

Predicting Post-Heart Transplant Composite Renal Outcome Risk in Adults: A Machine Learning Decision Tool



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Kidney Int Rep (2022) **7**, 1410–1415; https://doi.org/10.1016/j.ekir.2022.04.004 KEYWORDS: dialysis; end-stage renal disease; heart transplant; machine learning; prediction; random forest © 2022 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

INTRODUCTION

E nd-stage renal disease after heart transplant (HT) is associated with higher mortality and cost of care.^{1,2} Early and late renal failure after HT are caused by pretransplant comorbid factors (age, chronic kidney disease [CKD], diabetes mellitus, hypertension, and smoking), perioperative recurrent acute kidney injury (AKI), and use of nephrotoxic immunosuppressive agents (calcineurin inhibitors).^{3,4}

The rate of simultaneous heart-kidney transplantation (SHKT) due to comorbid kidney disease has increased in the past decade.⁵ The Organ Procurement and Transplant Network/the United Network for Organ Sharing, which oversees organ transplantation in the United States, has not set a national policy to guide SHKT. Thus, the decision for SHKT is currently left to individual transplant centers' discretion. A consensus conference in 2019 on heart-kidney transplantation set the stage for developing guidelines for medical eligibility criteria for SHKT for candidates with established CKD (glomerular filtration rate [GFR] <60 ml/min per 1.73 m²) and persistent AKI.⁶ Their Heart/Kidney Workgroup advised that, based on 2 independent GFR measurements at least 2 weeks apart, patients with established GFR <30 ml/min per 1.73 m² and selected candidates with GFR of 30 to 44 ml/min per 1.73 m² (having strong evidence of CKD including small kidney sizes and proteinuria >0.5 g/d) should be considered for SHKT. Remaining patients with CKD with GFR of 45-59 ml/min per 1.73 m² may not be suitable for SHKT. Nevertheless, applying these criteria to HT alone recipients between 2000 and 2019, approximately 33% of them with an estimated GFR of $30-59 \text{ ml/min per } 1.73 \text{ m}^2$ pretransplant (Supplementary Table S1), not considered as eligible for SHKT, may still be at risk of developing end-stage renal disease. Therefore, a personalized computer-aided model to predict the possibility of advanced kidney failure in early post-transplant period is needed to identify at-risk candidates.

In this study, we developed a machine learning (random forest [RF])–based algorithm to predict composite renal outcomes (CRO defined as dependence on chronic dialysis, GFR <20 ml/min per 1.73 m², or having received a kidney transplant) among adult HT recipients at risk (GFR <60 ml/min per 1.73 m²) at post-transplant 1 year. We also built a web-based decision tool based on the RF model (Figure 1). The

Composite Renal Outcome [*] Risk Calculator for Adult Heart Transplant Alone Patients							
Age:	(years)	Height:	(inch)				
Sex:	○ Male ○ Female	Weight:	(kg) / (lbs)				
Race:	 White Black Hispanic Asian Others 	BMI:	kg/m²				
Current serum creatinine:	(mg/dl)	Diabetes status:	 No diabetes Type I Type II 				
Current eGFR:§	ml/min per 1.73 m ²	Pulmonary artery mean pressure:	mmHg				
Current dialysis status:	\bigcirc Yes \bigcirc No	Pulmonary artery wedge pressure	mmHg				
Previous serum creatinine: (within last 3 months)	(mg/dl)	Cardiac index:	(L/m ²)				
Previous eGFR: [§]	ml/min per 1.73 m ²	Ventricular assist device type:	 No VAD LVAD RVAD/BiVAD/TAH 				
Previous dialysis status: (within last 3 months)	○ Yes ○ No	Functional status category: (based on Karnofsky score)	 Mild Impairment (80-100%) Moderate Impairment (50-70%) Severe Impairment(0-40%) 				
eGFR ratio (current eGFR/previous eGFR)		UNOS Region: [‡]					
This calculator uses a random forest c composite renal outcome(CRO) withi sensitivity of 80%, specificity of 46% of 8%.	classifier and correctly classif in first year of heart transplan , negative predictive value of	tes patients at risk of developing tation with an AUC of 70%, f 98%, and positive predictive value					
*Composite renal outcome (CRO) det m ² or received a kidney transplantation alone recipients. \$Default eGFR value is 10 ml/min/1.7	fined as dependence on chron on within first year of transpla 73 m ² if on dialysis	tic dialysis, eGFR < 20 ml/min/1.73 ant among adult heart transplant	Calculate				

[‡]https://unos.org/community/regions/

Figure 1. Web calculator for predicting the composite renal outcome (defined as dependence on chronic dialysis, eGFR <20 ml/min per 1.73 m², or a received kidney transplantation risk at 1 year) in adult HT alone recipients. AUC, area under the curve; BiVAD, biventricular assist device; BMI, body mass index; CRO, composite renal outcome; eGFR, estimated glomerular filtration rate; HT, heart transplant; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart; UNOS, United Network of Organ Sharing; VAD, ventricular assist device.

details regarding the study cohort selection (Supplementary Figure S1) and the methods are provided in the Supplementary Materials.

