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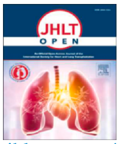

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Nonlinear effect of body mass index on postoperative survival following isolated heart transplantation

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KEYWORDS:
body mass index;
donor selection;
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organ utilization;
recipient selection

BACKGROUND: Guidelines regarding recipient's body mass index (BMI) for heart transplant are evolving with variable cutoffs depending on the country and institution. It is imperative to provide updated nonlinear estimates of postoperative risk attributable to a recipient's BMI to evaluate the relevance of existing cutoffs.
METHODS: A total of 30,787 patients were analyzed from the United Network for Organ Sharing (UNOS) database. Patients receiving an isolated heart transplant ages 18 and older since 2010 were included. Overall survival was the primary outcome. A multivariate Cox proportional hazards model was applied and included a penalized smoothing spline term for recipient BMI and risk factors such as diabetes. We assessed the overall significance of the nonlinear penalized spline terms using an asymptotic Wald test.
RESULTS: The cohort consisted of 662 (2.2%) BMI < 18.5, 9,359 (30%) BMI 18.5 to 24.9, 10,997 (36%) BMI 25 to 29.9, 9,550 (31%) BMI 30 to 39.9, and 206 (0.7%) BMI ≥40 patients. The nonlinear spline terms for recipient BMI were statistically significant ($p < 0.01$). The hazard ratio (HR) appeared to grow linearly in BMI at an inflection point of BMI = 26. No inflection point was observed at either of the International Society for Heart and Lung Transplantation recommended cutoffs of BMI = 30 (HR 1.11, confidence interval [CI] 1.07-1.15) or BMI = 35 (HR 1.29, CI 1.24-1.37).
CONCLUSIONS: After multivariable adjustment, there is no sharp cutoff in survival risk at either BMI = 30 or BMI = 35. Unlike previously reported, postoperative survival risk grows approximately linearly in the BMI range from 26 to 40.
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Background

The number of people who are obese has increased in recent years. In 2020, 14% of the proportion of global population was obese (body mass index [BMI] ≥30 kg/m^2) with a predicted increase to 24% by 2035.[1] Projections in the US population show that about 1 in 2 adults be obese

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(BMI ≥30 kg/m^2) and 1 in 4 adults will have severe obesity (BMI ≥35 kg/m^2) by 2030.[2] Concurrently, the heart failure population is also increasing with 6.7 million Americans over the age of 20 having heart failure with expectation to increase to 8.5 million Americans by 2030.[3] Additionally, heart failure patients tend to have a greater number of comorbidities: patients with ≥3 comorbidities rates rose from 68% in early 2000s to 87% in the early 2010s, with risk factors such as hypertension, obesity, and smoking as being the most prevalent.[3] These trends are also reflected in heart transplantation recipient and donor pools. Specifically, Chouairi et al showed that there is increasing BMI of waitlisted patients, transplanted patients, and donors all with medians below BMI = 30 kg/m^2 with recipients starting at BMI = 25 kg/m^2 having lower chance of transplantation.[4] Moreover, patients with BMI exceeding 30 kg/m^2 having highest risk of death on the waitlist with hazard ratio (HR) of 1.40 (confidence interval [CI] 1.07-1.84).[4] The effects of obesity on recipients and donor pools have also been reflected in the International Society for Heart and Lung Transplantation (ISHLT) guidelines, with 2006 guidelines stating that pretransplant recipients with BMI > 30 kg/m^2 should undergo weight loss before listing while most recent 2016 guidelines stating that pretransplant recipients with BMI > 35 kg/m^2 should consider weight loss.[5] Such a change in the guidelines was based on 3 studies of retrospective nature and database analysis showing comparable outcomes of patients with BMI between 30 and 35 kg/m^2 with transplantations performed through 2007.[6-8] Despite these changes in the guidelines, increasing transplantation of patients with BMI between 30 and 35 kg/m^2 has not been reflected in clinical practice according to prior analysis of the UNOS database through 2020 and a thorough statistical analysis of interaction between BMI and survival outcomes has not been previously performed.[4]

The goal of our analysis was to understand the relationship between BMI and survival outcomes and provide a valid risk stratification for clinical use. Given the importance of predicted heart mass (PHM) in survival outcomes, we also examined the relationship between PHM and BMI. Last, we evaluated whether the 2016 ISHLT recommended sharp cutoff of BMI = 35 kg/m^2 actually reflects significant risk as previously described using more recent data.[6-8]

Materials and methods

Study design

We selected patients in the United Network for Organ Sharing Standard Transplant Analysis and Research (UNOS STAR) File database from January 1, 2010 to December 31, 2022. We excluded patients under 18 at the time they were added to the waitlist, multiorgan transplant, and retransplants.

The measure of recipient BMI used in this analysis was the variable "BMI_CALC" in the UNOS STAR database.

Our primary outcome was overall post-transplant survival. Our secondary outcomes include stroke before discharge, dialysis before discharge, and treatment for acute rejection within 1 year.

Statistical analysis

Descriptive analysis of the prevalence of size-compatible donors for patients with high BMI

Donor-recipient size mismatch is a critical postoperative risk factor affecting the compatibility of a donor and recipient. For each recipient, we calculated the proportion of successfully transplanted donors within our cohort that are size-sufficient, defined as having a donor/recipient PHM ratio > 0.86 following Kransdorf et al.[9] We calculated the median and interquartile range (IQR) of these values within BMI bins in increments of 5 kg/m^2. We assessed the linear association between recipient BMI and donor/recipient PHM ratio.

Primary and secondary outcomes

To estimate the effect of recipient BMI on time to death, we utilized a Cox proportional hazards model. To model the nonlinear effect of BMI on survival, we added a penalized smoothing spline with 4 degrees of freedom with multivariate adjustment on the following risk factors: age, cigarette usage, donor age, inotropes at transplant, history of hypertension in the transplant donor, recipient gender, diabetes, bilirubin (mg/dl), the left ventricular (LV) ejection fraction of the donor, extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), transplant year, recipient's creatinine at time of transplant, mean pulmonary artery (PA) pressure at time of transplant, recipient cardiac index at transplant, donor/recipient PHM ratio, and the recipient's peak calculated panel reactive antibodies (CPRA).

Since the timing of a patient's BMI measurement is not captured within UNOS, we performed a sensitivity analysis for our penalized spline model of survival under a measurement timing model of timing-related error in BMI measurement. In this model, we assumed that the main source of error for BMI would be overstating BMI at time of transplant due to not measuring it after a patient underwent a nutrition regimen to reduce their BMI below a clinically relevant threshold. Since a BMI of 35 is the most recent BMI cutoff recommendation, we performed 1,000 simulations of the following model: if a patient's reported

BMI was greater than 35, then with probability 50% of their BMI was incorrectly reported and the surgery was instead performed at a BMI = 35 following a nutrition regimen. We examined the median, 2.5%, and 97.5% percentiles for the pointwise estimates of HR of BMI to assess the sensitivity of the model to this error process.

