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Low body mass index is associated with increased waitlist mortality among children listed for heart transplant

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BACKGROUND: In adults, low body mass index (BMI) and high BMI have been associated with increased mortality after heart transplantation. Studies of BMI in children with heart failure have had inconsistent results.

METHODS: The United Network for Organ Sharing database has 4,035 listings for primary, isolated heart transplant in patients 3 to 18 years old (1995–2012). BMI percentile-for-age (BMI%) was calculated, and patients were stratified based on BMI% into 4 groups: underweight (BMI% <5, $n = 701$ [17.4%]), normal weight (BMI% 5–84, $n = 2{,}321$ [57.5%]), overweight (BMI% 85–94, $n = 440$ [10.9%]), or obese (BMI% ≥ 95, $n = 573$ [14.2%]). Outcomes of patients on the waitlist and after transplantation were assessed.

RESULTS: Unadjusted early waitlist mortality was highest in underweight patients (16.7%) compared with normal-weight (11.4%), overweight (10.9%), and obese (12.9%) patients ($p = 0.04$). In multivariable analysis, underweight patients had elevated risk-adjusted waitlist mortality (odds ratio = 1.4, 95% confidence interval = 1.0–2.2). Unadjusted post-transplant mortality did not differ across BMI % groups (underweight, 5.7%; normal weight, 5.4%; overweight, 5.5%; obese, 5.8%), but obese patients had borderline higher risk-adjusted post-transplant mortality (odds ratio = 1.7, 95% confidence interval = 1.0–3.0). Change in BMI% while waiting did not affect post-transplant mortality.

CONCLUSIONS: Children listed for heart transplant are commonly either underweight or obese. Underweight patients have high risk-adjusted mortality before transplantation, whereas obese patients have borderline higher adjusted post-transplant mortality.

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The impact of body mass index (BMI) on outcomes in health care in general—and pediatrics in particular—has taken on added importance with increased obesity rates across age groups.[1,2] Traditionally, obesity has been associated with high risk in health care, including surgical procedures.[1,3,4] Obese patients may be at higher risk for many diseases including heart failure and certain complications, including pulmonary and wound infections, disease-free survival after cancer resections, and myocardial infarction.[4] However, the "obesity paradox," in which overweight patients have better outcomes than patients of normal or low weight when a diagnosis is established, has been increasingly recognized.[3,5–7] The relationship between BMI and surgical outcomes is not straightforward and may vary across procedures.

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In adults, the relationship between BMI and outcomes after cardiac surgery has been variable.[7–13] Although differing methodologies explain some of this variability, an emerging consensus suggests that the lowest mortality and major morbidity rates occur among adult patients with a BMI of 30 (the traditional boundary between overweight and obese); patients with extreme obesity and patients with extremely low BMI have increased mortality.[10] Similar results have been identified in adult recipients of heart transplants, with low BMI ($\leq$18.5) and obesity (BMI $\geq$35) being associated with poorer outcomes.[14]

Assessing the relationship between BMI and health outcomes in children entails additional challenges. BMI in children must be analyzed in the context of normative data to account for growth. Obesity has been associated with increased complication rates among children undergoing general surgical procedures,[15,16] but to our knowledge no data exist specific to pediatric cardiac surgery. Despite conflicting results from single-institution studies of obese transplant recipients,[17,18] obesity continues to be considered a relative contraindication to transplantation.[19] The aims of this study were to determine (1) the relationship between BMI and waitlist survival, (2) the relationship between BMI and post-transplant survival, and (3) the long-term complications of cardiac transplantation in pediatric recipients of heart transplants.

Methods

Data source

This retrospective study uses de-identified, patient-level data from the United Network for Organ Sharing (UNOS) (source 12/01/2011-2, data as of September 30, 2012). This is a mandatory registry that collects information at listing, at transplant, and during long-term follow-up for all transplants performed within the United States. Use of these data is consistent with the regulations of the Nemours Institutional Review Board.