RESULTS

Characteristics of the Study Cohort

In this retrospective study, we analyzed a cohort of adult recipients who received HT alone transplants

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(regardless of listing intention) between January 1, 2000, and September 30, 2019, using the Organ Procurement and Transplant Network national registry, which included 19,861 adult HT recipients with eGFR <60 ml/min per 1.73 m² at listing and/or pretransplant.

The incidence of the CRO at 1 year between 2000 and 2019 is found in Supplementary Figure S2 (ranging from 2.2% to 6.1%). The characteristics of the study cohort and corresponding deceased donors are found in

Table 1. Characteristics and outcomes of the HT alone recipients (eGFR \leq 60 ml/min per 1.73 m² at listing and/or before transplant) between 2000 and 2019 by composite renal outcomes at 1 year in the United States

n(%) 19,361 19,269 19,361,30 ymoleti (100) 19,061-62 50,61-62 50,61-62 0.017 Sec, mole, (100) 14,106,74.32 14,106,74.43 50,60,72.83 0.018 White 14,305,72.25 13,366,72.26 51,20,66,0 - - - 0.001 Base 33,22,76,0 13,22,76,0 149,00 149,00 - - 0.001 - - 0.001 - - 0.001 - - 0.001 - - 0.001 - - 0.001 -	Recipient characteristics	Whole cohort	No-CRO	CRO	P value ^a
gen metan (vdi) yr 90 (1-40) 90 (21-40) 90 (22-40) 0.01 ison (value) 14.781 (7.42) 14.186 (7.44) 4.680 (7.5) .010 ison .0101 .0101 .0001 .0001 ison .012 (7.6) .012 (7.6) .016 (7.5) .0001 ison .012 (7.6) .012 (7.6) .016 (7.5) .0001 ison .012 (7.6) .000 (7.5) .0001 .0001 ison .025 (1.1) .012 (1.6) .0001 .0001 ison (range) .024 (1.1) .016 (1.5) .0001 .0001 ison (range) .024 (1.2) .024 (2.5) .0001 .0001 ison (range) .024 (1.2) .026 (1.6) .0001 <t< td=""><td>n (%)</td><td>19,861</td><td>19,708 (96.1)</td><td>783 (3.9)</td><td></td></t<>	n (%)	19,861	19,708 (96.1)	783 (3.9)	
bar (mein) b. (b. (b. (b. (b. (b. (b. (b. (b. (b.	Age, median (IQR) yr	59 (51–64)	59 (51–64)	59 (52–64)	0.17
box	Sex (male)	14,761 (74.3)	14,195 (74.4)	566 (72.3)	0.18
White [1,4]395 (72,5) [13,883 (72,8) [15] (66) [200 (25,5) Hagenic 1302 (66) 1257 (66) 46 (6.8)	Race				< 0.001
Book 3416 (172) 3216 (16 9) 200 (5) Asian 1524 (26) 1550 (26) 19 (24) Asian 1524 (26) 1550 (26) 19 (24) Therpise Insign (m) 173 9 ± 58 173 4 ± 101 16 Respine Insign (m) 173 9 ± 58 173 4 ± 101 16 Respine Insign (m) 173 9 ± 58 174 4 ± 8 2.0 ± 108 0.000 Status (flow) 173 9 ± 58 174 ± 48 2.0 ± 10 0.001 Status (flow) 175 1 ± 48 174 ± 48 2.0 ± 10 0.001 Status (flow) 175 0 (29 + 1) 305 (29 0) 20 (26) <td>White</td> <td>14,395 (72.5)</td> <td>13,883 (72.8)</td> <td>512 (65.4)</td> <td></td>	White	14,395 (72.5)	13,883 (72.8)	512 (65.4)	