We assessed the nonlinear association between BMI on postoperative stroke, dialysis, and acute rejection within 1 year using logistic regression. Again, we added a penalized smoothing term with 4 degrees of freedom on recipient BMI, and we reported the odds ratio (OR) at various recipient BMI values for our secondary outcomes when the nonlinear term was statistically significant.

Ethical considerations

This study is a retrospective review of deidentified data supplied by UNOS in the form of a deidentified STAR file. Our project was determined to be Institutional Review Board exempt following a human subjects research determination (protocol #74781).

Results

Population

A total of N = 30,629 patients met our inclusion criteria. The mean age of patients was 53.59 [standard deviation (SD), 12.76] years at times of transplant; 8,142 patients (26.58%) were women. At inclusion, 2.16%, 30.4%, 35.75%, 31.02%, and 0.67% belong to BMI classes I, II, III, IV, and V, respectively. The patient and donor characteristics for BMI classes are reported in Tables 1 and 2.

In the cohort, only 13 (0.04%) patients had missing BMI_CALC and were excluded from the model. Three hundred and sixty-eight (1.2%) did not have survival outcomes reported. However, all 368 received their transplant in 2022, consistent with not having yet had a reported follow-up or a lag in UNOS' data harvest.

Distribution of PHM-compatible donors and recipient BMI

We show the relationship between recipient BMI and donor-recipient PHM ratio in Figure 1. The data are most concentrated near a PHM ratio of 1 and a BMI between 25 and 30. The linear regression line indicates that as BMI increases, there are fewer size-compatible donors available. Currently, high BMI patients have lower PHM ratios—patients with a higher BMI have a higher increased risk of receiving an undersized donor heart.

As seen in Figure 2, we show a linear decrease in the percentage of PHM-compatible donors as a transplant recipient's BMI increases. For example, at a BMI between 25 and 30, a transplant recipient would have had a median compatibility of 87.3%, whereas recipients with a BMI of 45 to 50 would have had a median compatibility of 17.2%. This indicates that patients with a high BMI have fewer size-compatible donors.

All-cause mortality

The cohort had a mean follow-up time of 1,557 days (SD, 1,244; range, 0-4,746 days). The incidence of mortality in classes 1, 2, 3, 4, and 5 were 19.45%, 21.16%, 22.25%, 25.55%, and 31.19%, respectively.

The change in HR across the range of recipient BMI values is visualized in Figure 3. Recipient BMI was nonlinearly associated with post-transplant all-cause mortality upon multivariate adjustment ($p < 0.001$). In addition, we find that the overall nonlinear effect of the BMI term was also significant ($p < 0.001$). The HR appears to grow linearly in BMI at an inflection point of BMI = 26. No inflection point was observed at either of the recommended cutoffs of BMI at 30 or BMI at 35. However, growth in hazard does appear to grow quadratically above a BMI of 37. We further report specific HRs and their CIs at various recipient BMI levels in Table 3. In Table 4, we report the HRs associated with the other adjusted variables in our multivariate Cox proportional hazards model.

Length of stay

Our cohort had a mean length of stay (LOS) of 15 days (IQR 11, 23). The LOS in classes I, II, III, IV, and V were 16 (IQR 12, 26), 15 (IQR 11, 22), 15 (IQR 11, 23), 16 (IQR 12, 26), and 17 (IQR 12, 26) days, respectively (Table 5). Since shorter LOS is desirable, larger HRs are preferable for this outcome. The change in HR for recipient LOS across the range of recipient BMI values and classes is visualized in Figure 4. Recipient BMI was nonlinearly associated with post-transplant LOS upon multivariate adjustment ($p < 0.001$). In addition, we find that the overall nonlinear effect of the BMI term on LOS was also significant ($p < 0.001$).

Recipients with a BMI below 20 and above 30 had worse postoperative LOS, as shown in Figure 4.

Secondary outcomes

The incidence rates of our secondary outcomes by BMI class can be found in Table 5. Logistic regression revealed that each unit increase in recipient BMI was associated with an OR of 1.21 for acute rejection within 1 year (95% CI [1.13, 1.29], $p < 0.001$) and an OR of 1.56 for requiring dialysis before hospital discharge (95% CI [1.46, 1.67], $p < 0.001$). The association between BMI and stroke before discharge was not statistically significant, with an OR of 0.90 (95% CI [0.79, 1.03], $p = 0.12$).

