outcome between the epochs in the 2 groups of hospitals. This raises the possibility of a statistical calculation error because the authors do not provide an explanation for this degree of deviation of aOR from the raw unadjusted OR. If the aOR for this measure is indeed insignificant, then the author's conclusion that $SpO_2$ policy changes had no impact on any ROP incidence needs to be revised.

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https://doi.org/10.1016/j.jpeds.2020.11.005

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## Reply

***To the Editor:***

Dr Srivatsa voiced concerns about our report investigating the impact of changing oxygen saturation alarm limit policies on neonatal outcomes among extremely preterm infants. Dr Srivatsa correctly notes that the magnitude of difference between the unadjusted ORs and aORs for the outcome of "any retinopathy of prematurity (ROP)" was approximately 40% for infants in hospitals without a policy change. This magnitude of difference was not seen for other outcomes.

In fact, the aORs are less than the unadjusted ORs across epochs for most outcomes assessed in both hospital groups. We could speculate about exactly why the degree of difference is higher for the outcome of "any ROP," but we know it is due to adjustment for 1 or more of the important baseline covariates included in the model. Many of these covariates varied significantly between epochs. We confirm that the observed difference was not due to a calculation or reporting error.

Further, we dispute the notion that our conclusion need be revised. The strength of our study design is that we included hospitals without a policy change as a comparison group. This allowed us to isolate the impact of the policy change itself from secular trends in practice and outcomes that would be observed in a traditional before/after study following a policy change. Although the aOR for "any ROP" suggested improved outcomes in epoch 2 for both groups, the interaction between hospital group and epoch was not significant. This supports our conclusion that a policy change was not associated with meaningful improvements in the outcome of any ROP.

In conclusion, the difference between the unadjusted ORs and aORs is due to the adjustment for covariates that may have differentially impacted the outcomes, leading to different degrees of difference between the unadjusted ORs and aORs across outcomes.

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## Do B-type natriuretic peptide levels accurately predict outcome in infants with congenital diaphragmatic hernia?

***To the Editor:***

We have read with interest the study by Guslits et al that investigated the prognostic effect of B-type natriuretic peptide (BNP) in predicting the outcomes of infants with congenital diaphragmatic hernia (CDH).[1] Infants with atrial septal defect, ventricular septal defect, or patent ductus arteriosus were included. However, it may be important to exclude subjects with any other disease that influences ventricular volume expansion and pressure overload, because BNP is a cardiac neurohormone secreted by the ventricles in response to volume expansion and pressure overload.[2] We are very interested in the echocardiographic parameters of those infants, to understand if these heart diseases could have an impact on their right volume and pressure. Alternatively, an additional control group with similar heart diseases but without CDH could be included.

In the present study, the authors sought additional biomarkers that could longitudinally assess illness severity due to pulmonary vascular disease and right ventricle

dysfunction.[1] The measurements of pulmonary hypertension and right ventricle performance provided by echocardiography are variable and less consistent with the clinical outcomes of CDH.[3,4] It is of interest to see the advantage of BNP over echocardiography in the same cohort. In addition, the authors performed receiver operating characteristic curves to identify BNP cut-offs for maximizing correct outcome classification at each time point. They concluded that BNP accurately predicted outcome at 3-5 weeks. However, the total sample size of 49 infants may be not enough to acquire an accurate information on BNP cut-off, consistent with the wide ranges of the 95% CIs. When the hypothesized area under the receiver operating characteristic curve is approximate to 0.8, as provided by this study, the estimated sample size should be no less than 208-274 (area under the receiver operating characteristic curve = 0.8 ± 0.1) subjects (**Figure**; available at www.jpeds.com).[5,6]

