

Balancing Value and Risk in Early Discharge of Patients With Kawasaki Disease

Nathan M. Money, DO,^a John B. Darby, MD^b

Kawasaki disease (KD) continues to present clinicians with challenges and uncertainties. When diagnosing and treating KD, lack of a definitive diagnostic test, symptom overlap, and atypical presentations can perplex even experienced physicians. Treatment is costly because of hospitalization and subspecialist follow-up. Although concerns exist that KD may be overdiagnosed,¹ a missed diagnosis of KD may have severe consequences.

A particular challenge for clinicians caring for a child with KD is the timing of discharge. Because 10% to 20% of patients are refractory to initial therapy with intravenous immune globulin (IVIg),² clinicians must decide how long to observe patients post-IVIg treatment and when to retreat if fever recurs, understanding that IVIg can also cause fever.³ The American Heart Association KD guidelines do not specify post-IVIg observation time,² which varies between clinicians.⁴ KD is estimated to account for 5000 to 6000 hospitalizations a year in the United States⁵ with an average length of stay of 3 days.⁶ Identifying patients at low risk for IVIg resistance could characterize patients safe for early discharge and may reduce costs and resource use.

In this month's issue of *Hospital Pediatrics*, Hester et al⁷ present an IVIg nonresponse risk model from the angle of high-value care by focusing on patients at low risk of IVIg resistance. This contrasts with previous KD risk models, which have been aimed to identify high-risk patients who may benefit from more aggressive initial therapies.^{8,9} Sensitive and specific risk scores have been successfully developed in Japanese populations but discriminate poorly in other populations.^{10,11}

Hester et al⁷ analyzed a retrospective cohort of 430 patients with KD from a single, large Midwestern hospital to create a clinical prediction model for IVIg nonresponse in patients with KD. Eighty one (18.9%) patients met the criteria for IVIg nonresponse, defined as meeting 1 or more of the following criteria: (1) fever 36 hours to 7 days after IVIg completion, (2) a second dose of IVIg administered at least 20 hours after IVIg completion, or (3) readmission within 7 days of discharge and receipt of a second dose of IVIg. Eight variables were selected by using a multivariate stepwise regression model: white blood cell count, platelets, hemoglobin, aspartate aminotransferase, sodium, albumin, classic presentation (versus incomplete), and maximum temperature within 6 hours of completing IVIg. The authors present their stratification of model accuracy at various predictive probabilities. For example, by using a predictive probability cutoff of 0.10 (ie, 10% probability for nonresponse to IVIg), the model has a 90% sensitivity for determining risk for nonresponse to IVIg and identifies 26% of children that are IVIg responders within the population and eligible for early discharge. At this predictive cutoff, the model provides a negative predictive value of 93%, indicating that 7% of patients could be falsely identified as low risk.

www.hospitalpediatrics.org

DOI: <https://doi.org/10.1542/hpeds.2019-0204>

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Address correspondence to Nathan M. Money, DO, Section of Pediatric Hospital Medicine, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, 1102 Bates Ave, #FC1860, Houston, TX 77030. E-mail: nmoneydo@gmail.com

HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

^aSection of Pediatric Hospital Medicine, Department of Pediatrics, Texas Children's Hospital and Baylor College of Medicine, Houston, Texas; and ^bSection of Pediatric Hospital Medicine, Department of Pediatrics, Brenner Children's Hospital and School of Medicine, Wake Forest University, Winston-Salem, North Carolina

The authors' clinical prediction rule improved on current existing tools by having a larger sample size and by using commonly obtained laboratories as potential predictors. The derived model was also found to have a better fit for the data than previous studies (concordance index = 0.7). Additionally, the authors describe the model with various predictive probabilities, giving providers the ability to make shared decisions with families by incorporating the risk preferences of both groups.

The study has several limitations. The single-center nature of this study precludes generalizability. Geographical and racial differences in IVIg resistance have been described^{12,13}; therefore, a larger, more diverse population would likely yield more externally valid results. Also, nonresponse to IVIg, as defined in this study, may not be generalizable to institutions that strictly adhere to American Heart Association guidelines. For example, only 46 (57%) patients classified as IVIg-resistant in this study had fever >36 hours, and 22 (27%) did not receive a second dose of IVIg. Furthermore, the risk model has questionable usability in its present form and would likely require an electronic health record–based calculation tool for use because of its reliance on continuous variables.