Table 1 Recipient Baseline Characteristics Stratified by Recipient BMI Class

Variable	Overall, N = 30,616[a]	Class I (underweight), N = 660[a]	Class II (healthy), N = 9,308[a]	Class III (overweight), N = 10,946[a]	Class IV (obese), N = 9,498[a]	Class V (morbidly obese), N = 204[a]
Recipient age, year	57 (47, 63)	48 (30, 60)	57 (46, 64)	58 (49, 64)	55 (46, 62)	46 (38, 55)
Recipient race						
American Indians/ Alaska Native, non-Hispanic	94 (0.3%)	1 (0.2%)	26 (0.3%)	35 (0.3%)	32 (0.3%)	0 (0%)
Asian, Non-Hispanic	1,085 (3.5%)	70 (11%)	564 (6.1%)	318 (2.9%)	130 (1.4%)	3 (1.5%)
Black, non-Hispanic	6,841 (22%)	152 (23%)	1,917 (21%)	2,265 (21%)	2,425 (26%)	82 (40%)
Hispanic/Latino	2,718 (8.9%)	59 (8.9%)	890 (9.6%)	1,006 (9.2%)	747 (7.9%)	16 (7.8%)
Multiracial, non-Hispanic	148 (0.5%)	4 (0.6%)	48 (0.5%)	42 (0.4%)	53 (0.6%)	1 (0.5%)
Native Hawaiian/ other Pacific Islander, non-Hispanic	102 (0.3%)	2 (0.3%)	23 (0.2%)	31 (0.3%)	45 (0.5%)	1 (0.5%)
White, non-Hispanic	19,628 (64%)	372 (56%)	5,840 (63%)	7,249 (66%)	6,066 (64%)	101 (50%)
Recipient BMI kg/m^2	27.3 (24.0, 31.1)	17.6 (16.9, 18.2)	22.8 (21.2, 24.0)	27.4 (26.2, 28.6)	32.9 (31.3, 34.8)	41.3 (40.5, 42.4)
Diabetes mellitus	8,574 (28%)	78 (12%)	1,761 (19%)	3,137 (29%)	3,531 (37%)	67 (33%)
Total waitlist time, days	73 (18, 253)	34 (11, 114)	44 (13, 159)	78 (20, 258)	116 (27, 367)	72 (21, 289)
Prior cardiac surgery, *n* (%)	15,043 (49%)	250 (38%)	4,070 (44%)	5,480 (50%)	5,146 (54%)	97 (48%)
Prior lung surgery, *n* (%)	126 (0.4%)	6 (0.9%)	44 (0.5%)	41 (0.4%)	35 (0.4%)	0 (0%)
Hospitalization status at time of transplant						
Hospitalized not in ICU	4,445 (15%)	122 (19%)	1,410 (15%)	1,501 (14%)	1,376 (15%)	36 (18%)
Hospitalized in ICU	11,386 (38%)	320 (49%)	4,126 (45%)	3,978 (37%)	2,905 (31%)	57 (28%)
Not hospitalized	14,451 (48%)	214 (33%)	3,691 (40%)	5,350 (49%)	5,087 (54%)	109 (54%)
Blood type, *n* (%)						
A	12,198 (40%)	242 (37%)	3,661 (39%)	4,419 (40%)	3,800 (40%)	76 (37%)
AB	1,675 (5.5%)	40 (6.1%)	532 (5.7%)	598 (5.5%)	493 (5.2%)	12 (5.9%)
B	4,591 (15%)	131 (20%)	1,455 (16%)	1,595 (15%)	1,371 (14%)	39 (19%)
O	12,138 (40%)	247 (37%)	3,654 (39%)	4,328 (40%)	3,832 (40%)	77 (38%)
Total bilirubin, mg/dl	0.70 (0.50, 1.10)	0.80 (0.50, 1.20)	0.70 (0.50, 1.20)	0.70 (0.50, 1.10)	0.70 (0.40, 1.00)	0.70 (0.50, 1.20)
Transplant year	2017 (2014, 2020)	2017 (2014, 2020)	2017 (2013, 2020)	2017 (2014, 2020)	2017 (2014, 2020)	2017 (2013, 2020)
Weight (kg)	83 (71, 96)	50 (45, 55)	68 (60, 75)	84 (77, 91)	101 (92, 110)	123 (111, 133)
Height (cm)	175 (168, 180)	170 (163, 178)	173 (165, 180)	175 (168, 180)	175 (168, 180)	173 (163, 179)
Waitlist priority status at time of transplant						
HR: adult status 1	1,075 (3.5%)	29 (4.4%)	337 (3.6%)	348 (3.2%)	347 (3.7%)	14 (6.9%)
HR: adult status 2	5,703 (19%)	125 (19%)	1,861 (20%)	1,970 (18%)	1,718 (18%)	29 (14%)
HR: adult status 3	2,055 (6.7%)	41 (6.2%)	520 (5.6%)	719 (6.6%)	757 (8.0%)	18 (8.8%)
HR: adult status 4	2,263 (7.4%)	41 (6.2%)	535 (5.7%)	842 (7.7%)	829 (8.7%)	16 (7.8%)
HR: adult status 5	6 (< 0.1%)	0 (0%)	1 (< 0.1%)	2 (< 0.1%)	2 (< 0.1%)	1 (0.5%)
HR: adult status 6	634 (2.1%)	13 (2.0%)	150 (1.6%)	245 (2.2%)	224 (2.4%)	2 (1.0%)
HR: status 1A	12,112 (40%)	279 (42%)	3,859 (41%)	4,296 (39%)	3,593 (38%)	85 (42%)
HR: status 1B	6,030 (20%)	109 (17%)	1,787 (19%)	2,265 (21%)	1,833 (19%)	36 (18%)
HR: status 2	738 (2.4%)	23 (3.5%)	258 (2.8%)	259 (2.4%)	195 (2.1%)	3 (1.5%)
VAD device type						
LVAD	12,258 (40%)	132 (20%)	2,747 (30%)	4,422 (41%)	4,840 (52%)	117 (58%)
LVAD+RVAD	570 (1.9%)	20 (3.0%)	225 (2.4%)	193 (1.8%)	126 (1.3%)	6 (3.0%)
RVAD	76 (0.3%)	0 (0%)	15 (0.2%)	33 (0.3%)	28 (0.3%)	0 (0%)
TAH	266 (0.9%)	6 (0.9%)	88 (1.0%)	95 (0.9%)	73 (0.8%)	4 (2.0%)
None	17,118 (57%)	498 (76%)	6,153 (67%)	6,089 (56%)	4,303 (46%)	75 (37%)

(*continued on next page*)

Table 1 (*Continued*)

Variable	Overall, N = 30,616[a]	Class I (underweight), N = 660[a]	Class II (healthy), N = 9,308[a]	Class III (overweight), N = 10,946[a]	Class IV (obese), N = 9,498[a]	Class V (morbidly obese), N = 204[a]
ECMO	746 (2.4%)	25 (3.8%)	257 (2.8%)	243 (2.2%)	212 (2.2%)	9 (4.4%)
IABP	4,396 (14%)	120 (18%)	1,616 (17%)	1,547 (14%)	1,092 (11%)	21 (10%)
Etiology of heart failure						
Congenital	1,006 (3.3%)	77 (12%)	436 (4.7%)	285 (2.6%)	205 (2.2%)	3 (1.5%)
Idiopathic	11,004 (36%)	230 (35%)	3,217 (35%)	3,756 (34%)	3,702 (39%)	99 (49%)
Ischemic	9,907 (32%)	101 (15%)	2,619 (28%)	3,942 (36%)	3,199 (34%)	46 (23%)
Other	8,699 (28%)	252 (38%)	3,036 (33%)	2,963 (27%)	2,392 (25%)	56 (27%)
Cockcroft creatinine clearance	805 (618, 1,052)	631 (464, 835)	696 (537, 905)	794 (625, 1,014)	951 (740, 1,218)	1,214 (945, 1,662)
UNOS region						
1	1,459 (4.8%)	39 (5.9%)	463 (5.0%)	504 (4.6%)	440 (4.6%)	13 (6.4%)
2	3,472 (11%)	58 (8.8%)	1,008 (11%)	1,255 (11%)	1,132 (12%)	19 (9.3%)
3	3,531 (12%)	84 (13%)	1,082 (12%)	1,261 (12%)	1,087 (11%)	17 (8.3%)
4	3,181 (10%)	64 (9.7%)	947 (10%)	1,226 (11%)	929 (9.8%)	15 (7.4%)
5	4,737 (15%)	132 (20%)	1,798 (19%)	1,667 (15%)	1,123 (12%)	17 (8.3%)
6	974 (3.2%)	15 (2.3%)	276 (3.0%)	349 (3.2%)	329 (3.5%)	5 (2.5%)
7	2,702 (8.8%)	41 (6.2%)	761 (8.2%)	968 (8.8%)	910 (9.6%)	22 (11%)
8	2,045 (6.7%)	47 (7.1%)	551 (5.9%)	742 (6.8%)	684 (7.2%)	21 (10%)
9	2,089 (6.8%)	64 (9.7%)	704 (7.6%)	767 (7.0%)	537 (5.7%)	17 (8.3%)
10	2,422 (7.9%)	48 (7.3%)	698 (7.5%)	834 (7.6%)	833 (8.8%)	9 (4.4%)
11	4,004 (13%)	68 (10%)	1,020 (11%)	1,373 (13%)	1,494 (16%)	49 (24%)

