless, clinicians are left without concrete direction as to what thresholds of HeRO Score are actionable.

Of utmost difficulty for the practicing neonatologist is a patient with persistently elevated HeRO Scores. Although the numeric value is high, there is no discernible trend to guide the clinician that this patient is trending "better" or "worse".

In the present analysis, we have re-analyzed control patients in the HeRO randomized controlled trial to identify patients with persistently elevated HeRO Scores. We found that those patients with a maximum 7-day median HeRO Score of 7 or more had a profound risk of death when compared to other patients (37.2% versus 5.1%, respectively).

Furthermore, we found that patients with low maximum 7-day median HeRO Scores had remarkably low rates of death. For the 35% of patients for whom the maximum 7-day median HeRO Score fell below 1.0, survival was 99.8%, and these patients are more than 50x less likely to die than other patients. The mean HeRO Score over the previous 7 days appeared to have even better performance because it was able to capture late spikes in HeRO prior to death better than the median over the previous seven days. Essentially, patients did not die without elevations in their HeRO Scores.

These results remained true when controlling for demographic predictors.

Weaknesses of the current analysis are its retrospective nature and lack of a complete set of demographic predictors. A strength is that it is a large dataset of patients for whom the HeRO Score was generated but not displayed to clinicians, eliminating a potential feedback loop of scores affecting outcomes.

Conclusion

Clinicians should remain vigilant to the subgroup of patients with persistently elevated HeRO Scores due to their profound risk of death, whereas consistently low HeRO Scores provide reassurance of low risk.

References

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