stepsenic 1302 (66) 127 (65) 45 (6.6) Aster 554 (26) 556 (26) 18 (2.4) 7.09 Other 225 (1.1) 216 (1.1) 7.09 0.16 Recipient leight (m) 173 9 ± 0.8 173 9 ± 1.8 173.4 ± 1.01 0.16 Recipient leight (m) 83 ± 17.4 83.2 ± 17.4 85.2 ± 17.8 0.000 No 13.332 (70.2) 13.465 (70.6) 48 (69.9)	Black	3415 (17.2)	3215 (16.9)	200 (25.5)	
Asim S24 (26) S50 (26) 19 (24) Other 225 (1) 27.8 (2) 27.8 (2) 27.8 (2) 0.03 Recipies height (0m) 173.9 (2) 33.4 (2) 33.4 (2) 0.03 0.00 Recipies height (0m) 27.5 ± 4.8 27.4 ± 4.8 28.2 ± 5.0 <0.001	Hispanic	1302 (6.6)	1257 (6.6)	45 (5.8)	
Offer 228 (1.1) 218 (1.1) 7 (0.9) Respect lengt (r) 173 9 ± 68 173 9 ± 68 173 4 ± 10.1 0.16 Respect lengt (r) 27 5 ± 4.8 27 5 ± 4.8 28 ± 20.0 <0.0001	Asian	524 (2.6)	505 (2.6)	19 (2.4)	
Bespent height (cm) 173 4 + 9.8 173.9 ± 9.8 <td>Other</td> <td>225 (1.1)</td> <td>218 (1.1)</td> <td>7 (0.9)</td> <td></td>	Other	225 (1.1)	218 (1.1)	7 (0.9)	
Bespin quipt (Qp) 83.4 ± 17.4 83.3 ± 17.4 83.2 ± 17.8 0.003 Biopr mass now (Qnm*) 27.5 ± 4.8 27.4 ± 4.8 28.2 ± 5.0 <0.001	Recipient height (cm)	173.9 ± 9.8	173.9 ± 9.8	173.4 ± 10.1	0.16
<tbody </tbody blody magnetides (ng/m²)27 5 ± 4.827 4 ± 4.828 2 ± 5.0<0001No13,932 (70.2)13 463 (70.6)468 (59.9)<0001	Recipient weight (kg)	83.4 ± 17.4	83.3 ± 17.4	85.2 ± 17.8	0.003
inscript of indicates	Body mass index (kg/m ²)	27.5 ± 4.8	27.4 ± 4.8	28.2 ± 5.0	<0.001
No 13,932 (70.2) 13,483 (70.6) 469 (69.9) Type II 6547 (27.9) 2620 (27.5) 294 (7.5) Extendio Conditinyopothy	History of diabetes				< 0.001
pp I 382 (19) 382 (19) 292 (26) Type I 5547 (27 9) 5253 (27.5) 291 (37.6) Ischama 7815 (38.4) 7515 (37.5) 228 (37.6) Ischama 7815 (38.4) 7515 (37.5) 228 (35.6) Corogenial 4162.1) 401 (2.1) 155 (37.5) 228 (35.6) Other 4167 (21.1) 401 (2.1) 155 (37.5) 32 (4.1) 0.36 Corogenial 4167 (21.1) 401 (2.1) 165 (28.6) - - Other 856 (3.5) 663 (3.5) 32 (4.1) 0.36 - - 0.001 Cordination transported by more pressure, mm Hg 18.8 ± 8.6 18.8 ± 8.6 18.8 ± 8.4 0.33 - 0.001 Pulmonory othey more pressure, mm Hg 28.3 ± 9.9 28.3 ± 9.3 25 (3.2) 0.10 Pulmonory othey more pressure, mm Hg 263 (2.9) 263 (2.4) 20.002 - - - 0.001 Cologen bio more pressure, mm Hg 10.10 (6.69.3) 10.00 0.010 - 0.001 -<	No	13,932 (70.2)	13,463 (70.6)	469 (59.9)	
Type II 6547 (27.9) 5283 (27.5) 24 (37.6) Ekology of cardiomyopathy 0.365 (39.4) 306 (39.0) 0.34 Konstheme 7433 (37.4) 7156 (37.5) 27.84 (65.5) 0.24 Comparind 4167 (21.1) 40.12 (21.0) 155 (37.5) 27.84 (65.5) 0.33 Constraint 4197 (21.1) 40.12 (21.0) 45.62 (3.5) 0.33 0.33 Cardiace subpit, firmi 4.54 ± 1.46 4.54 ± 1.46 4.76 ± 1.53 <0.001	Type I	382 (1.9)	362 (1.9)	20 (2.6)	
Elsology i cordionyopathy 0.34 Ischemic 7815 (39.4) 7510 (39.4) 305 (39.0) Konsichemic 7833 (37.4) 7155 (37.5) 278 (35.5) Congantal 416(2.1) 401 (2.1) 15 (1.9) Othesi 4197 (2.1.) 401 (2.1) 15 (3.9) Penvious INT, n (%) 995 (3.5) 683 (3.5) 32 (4.1) 0.38 Cardiaci codupt, Umin 4.54 ± 1.46 4.54 ± 1.46 4.76 ± 1.53 <0.001	Type II	5547 (27.9)	5253 (27.5)	294 (37.6)	