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IABP, intra-aortic balloon pump; ICU, intensive care unit; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart; UNOS, United Network for Organ Sharing; VAD, ventricular assist device.

[a]Median (IQR); *n* (%).

Nonlinear analyses

We failed to find a significant effect for the nonlinear term of BMI for acute rejection ($p = 0.26$) and stroke ($p = 0.63$). However, we find a significant effect of the nonlinear term of BMI on dialysis before discharge ($p = 0.013$). We report the different ORs and CIs at various values of BMI for dialysis in Table 6. We plot the variation in OR across various BMI levels in Figure 5.

Sensitivity analysis of all-cause mortality

We performed a sensitivity analysis for the penalized spline estimates of the association of BMI with all-cause mortality as visualized in Figure 6. Due to the local knotting structure of the penalized smoothing spline model, the point estimate of the HR of BMI at values less than 35 exhibited minimal sensitivity to the assumptions of the measurement timing model. Moreover, under the measurement timing model, the median outcome was still a linear increase in hazard, but with considerable volatility by BMI = 40.

Discussion

This UNOS STAR database analysis revealed that higher recipient BMI is associated with a lower rate of sufficiently sized donors, reducing their adequate size-matched donor pool. Krebs et al have previously shown that severe obesity, defined as BMI ≥40 kg/m^2, in donors did not affect post-transplant outcomes.[10] Therefore, accepting donors with higher BMI could help address access to organs for recipients with higher BMI without negatively impacting PHM and allow for expansion of listing patients with BMI > 25 kg/m^2. Our results support the use of continuous measures of risk whereby donor-recipient compatibility is assessed on a continuous risk scale rather than the use of risk cutoffs. Therefore, rather than using strict donor or recipient factor cutoffs, such as BMI, donor and recipient characteristics are assessed more holistically. This would also enable higher BMI donors and recipients to be considered for matching.

While adequate heart sizing may offset some risk, even when matched for PHM, high recipient BMI remains independently associated with postoperative mortality with

Table 2 Donor/Recipient and Donor Baseline Characteristics Stratified by Recipient BMI Class

Variable	Overall, N = 30,616[a]	Class I (underweight), N = 660[a]	Class II (healthy), N = 9,308[a]	Class III (overweight), N = 10,946[a]	Class IV (obese), N = 9,498[a]	Class V (morbidly obese), N = 204[a]
Donor/recipient PHM ratio	1.01 (0.91, 1.13)	1.20 (1.06, 1.35)	1.07 (0.97, 1.21)	1.00 (0.91, 1.10)	0.96 (0.88, 1.05)	0.91 (0.84, 1.03)
Donor age	31 (23, 40)	29 (20, 39)	30 (22, 40)	31 (23, 40)	32 (24, 40)	33 (24, 41)
Donor sex						
Female	8,929 (29%)	320 (48%)	3,294 (35%)	3,026 (28%)	2,235 (24%)	54 (26%)
Male	21,687 (71%)	340 (52%)	6,014 (65%)	7,920 (72%)	7,263 (76%)	150 (74%)
Donor height (cm)	175 (168, 180)	168 (161, 175)	173 (165, 178)	175 (168, 180)	178 (170, 183)	178 (170, 183)
Donor weight (kg)	81 (70, 95)	67 (59, 80)	74 (65, 86)	81 (71, 93)	88 (77, 102)	95 (81, 113)
Donor BMI kg/m^2	26.6 (23.4, 30.8)	23.8 (21.0, 27.5)	25.1 (22.2, 28.9)	26.4 (23.5, 30.5)	28.5 (25.0, 32.8)	30.2 (26.3, 35.7)
Donor LV ejection fraction	60 (56, 65)	60 (57, 65)	60 (56, 65)	60 (55, 65)	60 (56, 65)	61 (56, 65)
Ischemic time	3.27 (2.55, 3.90)	3.35 (2.75, 3.97)	3.25 (2.52, 3.87)	3.27 (2.53, 3.88)	3.30 (2.58, 3.92)	3.28 (2.67, 3.90)
Diabetes mellitus	1,159 (3.8%)	15 (2.3%)	322 (3.5%)	392 (3.6%)	425 (4.5%)	5 (2.5%)
Donor hypertension	4,775 (16%)	83 (13%)	1,299 (14%)	1,632 (15%)	1,724 (18%)	37 (18%)
Donor total bilirubin, mg/dl	0.70 (0.50, 1.10)	0.70 (0.50, 1.10)	0.70 (0.50, 1.10)	0.70 (0.50, 1.20)	0.70 (0.50, 1.10)	0.70 (0.50, 1.10)
Blood type donor, *n* (%)						
A	10,971 (36%)	216 (33%)	3,230 (35%)	3,956 (36%)	3,502 (37%)	67 (33%)
AB	674 (2.2%)	11 (1.7%)	187 (2.0%)	264 (2.4%)	205 (2.2%)	7 (3.4%)
B	3,378 (11%)	79 (12%)	1,037 (11%)	1,215 (11%)	1,020 (11%)	27 (13%)
O	15,593 (51%)	354 (54%)	4,854 (52%)	5,511 (50%)	4,771 (50%)	103 (50%)

Abbreviations: BMI, body mass index; LV, left ventricle; PHM, predicted heart mass.
[a]Median (IQR); *n* (%).