The role of risk models also warrants discussion. Clinical risk prediction models have become increasingly prevalent; a PubMed search reveals a near 40-fold increase in article titles containing “risk score” over the last 2 decades (9 in 1998; 342 in 2018). Risk models provide valuable information, but overreliance on them may lead to missed cases or overtreatment. For example, authors of a recent analysis of multiple appendicitis risk prediction models found that none of the models reached appropriate performance benchmarks, which may lead to overdiagnosis and increased imaging.¹⁴ The Kaiser Permanente neonatal early-onset sepsis calculator, although having led to significant decreases in antibiotic use and sepsis evaluations, has received scrutiny for its susceptibility to miss cases of neonatal sepsis in some

patients,¹⁵ which may have catastrophic consequences.

Risk prediction tools should be used to augment clinical decisions rather than make them and simultaneously incorporate patient-specific circumstance and preference in joint decision-making. Providers should carefully scrutinize a risk model before implementation into personal or institutional practice. After development and internal validation, risk models should be tested further for external validity, as well as through impact studies assessing the ability to improve outcomes in a cost-effective manner.¹⁶ With respect to KD, the harms of missing refractory KD should be balanced with the benefits of early discharge, which allows for avoiding unnecessary costs and iatrogenic harms. Family health literacy should also be considered because unnoticed fever at home could lead to unnecessary disease progression and significant morbidity.¹⁷

The risk model described by Hester et al⁷ identifies patients at lower risk of IVIg nonresponse who may be safe for early discharge in the study population. Multicenter, prospective studies used to test external validity, as well as impact studies investigating clinical and cost-effectiveness, are necessary before implementation and dissemination. Although more work is needed before adopting a clinical prediction rule for early discharge, Hester et al⁷ have helped pave the road toward high-value care in children with KD.

REFERENCES

1. Coon ER, Wilkes J, Bratton SL, Srivastava R. Paediatric overdiagnosis modelled by coronary abnormality trends in Kawasaki disease. *Arch Dis Child*. 2018; 103(10):937–941
2. McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and

Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association [published correction appears in *Circulation*. 2019;140(5): e181–e184]. *Circulation*. 2017;135(17): e927–e999

3. Singh-Grewal D, Kemp A, Wong M. A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. *Arch Dis Child*. 2006;91(8):651–654
4. Darby JB, Tamaskar N, Kumar S, et al. Variability in Kawasaki disease practice patterns: a survey of hospitalists at Pediatric Hospital Medicine 2017. *Hosp Pediatr*. 2019;9(9)
5. Okubo Y, Nochioka K, Sakakibara H, Testa M, Sundel RP. National survey of pediatric hospitalizations due to Kawasaki disease and coronary artery aneurysms in the USA. *Clin Rheumatol*. 2017;36(2):413–419
6. Ghelani SJ, Pastor W, Parikh K. Demographic and treatment variability of refractory Kawasaki disease: a multicenter analysis from 2005 to 2009. *Hosp Pediatr*. 2012;2(2):71–76
7. Hester G, Watson D, Nickel AJ, et al. Identifying patients with Kawasaki disease safe for early discharge: development of a risk prediction model at a US children's hospital. *Hosp Pediatr*. 2019;9(10)
8. Seki M, Kobayashi T, Kobayashi T, et al. External validation of a risk score to predict intravenous immunoglobulin resistance in patients with Kawasaki disease. *Pediatr Infect Dis J*. 2011;30(2): 145–147
9. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. 2006;113(22):2606–2612
10. Sleeper LA, Minich LL, McCrindle BM, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr*. 2011;158(5):831–835.e3

11. Tremoulet AH, Best BM, Song S, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. *J Pediatr*. 2008;153(1):117–121
12. Clark DE, Denby KJ, Kaufman LM, et al. Predictors of intravenous immunoglobulin nonresponse and racial disparities in Kawasaki disease. *Pediatr Infect Dis J*. 2018;37(12):1227–1234
13. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, et al. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. *J Am Heart Assoc*. 2016;5(9):e003289
14. Kulik DM, Uleryk EM, Maguire JL. Does this child have appendicitis? A systematic review of clinical prediction rules for children with acute abdominal pain. *J Clin Epidemiol*. 2013;66(1):95–104
15. Carola D, Vasconcellos M, Sloane A, et al. Utility of early-onset sepsis risk calculator for neonates born to mothers with chorioamnionitis. *J Pediatr*. 2018; 195:48–52.e1
16. Moons KG, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart*. 2012;98(9):691–698
17. Qiu H, He Y, Rong X, et al. Delayed intravenous immunoglobulin treatment increased the risk of coronary artery lesions in children with Kawasaki disease at different status. *Postgrad Med*. 2018;130(4):442–447

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Hospital Pediatrics 2019;9;824

DOI: 10.1542/hpeds.2019-0204 originally published online September 23, 2019;

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