scheme 7815 (39.4) 7510 (39.4) 905 (39.0) Nonischemic 7433 (37.4) 7155 (37.5) 278 (35.5) Congentlal 416(2,1) 401 (2,1) 15 (19) Other 4197 (21.1) 401 (2,1) 185 (23.5) Derivals H1, r0(%) 996 (3.5) 683 (3.5) 32 (4.1) 0.36 Dardioc output, Wmin 4.54 ± 1.46 4.54 ± 1.46 4.76 ± 1.53 <0.001	Etiology of cardiomyopathy				0.34
Nonsciencic 7433 (37.4) 7165 (37.5) 278 (35.5) Conganital 416(2.1) 401 (2.1) 15 (1.9) Other 4197 (21.1) 401 (2.1) 15 (1.9) Orbitalize output, Urbin 455 (4.1) 0.38 Candiace output, Urbin 455 (4.1) 0.38 Candiace output, Urbin 455 (4.1) 0.38 Candiace output, Urbin per m ² 2.31 ± 0.70 2.30 ± 0.70 2.21 ± 0.67 <0.001	Ischemic	7815 (39.4)	7510 (39.4)	305 (39.0)	
Congenial 416(2.1) 401(2.1) 15 (1.9) Other" 4197 (21.1) 4012 (21.0) 185 (23.6) Previous H7, 16%) 669 (3.5) 663 (3.5) 32 (4.1) 0.38 Cardiac output, Wrin 4.54 ± 1.46 4.54 ± 1.46 4.76 ± 1.53 <0.001	Nonischemic	7433 (37.4)	7155 (37.5)	278 (35.5)	
Other 4197 (21.1) 4012 (21.0) 185 (23.6) Previous PT, n (%) 665 (3.5) 663 (3.5) 32 (4.1) 0.36 Cardice output, Irkin 4.54 ± 1.46 4.76 ± 1.53 <0.001	Congenital	416(2.1)	401 (2.1)	15 (1.9)	
Previous HT, n (%) 685 (3.5) 663 (3.5) 32 (4.1) 0.36 Cardiac dude, l/min per m ² 2.31 ± 0.70 2.30 ± 0.70 2.21 ± 0.67 <-0.001	Other ^b	4197 (21.1)	4012 (21.0)	185 (23.6)	
Cardiac output, Irmin 4.54 ± 1.46 4.54 ± 1.46 4.76 ± 1.53 <0.001	Previous HT, n (%)	695 (3.5)	663 (3.5)	32 (4.1)	0.36
Cardiac index, l/min per m ² 2.31 ± 0.70 2.30 ± 0.70 2.21 ± 0.67 <0001 Pulmonory copilitory wedge 18 ± 8.6 185 ± 8.4 0.33 pressue, mm Hg 28.3 ± 9.9 28.3 ± 9.9 28.1 ± 9.3 0.68 mm Hg 462 (2.3) 437 (2.3) 25 (3.2) 0.10 SCMO 207 (1.0) 190 (1.0) 17 (2.2) 0.02 ABP 1536 (7.7) 73 (3.3) 296 (57.6) <0.001 None 11.696 (68.9) 11.306 (69.3) 392 (50.1) <0.001 LVAD down 796 (3.9) 741 (3.9) 283 (3.6 <0.001 RVAD/BVAD/TAH 864 (4.4) 797 (4.2) 67 (8.6) <0.001 RVAD/BVAD/TAH 864 (5.9) 741 (3.9) 283 (5.0 <0.001 BeffR indin per 1.73 m ² data 53.3 ± 17.6 54.5 ± 17.6 45.8 ± 17.0 <0.001 Ibarsjand (fund on diolysis) 10.1 ± 0.90 10.99 ± 0.45 <0.001 BeffR indic (before forsplant/Wadt	Cardiac output, I/min	4.54 ± 1.46	4.54 ± 1.46	4.76 ± 1.53	< 0.001
Palmonany applilary wedge 18.8 ± 8.6 18.8 ± 8.6 18.8 ± 8.6 18.5 ± 8.4 0.33 pressure, rm Hg 28.3 ± 9.9 28.3 ± 9.9 28.1 ± 9.3 0.58 mm Hg 462 (2.3) 437 (2.3) 25 (3.2) 0.10 CKMO 207 (1.0) 190 (1.0) 17 (2.2) 0.002 ABP 1536 (7.7) 1463 (7.7) 73 (9.3) 0.08 VAD	Cardiac index, I/min per m ²	2.31 ± 0.70	2.30 ± 0.70	2.21 ± 0.67	<0.001
Pulmonary antery mean pressure, mm Hg 28.3 ± 9.9 28.3 ± 9.3 28.1 ± 9.3 0.58 mm Hg 462 (2.3) 437 (2.3) 25 (3.2) 0.10 ECMO 207 (1.0) 190 (1.0) 17 (2.2) 0.002 ABP 158 (7.7) 1463 (7.7) 73 (9.3) 0.09 MO .0001 .0001 None 11,698 (58.9) 11,306 (59.3) 392 (50.1) .0001 LVAD olone 6530 (32.9) 6234 (32.7) 296 (37.8) .0001 BdFR, ml/min per 1.73 m ² dt 864 (4.4) 797 (4.2) 67 (8.6) .0001 Linknown 769 (3.9) 741 (3.9) 28 (3.6) .0001 BdFR, ml/min per 1.73 m ² dt 53.3 ± 17.6 54.5 ± 17.6 45.8 ± 17.0 <0.001	Pulmonary capillary wedge pressure, mm Hg	18.8 ± 8.6	18.8 ± 8.6	18.5 ± 8.4	0.33