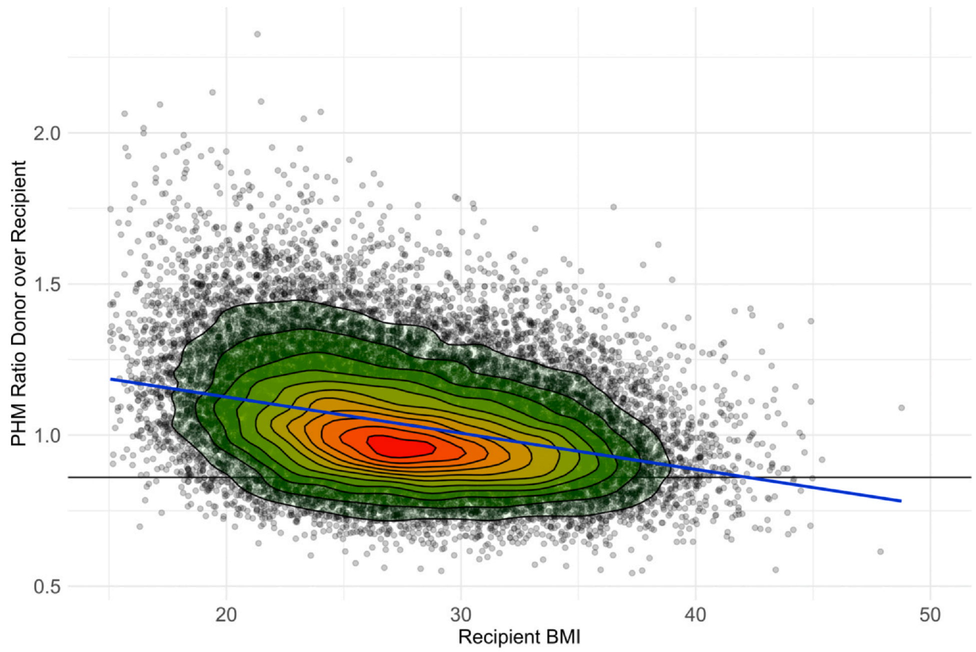

Figure 1 Association between recipient BMI and donor-recipient PHM ratio. BMI, body mass index; PHM, predicted heart mass.

minimal risk up until BMI = 26 kg/m^2, which was an inflection point in our penalized spline plot analysis. No inflection points were observed at either of the historical ISHLT recommended cutoffs of BMI = 30 kg/m^2 (HR 1.11, CI 1.07-1.15) or BMI = 35 kg/m^2 (HR 1.29, CI 1.24-1.37). Furthermore, higher BMI was also associated with increased risk of acute rejection at 1 year and rates of dialysis before discharge. This is consistent with prior studies

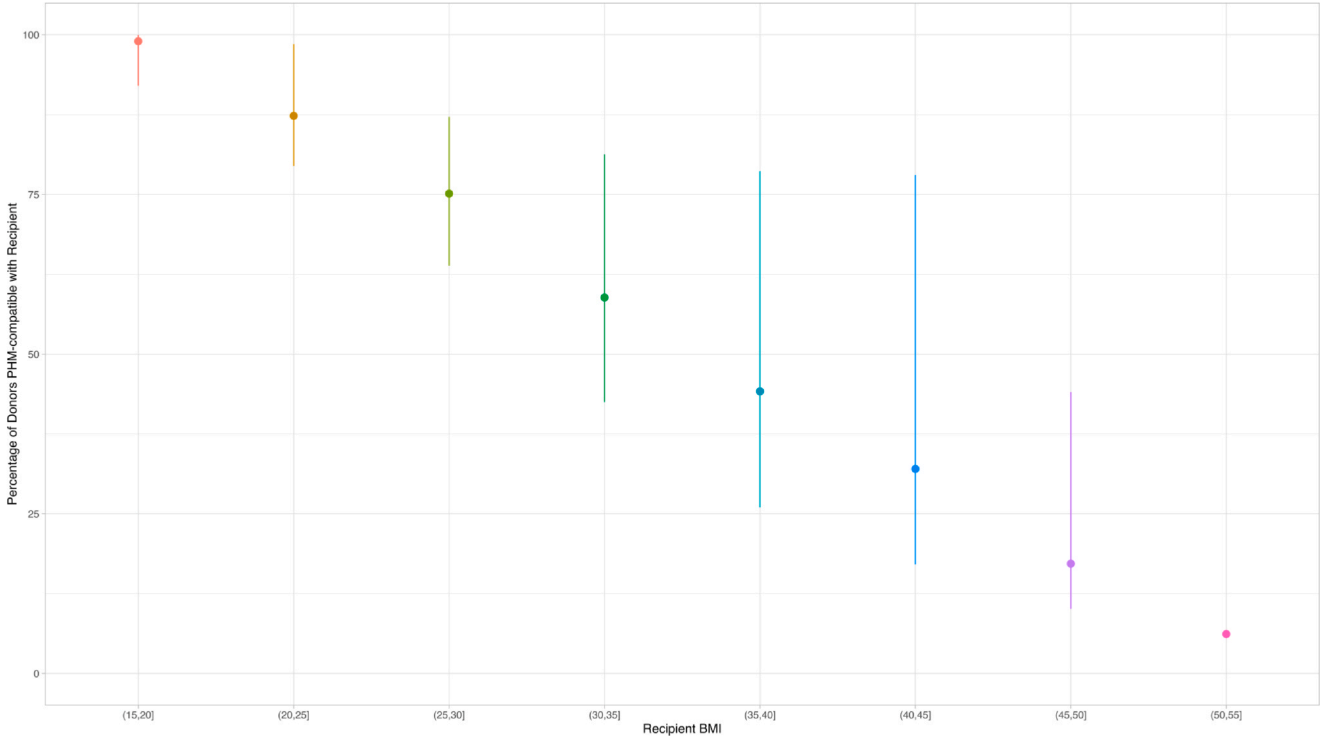

Figure 2 Distribution of percentage of donors PHM-compatible with recipients by BMI (median and interquartile range). BMI, body mass index; PHM, predicted heart mass.

