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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References

1. Guslits E, Steurer MA, Nawaytou H, Keller RL. Longitudinal B-type natriuretic peptide levels predict outcome in infants with congenital diaphragmatic hernia. J Pediatr 2021.;229:191-8.e2.
2. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161-7.
3. Patel N, Lally PA, Kipfmueller F, Massolo AC, Luco M, Van Meurs KP, et al. Ventricular dysfunction is a critical determinant of mortality in congenital diaphragmatic hernia. Am J Respir Crit Care Med 2019;200:1522-30.
4. Patel N, Massolo AC, Paria A, Stenhouse EJ, Hunter L, Finlay E, et al. Early postnatal ventricular dysfunction is associated with disease severity in patients with congenital diaphragmatic hernia. J Pediatr 2018;203:400-7.e1.
5. Power Analysis & Sample Size, PASS. Accessed October12, 2020. https://www.ncss.com/software/pass/
6. Negida A, Fahim NK, Negida Y. Sample size calculation guide—part 4: how to calculate the sample size for a diagnostic test accuracy study based on sensitivity, specificity, and the area under the ROC curve. Adv J Emerg Med 2019;3:e33.

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

represents in healthy newborns, whether it is related to changing pulmonary vascular resistance, changes in intracardiac or extracardiac shunts, fluid shifts, or all of these processes in concert.

With respect to the statistical analyses performed and our sample size, we created our hypothesis regarding differences in BNP trajectory based on our clinical experience and performed exploratory analyses based on this hypothesis. It is our practice to conduct power analyses in the context of negative findings to ensure that we have not encountered false-negative results. In the receiver operating characteristic curve analyses, we identify robust findings in the accuracy of BNP for prediction of clinical outcome during weeks 3 through 5, with cut-off values that maximize the percent correctly classified, and sensitivity and specificity without bias toward either measure. Despite our sample size, the positive findings for these weeks negates the potential for false-negative results. We are overall reassured that our findings are robust to multiple different analytic approaches.

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References

1. Steurer MA, Moon-Grady AJ, Fineman JR, Sun CE, Lusk LA, Wai KC, et al. B-type natriuretic peptide: prognostic marker in congenital diaphragmatic hernia. Pediatr Res 2014;76:549-54.
2. Menon SC, Tani LY, Weng HY, Lally PA, Lally KP, Yoder BA. Clinical characteristics and outcomes of patients with cardiac defects and congenital diaphragmatic hernia. J Pediatr 2013;162:114-9.e2.
3. Hanslik A, Pospisilb U, Salzer-Muhar U, Greber-Platzer S, Male C. Predictors of spontaneous closure of isolated secundum atrial septal defect in children: a longitudinal study. Pediatrics 2006;118:1560-5.
4. Lusk LA, Wai KC, Moon-Grady AJ, Steurer MA, Keller RL. Persistence of pulmonary hypertension by echocardiography predicts short-term outcomes in congenital diaphragmatic hernia. J Pediatr 2015;166:251-6.
5. Skinner JR, Boys RJ, Hunter S, Hey EN. Non-invasive assessment of pulmonary arterial pressure in healthy neonates. Arch Dis Child 1991;66(4 SPEC NO):386-90.
6. Cantinotti M, Storti S, Parri MS, Prontera C, Murzi B, Clerico A. Reference intervals for brain natriuretic peptide in healthy newborns and infants measured with an automated immunoassay platform. Clin Chem Lab Med 2010;48:697-700.

Coronavirus disease 2019, multisystem inflammatory syndrome in children, apolipoprotein E4, and race

To the Editor:

Kaushik et al presented a series of 33 children from New York City hospitals diagnosed with multisystem inflammatory syndrome in children (MIS-C); 81% had antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Similarly, Carter et al, reported on a series of 25 children diagnosed with MIS-C from the United Kingdom; 68% were SARS-CoV-2 seropositive.[2] The children in both groups exhibited a cytokine profile consistent with a robust innate immune response. At the same time, emerging evidence suggests the hypothesis that the apolipoprotein E4 (apoE4) genotype can predict coronavirus disease 2019 (COVID-19) severity in adults.[3,4] Accordingly, we propose the hypothesis that the apoE4 genotype may identify children at increased risk of developing MIS-C from SARS-CoV-2 infection.

Classically, the apoE4 genotype has been associated with cardiovascular disease and Alzheimer's disease[5]; however, it has also been associated with an enhanced in vivo innate immune response.[6] Notably, individuals of African descent may have twice the frequency of the ε4 allele (30%-40%) compared with those of European or Asian descent,[7] and therefore, they may be more likely to exhibit a stronger innate immune response to the SARS-CoV-2 infection.

In the series presented by Carter et al, the children who were SARS-CoV-2 seropositive exhibited more severe disease; 8 of 9 black children compared with 5 of 10 white children in the series were SARS-CoV-2 seropositive.[2] Of 21 patients with a depressed systolic ventricular function in the report by Kaushik et al, 11 were black and 1 white (Table 4).[1] This suggests an overrepresentation of black children diagnosed with MIS-C from severe SARS-CoV-2 infection.

Therefore, as seen with adults, the apoE4 genotype may identify children at a greater risk of severe SARS-CoV-2 infection; and in particular, MIS-C.

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