Mechanical ventilation requirement 462 (2.3) 437 (2.3) 25 (3.2) 0.10 CEMO 207 (1.0) 190 (1.0) 17 (2.2) 0.002 Map 1536 (7.7) 1463 (7.7) 73 (9.3) 0.09 VAD	Pulmonary artery mean pressure, mm Hg	28.3 ± 9.9	28.3 ± 9.9	28.1 ± 9.3	0.58
ECMO 207 (10) 190 (1.0) 17 (2.2) 0.002 MAP 1536 (7.7) 1463 (7.7) 73 (9.3) 0.09 VAD	Mechanical ventilation requirement	462 (2.3)	437 (2.3)	25 (3.2)	0.10
MABP 1536 (7.7) 1463 (7.7) 73 (9.3) 0.09 VAD <.0001	ECMO	207 (1.0)	190 (1.0)	17 (2.2)	0.002
VAD < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < <	IABP	1536 (7.7)	1463 (7.7)	73 (9.3)	0.09
None11,698 (58.9)11,306 (59.3)392 (50.1)LVAD olone6530 (32.9)6234 (32.7)296 (37.8)RVAD/BIVAD/TAH864 (4.4)797 (4.2)67 (8.6)Luknown769 (3.9)741 (3.9)28 (3.6)seGFR, ml/min per 1.73 m ² at54.3 \pm 17.654.5 \pm 17.550.9 \pm 18.7<0.001	VAD				<0.001
LVAD alone6530 (32.9)6234 (32.7)296 (37.8)RVAD DRVAD/TAH864 (4.4)797 (4.2) $67 (8.6)$ Unknown769 (3.9)741 (3.9)28 (3.6)GER, m/min per 1.73 m² at tasing (f not on diolysis) 54.3 ± 17.6 54.5 ± 17.5 50.9 ± 18.7 <0.001 BGFR, rulin or on diolysis) 53.3 ± 17.6 54.5 ± 17.6 45.8 ± 17.0 <0.001 BGFR, rulin (before transplant/wait listing, n%) 1.10 ± 0.90 1.10 ± 0.91 0.99 ± 0.45 <0.001 Diolysis before transplant/wait listing, n%) $370 (1.9)$ $339 (1.8)$ $31 (4.0)$ <0.001 Diolysis before transplant, n%) $1038 (5.2)$ $907 (4.8)$ $131 (16.7)$ <0.001 Score before transplant, n%) $3309 (16.7)$ $3213 (16.8)$ $96 (12.3)$ <0.001 Score before transplant, n% $300 (16.7)$ $3213 (16.8)$ $96 (12.3)$ <0.001 Nonvort $476 (7.4)$ $3213 (16.8)$ $96 (12.3)$ <0.001 String of <0.001 <0.001 <0.001 <0.001 Score before transplant, % $865 (4.5)$ $33 (4.2)$ <0.001 Unknown $1476 (7.4)$ $3223 (11.6)$ $38 (4.9)$ <0.001 Unknown $136 (15.8)$ $2229 (11.7)$ $142 (18.1)$ <0.001 1 $989 (4.5)$ $865 (4.5)$ $33 (4.2)$ <0.001 2 $237 (11.9)$ $2229 (11.7)$ $142 (18.1)$ <0.001 3 $233 (11.4)$ $2177 (11.4)$ $56 (7.2)$ <0.001 1 $989 $	None	11,698 (58.9)	11,306 (59.3)	392 (50.1)	
RVAD/BIVAD/TAH 864 (4.4) 797 (4.2) 67 (8.6) Unknown 769 (3.9) 741 (3.9) 28 (3.6) e6FR, ml/min per 1.73 m² dt 54.3 ± 17.6 54.5 ± 17.5 50.9 ± 18.7 <0.001	LVAD alone	6530 (32.9)	6234 (32.7)	296 (37.8)	