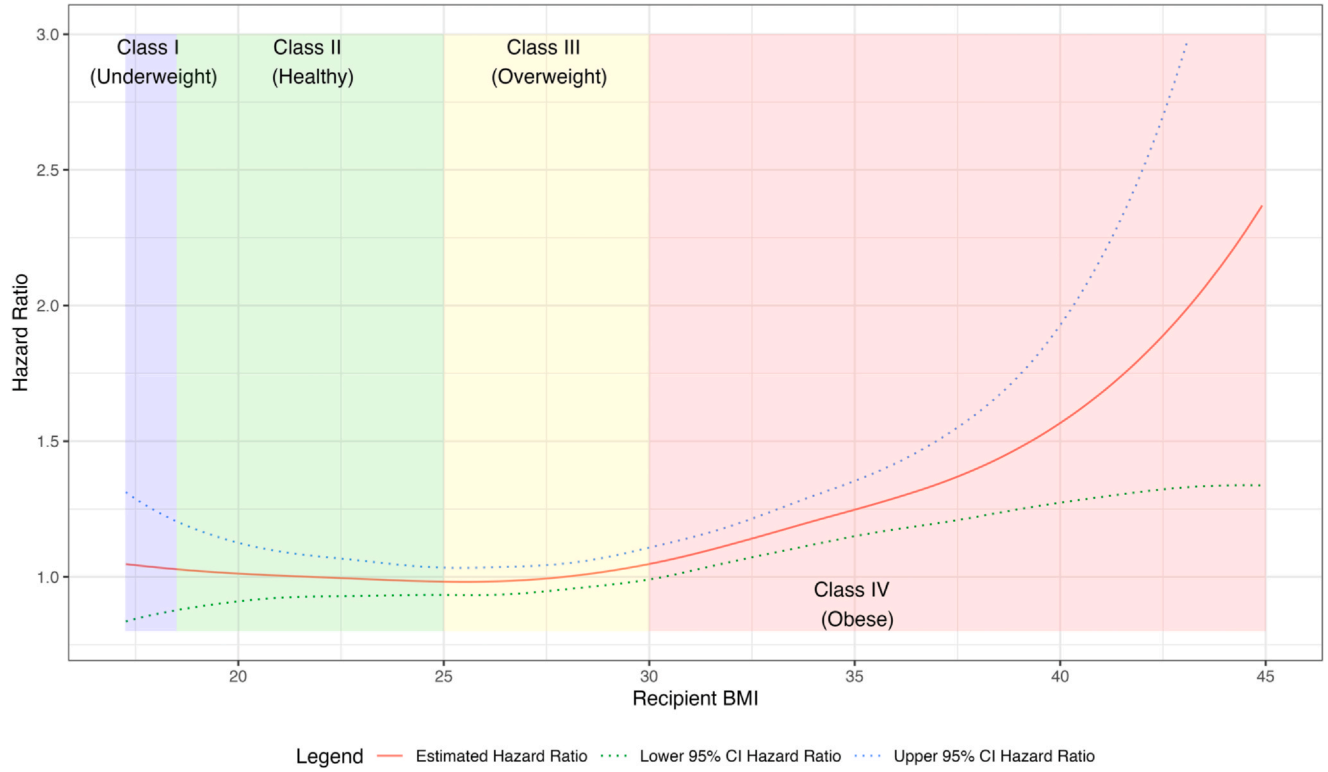

Figure 3 Smoothing spline term plot for the association between recipient BMI and all-cause mortality. BMI, body mass index; CI, confidence interval.

Table 3 Estimated Hazard Ratio and Pointwise 95% Confidence Intervals for Specific BMI Values for All-Cause Mortality

BMI	HR	Lower 95% CI	Upper 95% CI
26	0.98	0.93	1.03
30	1.05	0.99	1.11
35	1.25	1.15	1.35
40	1.57	1.27	1.93
45	2.37	1.34	4.19

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

showing that obesity is associated with type 2 diabetes, dyslipidemia, hypertension, pulmonary hypertension, kidney disease, and other comorbidities[11-14] as well as previous studies in kidney transplantation showing increased acute rejection with certain immunosuppression regimes.[15]

Transplant recipient obesity is associated with higher rates of hemodialysis. Previous studies have indicated that reduction in ischemic time, optimization of recipient blood management,[16] and optimizing workflow to reduce cardiopulmonary bypass time can mitigate the risk of postoperative hemodialysis.[17] Furthermore, minimization of surgical complications such as surgical site infection or blood loss anemia through diligent sterile technique is known to reduce the risk of acute kidney injury following cardiac surgery.[18]

Regarding acute rejection, recent studies have found that obesity is associated with delayed graft function in kidney transplant recipients. This may be partially due to a failure to achieve sufficient exposure to maintenance immunosuppression, though further research is necessary to identify improved maintenance regimes for obese patients.[19-21]

The estimates of postoperative risk at BMI of 35 and 40 are in line with 2 relatively common risk factors in the heart transplantation population: a BMI of 35 kg/m^2 is associated with similar risk as a history of cigarette usage (HR 1.23, CI 1.13-1.34) and a BMI of 40 kg/m^2 is associated with similar risk as ECMO utilization (HR 1.63, CI 1.30-2.05). This suggests that a threshold cutoff may exclude patients whose postoperative risk is commensurable with population groups commonly regarded as suitable for heart transplantation and listing. Nevertheless, these comparisons may be misleading because placement on venoarterial extracorporeal membrane oxygenation is an indicator of a patient's acuity and smoking is a modifiable behavior.

Table 4 Multivariate Cox Proportional Hazards Model for All-Cause Mortality

Variable	HR	Lower 95% CI	Upper 95% CI	*p*-value
Body mass index (BMI) Wald test	NA	NA	NA	< 0.001
BMI nonlinear term	NA	NA	NA	0.02
Diagnosis: idiopathic	0.63	0.49	0.80	< 0.001
Diagnosis: ischemic	0.74	0.57	0.95	0.019
Diagnosis: other	0.55	0.43	0.70	< 0.001
Age	1.01	1.00	1.01	< 0.001
Cigarette usage	1.23	1.13	1.34	< 0.001
Inotropes at transplant	1.06	0.96	1.17	0.262
Donor LV ejection fraction	1.00	1.00	1.01	0.343
LVAD+RVAD	1.11	0.79	1.55	0.539
No VAD	0.90	0.81	1.00	0.049
RVAD	1.07	0.40	2.87	0.888
TAH	1.96	1.27	3.02	0.002
Sex (female)	0.88	0.79	0.98	0.017
Total bilirubin, mg/dl	1.05	1.04	1.06	< 0.001
ECMO	1.63	1.30	2.05	< 0.001
IABP	1.02	0.90	1.16	0.763
Transplant year	1.09	1.07	1.12	< 0.001
Donor age	1.01	1.01	1.02	< 0.001
Recipient creatinine at transplant	1.17	1.13	1.21	< 0.001
Diabetes mellitus	0.85	0.78	0.93	< 0.001
History of hypertension donor	0.99	0.89	1.11	0.928
Mean PA pressure at transplant	1.00	1.00	1.01	0.257
Recipient cardiac index at transplant	1.03	0.97	1.09	0.394
Donor/recipient PHM ratio	0.99	0.76	1.28	0.93
Peak CPRA	1.00	1.00	1.00	0.007

Abbreviations: CI, confidence interval; CPRA, calculated panel reactive antibodies; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IABP, intra-aortic balloon pump; LV, left ventricle; LVAD, left ventricular assist device; PA, pulmonary artery; PHM, predicted heart mass; RVAD, right ventricular assist device; TAH, total artificial heart; VAD, ventricular assist device.

