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Commentary: Pediatric heart transplantation—Seeing the forest for the trees

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CENTRAL MESSAGE

Five easily obtained risk factors allow prediction of one-year survival after pediatric heart transplantation.

In this issue of the *Journal*, Riggs and colleagues¹ from the Cincinnati Children's Hospital examine the outcomes of heart transplantation in pediatric patients with important risk factors, those “limping” to transplantation. The study includes patients younger than 18 years of age from the United Network for Organ Sharing database for pediatric heart transplantation from 2000 to 2017. After various exclusions, the study population includes 4101 patients. Riggs and colleagues¹ select 5 risk factors for analysis. Two of these are not modifiable: age at listing younger than 1 year (infants), and a diagnosis of congenital heart disease. Three factors are modifiable: mechanical ventilation, renal dysfunction, and hepatic dysfunction. The latter factors might more accurately be termed potentially modifiable: once they have occurred, they may only be reversible with the use of mechanical support. In the study population, the selected risk factors occurred frequently: 32% of the patients were infants, 48% had congenital heart disease, 18% were on mechanical ventilation support, 21% had renal dysfunction, and 9% had hepatic dysfunction. Overall, 36% had at least 1 of the modifiable risk factors.

The study's primary finding is that patients with these risk factors have significantly reduced survival at 1 year after transplant, which worsens with an increasing number of risk factors. Patients with none of the 5 risk factors had a 1-year posttransplant survival of 95%. In multivariate analysis, each of the factors had a significant independent negative effect on survival. Sequential addition of the 5 risk factors

progressively decreased survival from 95% to less than 60%. The Kaplan-Meier analyses indicate that most of the increased mortality associated with these risk factors occurred early, within the first several months after transplant. These findings are in line with a previous study by the same group² that examined the effect of risk factors at the time of listing, rather than the time of transplant. The previous study found that factors associated with worse survival at 1 year from the time of listing were weight less than 2.5 kg, a diagnosis of congenital heart disease, need for ventilator support, and extracorporeal membrane oxygenation (ECMO).

There are several limitations of the current study of Riggs and colleagues.¹ It examines 5 risk factors, rather than a broader range of variables that could potentially affect outcomes. Some detail has been lost in favor of simplicity and clarity. Age is not broken down other than infant (<1 year old) as a categorical variable. It would have been of interest to examine the effects of both younger age (neonates) and older age (as seen in the population with failing Fontan circulations). Particularly problematic is the lack of inclusion of ECMO as one of the primary risk factors. Although only 6% of patients were supported by ECMO at the time of transplant, ECMO was the strongest risk factor for mortality in both univariate and multivariate analyses (see Table 2 in the article of Riggs and colleagues¹). ECMO also covaried with the presence of modifiable risk factors; however, it was not specifically factored into the primary analyses. We are left wondering how much of the effects described could have been due to ECMO, rather than, or in addition to,

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the 5 risk factors described. Finally, patients with a ventricular assist device (VAD; 826 of the total 6028 patients, or 14%) were excluded from the study, so this analysis cannot shed light on the possible effect of VAD support. Riggs and colleagues¹ imply that reversal of modifiable risk factors by the use of a VAD could improve outcomes. Of course, this would need to be balanced against the risks added by the use of a VAD, including bleeding, neurologic injury, and infection. At present, the risk-benefit balance of VAD use remains unclear for smaller, younger infants.

Riggs and colleagues¹ acknowledge that the negative effect of each of these risk factors is not novel. The additive effect of multiple risk factors is also not surprising. Nonetheless, I found this article compelling. Given the increasing numbers of both infants and older patients with failed

palliation for congenital heart disease on heart transplant wait lists, the article is timely. The selected risk factors occur commonly in pretransplant patients and are easily ascertained. The outcome variable, survival at 1 year, is clinically meaningful. The study's findings are easily understood and can be used to inform realistic expectations for both caregivers and families. By conveying a concise and useful main message, this study successfully keeps the focus on the forest rather than the trees.

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