Study population and design

Pediatric patients 3 to 18 years old listed for isolated primary cardiac transplant during the period 1995–2012 were included ($N = 4{,}035$). BMI percentiles-for-age (BMI%) were calculated for all patients. Percentiles were calculated using Epi Info 7 (Centers for Disease Control and Prevention, Atlanta, GA) and are based on Centers for Disease Control and Prevention 2000 growth charts.[20] Based on BMI%, patients were stratified into 4 groups at listing: underweight (BMI% <5, $n = 701$ [17.4%]), normal weight (BMI% 5–84, $n = 2{,}321$ [57.5%]) overweight (BMI% 85–95, $n = 440$ [10.9%]), and obese (BMI% >95, $n = 573$ [14.2%]). Patients who were transplanted ($n = 2{,}800$) were stratified by BMI% at transplantation as well: underweight ($n = 488$ [17.4%]), normal weight ($n = 1{,}622$ [57.9%]), overweight ($n = 325$ [11.6%]), and obese ($n = 365$ [13.0%]). These cutoffs were determined based on previous single-institution studies of the impact of body habitus on outcomes in pediatric patients undergoing heart transplant as well as standardized criteria for the assessment of obesity in children.[2,18,21]

The impact of BMI changes between listing and transplantation was evaluated in these patients by stratifying patients into patients whose BMI% had increased or decreased by >5 and evaluating patients who had either increased across a BMI group (e.g., underweight to normal, normal to overweight) or decreased across a BMI group. To assess the potential for a differential impact of BMI% across diagnoses, sub-group analysis was performed separately for patients with congenital heart disease (CHD) and cardiomyopathy. In addition, the impact of BMI $\geq$35 was evaluated in adolescents.

Statistical analysis

Statistical analysis was performed using SAS 9.21 for AIX (SAS Institute, Cary, NC). The primary outcomes were early waitlist mortality (within 2 months of listing) and postoperative mortality after transplant (within 30 days of transplant or before discharge, whichever was later). Secondary outcomes included patient and graft survival analyzed by the life-table method and the incidence of post-transplant complications (as defined by UNOS, including dialysis, drug-treated infection, stroke, and permanent pacemaker implantation).

Continuous variables were compared using the Student's *t*-test (2-tailed) and one-way analysis of variance. Logistic regression (backward selection, $p < 0.2$) was used to evaluate predictors of binary outcomes. To evaluate the differential impact of weight among patients with different etiologies of heart failure, following initial analysis, interaction terms between etiology (dilated cardiomyopathy or CHD) and BMI% category were added to the models. Categorical variables were compared by chi-square test. Kaplan-Meier analysis (log-rank test with Sidak correction, $p < 0.05$) and Cox regression (backward selection, $p < 0.2$) were used for time-to-event analysis; the assumption of hazards proportionality was tested by introducing terms of interaction with log(time) in the Cox model. Center-clustered data were fitted by marginal model using the robust sandwich estimate. For regression modeling, missing variables were imputed using the technique of multiple imputation (10 imputations, Markov chain Monte Carlo method).[22] The percentage of missing variables and the handling of missing data within the UNOS data set have been previously reported.[23]

Results

Baseline demographics at listing for transplantation

Baseline demographics for all patients stratified into groups are shown in Table 1. Obese patients were more commonly African-American ($p < 0.0001$) and of lower socioeconomic status ($p < 0.0001$), whereas underweight patients had a higher incidence of CHD. The incidence of obese (1995–1999, 13.2%; 2000–2004, 15.0%; 2005–2009, 14.0%; 2010–2012, 14.7%; $p = 0.7$) and overweight (1995–1999, 10.7%; 2000–2004, 10.5%; 2005–2009, 10.2%; 2010–2012, 12.9%; $p = 0.3$) patients remained stable over time. However, the percentage of underweight patients decreased (1995–1999, 21.3%; 2000–2004, 17.2%; 2005–2009, 16.2%; 2010–2012, 14.0%; $p < 0.0001$). There was an association between increased BMI at listing and longer time on the waitlist (underweight, 187 $\pm$ 471 days; normal weight, 207 $\pm$ 480 days; overweight, 245 $\pm$ 580 days; obese, 264 $\pm$ 560 days; $p = 0.02$).

Outcomes after listing

The unadjusted likelihood of transplantation was not significantly different across groups (71.9%, 74.0%, 74.3%,