These results have implications both for recipient selection and risk management. It has been known in statistical literature that binning continuous variables often leads to misleading estimates of effect size near the boundaries of the bins and, consequently, can lead to suboptimal clinical decision-making and biased access to life-saving organs.[22] Based on our findings, we would advocate for the use of continuous measures of risk and development of continuous risk models of donor-recipient compatibility in the future.

Limitations

This retrospective analysis was performed on prospectively maintained UNOS database and despite matching, could contain some center-specific selection bias for the recipients

Table 5 Incidence of Secondary Outcomes With Univariate Linear Association to BMI

Variable	Overall, N = 30,616[a]	Class I (underweight), N = 660[a]	Class II (healthy), N = 9,308[a]	Class III (overweight), N = 10,946[a]	Class IV (obese), N = 9,498[a]	Class V (morbidly obese), N = 204[a]	Linear association (per 10 kg/m^2)	CI	*p*-value
Length of stay following transplant	15 (11, 23)	16 (12, 26)	15 (11, 22)	15 (11, 23)	16 (12, 26)	17 (12, 26)	1.6	1.1, 2.2	< 0.001
Unknown	849	16	221	285	318	9			
Acute rejection within 1 year	4,471 (19%)	92 (18%)	1,290 (17%)	1,552 (18%)	1,498 (20%)	39 (27%)	1.21	1.13, 1.29	< 0.001
Unknown	6,528	144	1,889	2,263	2,170	62			
Dialysis before discharge	3,723 (12%)	63 (9.7%)	912 (9.9%)	1,229 (11%)	1,479 (16%)	40 (20%)	1.56	1.46, 1.67	< 0.001
Unknown	502	8	122	184	185	3			
Stroke before discharge	948 (3.2%)	27 (4.2%)	307 (3.4%)	331 (3.1%)	278 (3.0%)	5 (2.5%)	0.90	0.79, 1.03	0.12
Unknown	569	13	146	207	196	7			

Abbreviations: BMI, body mass index; CI, confidence interval.

[a] n (%)

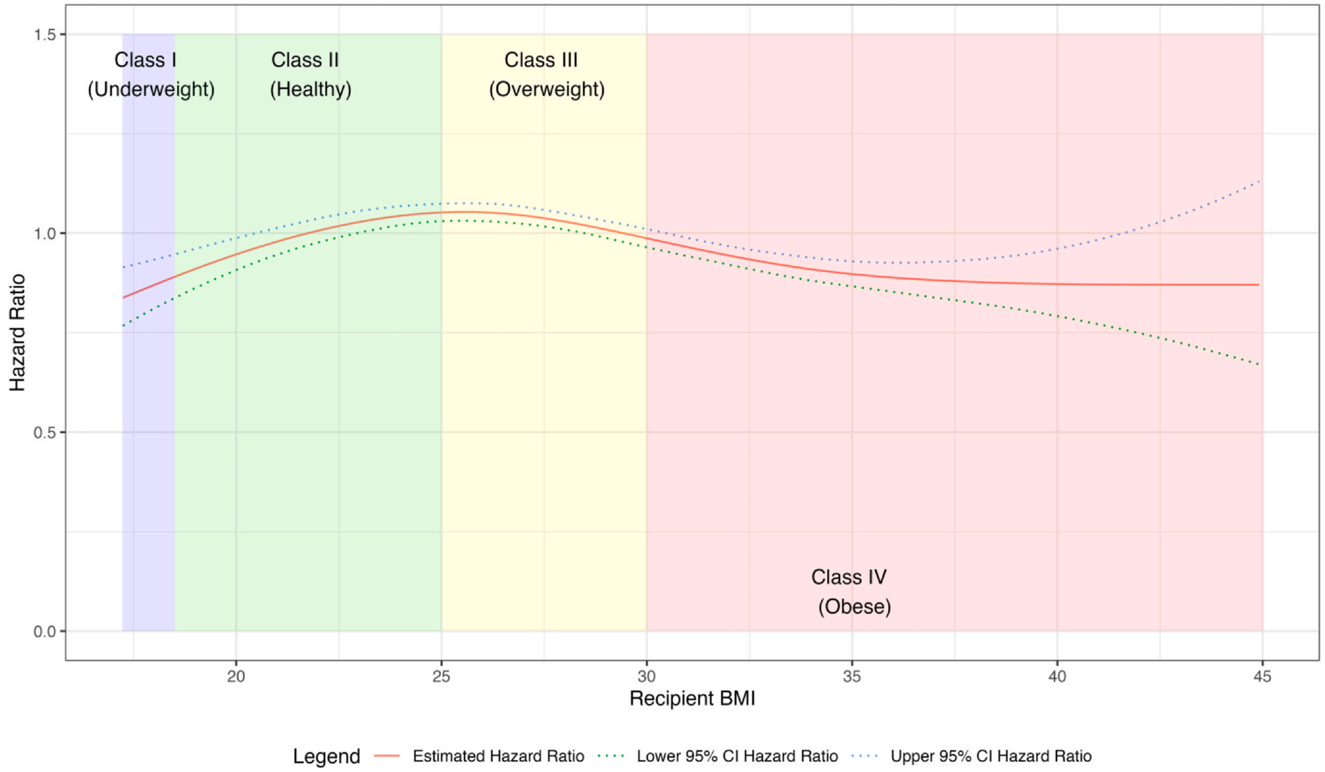

Figure 4 Smoothing spline term plot for the association between recipient BMI and length of stay. BMI, body mass index; CI, confidence interval.

Table 6 Estimated Odds Ratio and Pointwise 95% Confidence Intervals for Specific BMI Values for Postoperative Dialysis

BMI	OR	CI lower	CI upper
26	1.03	0.97	1.11
30	1.31	1.22	1.40
35	1.55	1.39	1.72
40	1.61	1.24	2.08
45	1.75	0.94	3.28

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

and donors. Furthermore, sample size was small at the extremes of the BMI, making statistical interpretation limited.

One limitation in using UNOS STAR data is that BMI_CALC calculates a recipient's BMI on the basis of their most recent recorded height and weight and is not done at a standard time point in relation to transplant, and so may not reflect a patient's true BMI at time of transplant.