Unknown $769 (3.9)$ $741 (3.9)$ $28 (3.6)$ eGR, Mr/min per 1.73 m² dt 54.3 ± 17.6 54.5 ± 17.5 50.9 ± 18.7 <0.001 lising (if not on dialysis) 53.3 ± 17.6 54.5 ± 17.6 45.8 ± 17.0 <0.001 fransplant (if not on dialysis) 53.3 ± 17.6 54.5 ± 17.6 45.8 ± 17.0 <0.001 lising (if not on dialysis) 1.10 ± 0.90 1.10 ± 0.91 0.99 ± 0.45 <0.001 lising not (before transplant/wait 1.10 ± 0.90 $339 (1.8)$ $31 (4.0)$ <0.001 Dialysis di listing , n (%) $370 (1.9)$ $339 (1.8)$ $31 (4.0)$ <0.001 Dialysis bifore transplant, n (%) $1038 (5.2)$ $907 (4.8)$ $131 (16.7)$ <0.001 Dialysis bifore transplant, $\%$ $3309 (16.7)$ $3213 (16.8)$ $96 (12.3)$ <0.001 Soco before transplant, $\%$ $3309 (16.7)$ $3213 (16.8)$ $96 (12.3)$ <0.001 Soco before transplant, $\%$ $339 (34.4)$ $6603 (34.6)$ $316 (40.4)$ <0.001 0-50 $8237 (41.5)$ $7824 (41.0)$ $396 (50.6)$ <0.001 UNOS region $1476 (7.4)$ $1438 (7.5)$ $38 (4.9)$ <0.001 1 $989 (4.5)$ $865 (45.5)$ $33 (4.2)$ <0.001 2 $2371 (11.9)$ $2229 (11.7)$ $142 (18.1)$ <0.001 3 $233 (1.4)$ $2177 (11.4)$ $56 (7.2)$ <0.001 4 $2340 (11.8)$ $2252 (11.8)$ $88 (11.2)$ <0.001 5 $3136 (15.8)$ $3017 (15.8)$ $119 (15$	RVAD/BiVAD/TAH	864 (4.4)	797 (4.2)	67 (8.6)	
aGFR, ml/min per 1.73 m^2 at lishing (if not on didivsits)54.3 \pm 17.654.5 \pm 17.550.9 \pm 18.7<0.001aGFR, ml/min per 1.73 m^2 before transplort (in or on didivsits)53.3 \pm 17.654.5 \pm 17.645.8 \pm 17.0<0.001	Unknown	769 (3.9)	741 (3.9)	28 (3.6)	
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accel R ratio (before transplant/wait) 1.10 ± 0.90 1.10 ± 0.91 0.99 ± 0.45 <0.001listing)370 (1.9)339 (1.8)31 (4.0)<0.001	eGFR, ml/min per 1.73 m ² before transplant (if not on dialysis)	53.3 ± 17.6	54.5 ± 17.6	45.8 ± 17.0	<0.001
Dialysis at listing, n (%) 370 (1.9) 339 (1.8) 31 (4.0) <0.001 Dialysis before transplant, n (%) 1038 (5.2) 907 (4.8) 131 (16.7) <0.001	eGFR ratio (before transplant/wait listing)	1.10 ± 0.90	1.10 ± 0.91	0.99 ± 0.45	<0.001
Dialysis before transplant, n (%) 1038 (5.2) 907 (4.8) 131 (16.7) <0.001 Functional status by Kamofsky score before transplant, % 3309 (16.7) 3213 (16.8) 96 (12.3) <0.001	Dialysis at listing, <i>n</i> (%)	370 (1.9)	339 (1.8)	31 (4.0)	<0.001
Functional status by Karnofsky score before transplant, % < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < <	Dialysis before transplant, n (%)	1038 (5.2)	907 (4.8)	131 (16.7)	< 0.001
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Unknown 1476 (7.4) 1438 (7.5) 38 (4.9) UNOS region	0–50	8237 (41.5)	7824 (41.0)	396 (50.6)	
UNOS region <th< th=""> <</th<>	Unknown	1476 (7.4)	1438 (7.5)	38 (4.9)	
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5 3136 (15.8) 3017 (15.8) 119 (15.2) 6 656 (3.3) 640 (3.4) 16 (2.0) 7 1900 (9.6) 1831 (9.6) 69 (8.8) 8 1107 (5.6) 1067 (5.6) 40 (5.1)	4	2340 (11.8)	2252 (11.8)	88 (11.2)	
6 656 (3.3) 640 (3.4) 16 (2.0) 7 1900 (9.6) 1831 (9.6) 69 (8.8) 8 1107 (5.6) 1067 (5.6) 40 (5.1)	5	3136 (15.8)	3017 (15.8)	119 (15.2)	
7 1900 (9.6) 1831 (9.6) 69 (8.8) 8 1107 (5.6) 1067 (5.6) 40 (5.1)	6	656 (3.3)	640 (3.4)	16 (2.0)	
8 1107 (5.6) 1067 (5.6) 40 (5.1)	7	1900 (9.6)	1831 (9.6)	69 (8.8)	
	8	1107 (5.6)	1067 (5.6)	40 (5.1)	