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## Reply

*To the Editor:*

We thank Drs Tang and Ji for their interest, correspondence, and thoughtful queries regarding our manuscript. To address their first question about the inclusion of infants with patent ductus arteriosus (PDA), atrial septal defect (ASD), and ventricular septal defect (VSD), we chose to include these cardiovascular defects to increase the generalizability of our data to the typical congenital diaphragmatic hernia (CDH) population, as these conditions are either part of the physiology of CDH or are more likely to be diagnosed in the relevant time period due to serial echocardiography. PDA is a physiologically important condition associated with pulmonary hypertension in newborns with CDH. The timing of spontaneous PDA closure is variable and related to clinical status in this patient population.[1] Further, one of the important interventions we employ when right-sided heart pressures are suprasystemic is to administer prostaglandin E1 to maintain ductal patency and help preserve right ventricular function. Congenital heart disease is common in CDH, with a prevalence of 17.8% reported in a large retrospective review of more than 4000 infants by Menon et al.[2] Overall, 8% of infants with CDH had an ASD or VSD, and these were the most common variants of congenital heart disease, comprising 34% and 23% of anomalies, respectively, in that cohort. In our cohort, the vast majority of infants had an atrial communication (patent foramen ovale vs ASD) throughout the study period. It is possible that many of these defects would not have been identified had the infants not undergone echocardiograms for the evaluation of underlying CDH, considering the mean age of diagnosis for an ASD is 5 months in otherwise-healthy infants.[3] Furthermore, only 1 of the 4 infants in our cohort with VSD required surgical intervention; therefore, with the exception of the sole operative VSD, these defects would be classified as minor and unrelated to hemodynamic status.[2] Finally, we believe that Drs Tang and Ji may be concerned that brain natriuretic peptide (BNP) levels are influenced by left-to-right shunting via these communications. We think left-to-right shunting is unlikely to substantially influence BNP in this cohort as a whole, as the fall in BNP mirrors the pattern of decreasing right-sided pressures we previously described in infants with CDH over the same time frame (discussed in the sections to follow), which would be inconsistent with increased shunt due to decreasing pulmonary vascular resistance.

As noted previously, with regard to echocardiographic evaluation of right-sided pressures for these infants, we retrospectively evaluated weekly serial echocardiograms in 140 infants with CDH over the first 6 weeks of life and believe the current data can be interpreted in the context of our greater experience with serial echocardiography.[4] We scored each echocardiogram for the degree of elevation in right-sided pressure estimates and found accurate prediction of various clinical outcomes by persistence of this elevation, including the 56-day respiratory outcome used in the current study. We showed that infants with CDH with the good outcome at 56 days primarily transitioned to lower right-sided pressure estimates by 2-3 weeks of age. This compares with healthy babies born at term, who usually transition by 2 days of age.[5] In the current study, the pattern we observed in BNP values, as compared with that seen with the changes in right-sided pressure estimates in our previous work, suggests interesting parallels to the BNP trajectory of healthy newborns born at term.[6] In healthy infants during the usual fall in right-sided pressure estimates,[5] BNP peaks at 24 hours and then declines steadily to 1 week of age.[6] It is not clear which part of the underlying physiology this pattern

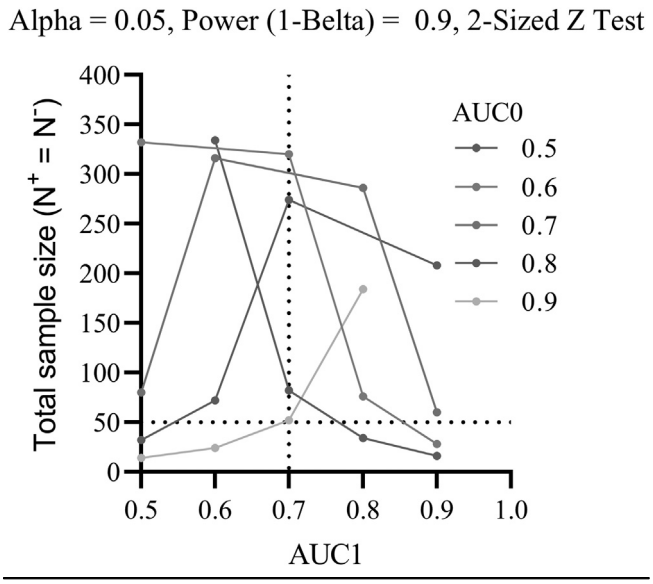


**Figure.** Estimated total sample size by Power Analysis & Sample Size 2020 calculator under various hypothesized AUC values (AUC0) and predicting AUC value (AUC1). *AUC,* area under the receiver operating characteristic curve; *N+,* number with positive outcome; *N–,* number with negative outcome.