The timing of the measurement is not available within the STAR database, so we had to posit a model of measurement error to perform our sensitivity analysis. Increased granularity on the timing of measurements in the UNOS STAR database can improve the quality of future work and

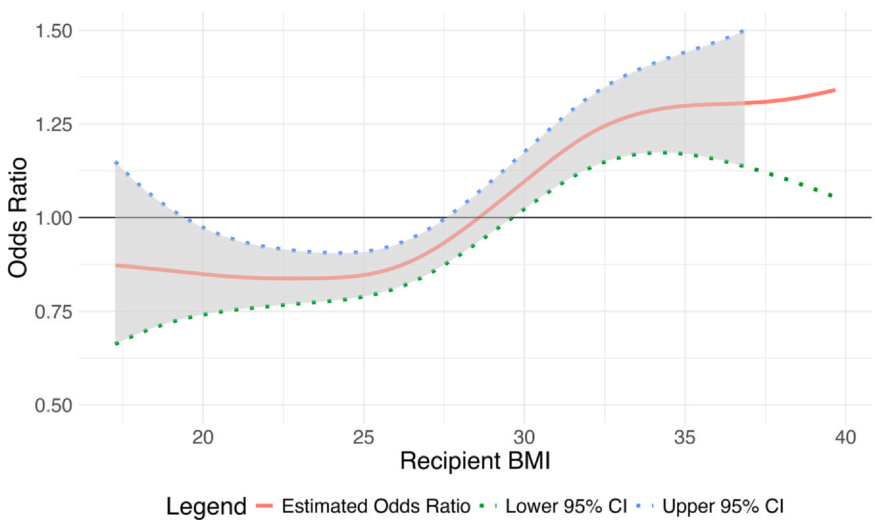

Figure 5 Smoothing spline term plot for the association between recipient BMI and postoperative dialysis. BMI, body mass index; CI, confidence interval.

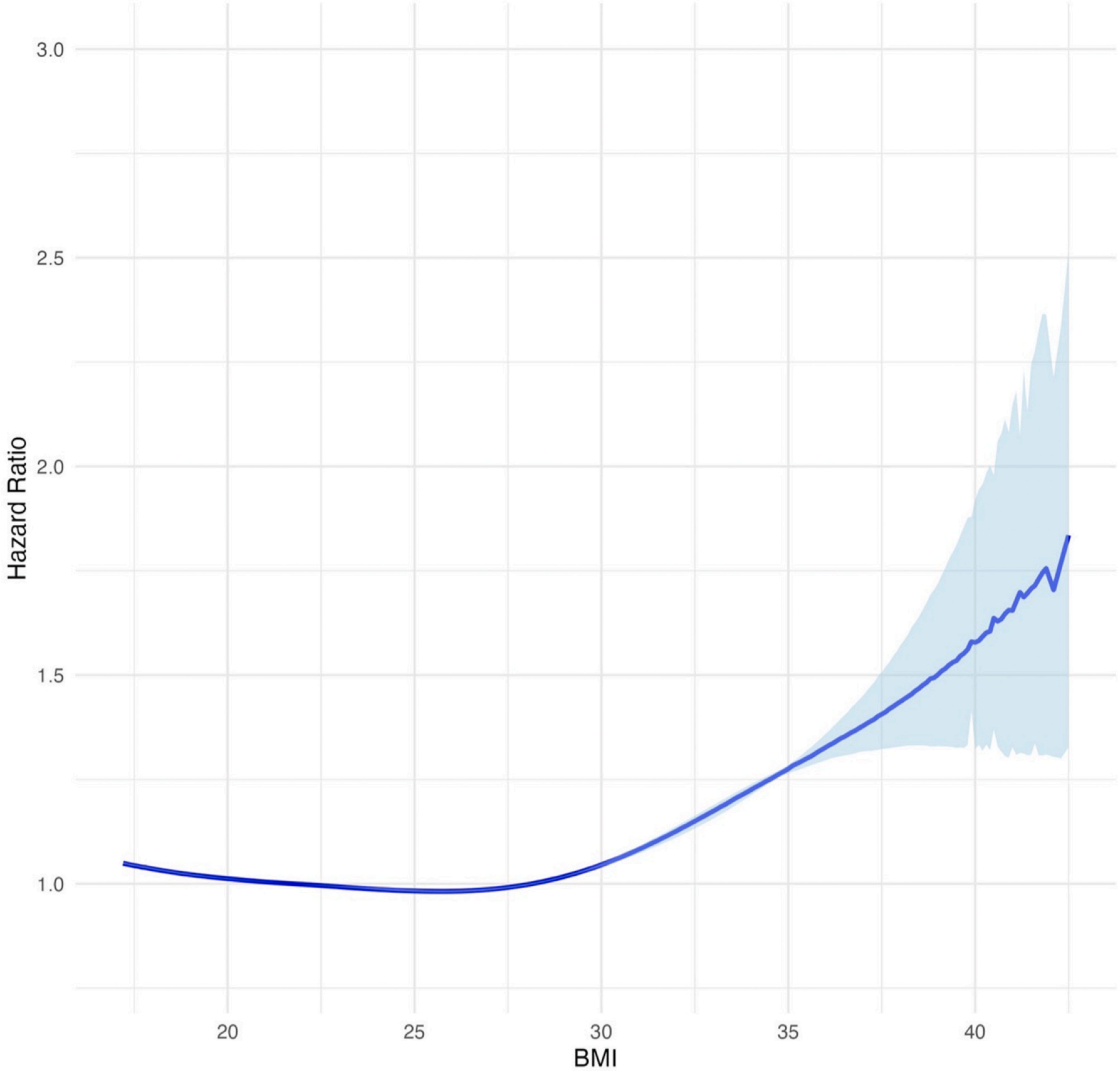

Figure 6 Sensitivity analysis of the association between BMI and all-cause mortality due to measurement timing-related error. BMI, body mass index.

lend visibility to timing-related effects of measures such as BMI.

Conclusion

After multivariable adjustment, there is no sharp cutoff in survival risk at either BMI = 30 or BMI = 35. Unlike previously reported results, postoperative survival risk grows approximately linearly in the BMI range from BMI = 26 to 40. Based on these findings, we would advocate for the use of continuous measures of risk and the development of continuous risk models of donor-recipient compatibility rather than the use of cutoffs. Therefore, a more holistic estimate of recipients' survival risk could be weighed against available potential donors. Increased acceptance of higher BMI donors could help address access to organs for recipients with higher BMI without negatively impacting PHM and allow for expansion of listing patients with higher BMI. Optimization in surgical workflow and future improvements in immunosuppression maintenance regimes for obese patients can mitigate the risks of secondary outcomes of hemodialysis and acute rejection.

Author contributions

Reid Dale: Conceptualization, Methodology, Formal Analysis, Writing—original draft, Writing—review and editing. Nataliya Bahatyrevich: Methodology, Writing—original draft, Writing—review and editing. Matthew Leipzig: Software, Formal analysis, Data curation.

Maria Elizabeth Currie: Conceptualization, Writing—original draft, Writing—review and editing.

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