(Continued on following page)

Table 1. (Continued) Characteristics and outcomes of the HT alone recipients (eGFR \leq 60 ml/min per 1.73 m² at listing and/or before transplant) between 2000 and 2019 by composite renal outcomes at 1 year in the United States

Recipient characteristics	Whole cohort	No-CRO	CRO	P value ^a
9	1202 (6.1)	1127 (5.9)	75 (9.6)	
10	1626 (8.2)	1583 (8.3)	43 (5.5)	
11	2392 (12.0)	2290 (12.0)	102 (13.0)	
Waitlisted time (including inactive status), median (IQR), d	87 (25–251)	87 (25–250)	104 (27–285)	
Post-transplant patient survival at 1 yr (based on Kaplan Meier estimates), %	87.3	88.3	71.0	<0.001
Composite renal outcome incidence within 1 yr of heart transplantation, mean (the year 2000, the year 2019), %	3.9 (2.6–6.1)			

BiVAD, biventricular assist device; CABG, coronary artery bypass graft; CRO, composite renal outcome; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HT, heart transplant; IABP, intra-aortic balloon pump; IQR, interquartile range; LV, left ventricular; LVAD, left ventricular assist device; TAH, total artificial heart; UNOS, United Network of Organ Sharing; VAD, ventricular assist device.

^aP value applies to the comparison of no-CRO and CRO groups.

^bOther: restrictive cardiomyopathy, congenital, arrhythmia, valvular, and heart transplant-related diagnosis.

Data are presented as n (%), median (IQR) as appropriate.

Table 1 and Supplementary Table S2. The final study cohort included 19,861 patients, of which 783 (3.9%) had incident CRO. The 1-year survival among the patients who developed post-HT CRO (71.0%) was significantly lower compared with the ones who did not (88.3%) (log-rank P < 0.001).

Predictors of Post-HT CROs

A total of 15 predictors of post-HT ROC were selected by the RBFOpt library and sorted by RF feature importance score (Supplementary Table S3) among 39 variables in the United Network for Organ Sharing-STAR Dataset (Supplementary Table S4).

Performance of the RF Model

The final RF model performed with a C-statistic of 0.70 (95% CI 0.67–0.74) (Supplementary Figure S3). At the fixed sensitivity of 80.0%, the model resulted in 46.2% specificity, 97.8% negative predictive value, and 8.1% positive predictive value. For the given negative predictive value performance, our RF model mislabeled 2.2% of cases (=100%–97.8%). On the basis of 2019 statistics, the absolute and relative reduction in risk prediction was 3.9% (=6.1%–2.2%) and 64% (=[6.1%–2.2%) / 6.1%] × 100), respectively.

Robustness of the Model

To find the robustness of our model, we conducted 2 separate analyses. First, we trained the RF model using a data set that excluded patients who died in the no-CRO group; the model resulted in a C-statistic of 0.71 (95% CI 0.69–0.75). At the fixed sensitivity of 80.0%, the model had 46.3% specificity, 98.1% negative predictive value, and 8.0% positive predictive value. In the second analysis, we developed a RF survival model by treating the death event in the first year as a competing event to CRO occurrence and reported the

accuracy of CRO prediction at 1 year. The competing event RF model classified CRO with 70.6% accuracy.

Characteristics of the Patients Who Died

Because post-transplant mortality is relevant to the analysis, we also described comparative characteristics of the patients who died in both groups within 1 year post-transplant (Supplementary Table S5). The post-HT patients with CRO who died were more likely to have diabetes and worse Karnofsky scores and require dialysis pretransplant than the patients in the no-CRO group who died.

DISCUSSION

Our decision tool with a web-based interface is practical as it uses readily existing recipient pretransplant variables and provides a personalized risk of developing CRO within 1 year of HT. The performance RF model did not significantly change with by censoring death in both robustness analyses.

The variables selected in the RF model mostly align with previously described factors, including pretransplant renal function and need for renal replacement treatment, age, sex, race, diabetes mellitus, body mass index, functional status, ventricular assist device requirement, and pretransplant cardiac index.^{4,7} Deranged cardiac along with heightened risk of individuals with elevated right- and left-sided filling pressures and biventricular dysfunction may predispose these individuals to a greater risk of postoperative AKI.⁸ If these individuals experience recurrent AKI post-transplantation, these episodes may result in lower GFR at 1 year post-HT and potentially transition into CKD, especially the ones complicated with stage 3 AKI according to the Kidney Disease Improving Global Outcomes guidelines.⁹

In the setting of pre-HT, a negative prediction by our RF model, which has high negative predictive value, can serve as additional evidence that the patient has a lower risk of CRO post-HT and no need for SHKT. Clinical judgment (thorough physical examination and history taking, medication review, trending renal function on multiple data points, renal imaging, urine analysis, renal biopsy findings if available, etc.) should play a more significant role when the RF model predicts a positive outcome owing to the high false-positive rate and low positive predictive value. This scenario is related to the inability to capture reversibility in certain features (such as postoperative improvement in renal perfusion and renal function), uncertainty around donor quality, and perioperative course.

We also evaluated our RF model with an external cohort (an external validation), 353 patients who underwent SHKT between January 10, 2019, and September 30, 2020. Our predictive model classified 93% of SHKT patient into the positive class and 7% of SHKT patients into the negative class, which suggests that the clinical re-evaluation of 7% of patients for SHKT eligibility is necessary.

Strengths of this study include large sample size and utilization of the RF method with a multidimensional dataset. Nevertheless, the limitations are as follows: (i) potential bias inherent to the observational study design owing to unmeasured patient characteristics; (ii) vulnerability to significant changes in heart donor allocation policies affecting center practice and patient characteristics; and (iii) not capturing uncertainties potentially introducing prolonged AKI resulting from donor characteristics and postoperative complications.

In conclusion, the proposed web-based decision tool powered by an RF-based machine learning method is an objective and cross-validated tool for patient-level identification of CRO risk among at-risk HT candidates.

DISCLOSURE

The author, JLG, served as a consultant in the advisory board of Pfizer, Inc., Alnylam, Eidos Therapeutics, and Sarepta. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Flow chart showing the final study cohort selection (SHKT = simultaneous heart-kidney transplant; eGFR = estimated glomerular filtration rate).

Figure S2. The number of adult heart transplants, the incidence of simultaneous heart kidney transplants, and the composite renal outcome (defined as dependence on chronic dialysis, estimated glomerular filtration rate [eGFR] < 20 ml/min/1.73 m², or received kidney transplantation) at one-year in the United States between 2000 and 2019.

Figure S3. C-statistic for the ten-fold cross-validation study cohort.

Table S1. Pre-transplant distribution of kidney function and dialysis status of recipients of adult heart transplant alone (excluding all multiorgan transplants, the ones waitlisted for other organs, pediatric group, and missing creatinine values at transplant) between 2000 and 2019 in the U.S.

 Table S2. Characteristics of the deceased donors of the study cohort between 2000 and 2019 in the U.S.

Table S3. Variable (feature) ranking in the final random forest prediction model based on the feature importance score (the higher the score, the more important the feature is for accurate prediction).

TableS4.The variables (pre-transplant recipientcharacteristics, total of 39) selected by the domainexperts from the UNOS-STAR Dataset (Thoracic_Data).

Table S5. Characteristics of the adult heart transplant alone patients who died within first year of transplantation in the study cohort (N=2525).

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