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CODUSA - Customize Optimal Donor Using Simulated Annealing In Heart Transplantation

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OUTCOMES RESEARCH

In heart transplantation, selection of an optimal recipient-donor match has been constrained by the lack of individualized prediction models. Here we developed a customized donor-matching model (CODUSA) for patients requiring heart transplantations, by combining simulated annealing and artificial neural networks. Using this approach, by analyzing 59,698 adult heart transplant patients, we found that donor age matching was the variable most strongly associated with long-term survival. Female hearts were given to 21% of the women and 0% of the men, and recipients with blood group B received identical matched blood group in only 18% of best-case match compared with 73% for the original match. By optimizing the donor profile, the survival could be improved with 33 months. These findings strongly suggest that the CODUSA model can improve the ability to select optimal match and avoid worst-case match in the clinical setting. This is an important step towards personalized medicine.

Heart transplantation is the only option for survival for selected patients with end-stage heart failure. In recent years, survival after heart transplantation has improved significantly. Reasons for improved outcome include refinement of donor and recipient selection methods, better donor organ preservation, lower perioperative mortality rates, and enhanced immunosuppressive protocols¹. The median survival is now more than 10 years². However, donor scarcity is a major issue. In addition, suboptimal recipient-donor match may lead to acute rejection and cardiac allograft vasculopathy, leading to early and late mortality. Much research has been directed towards identifying factors predicting survival and optimal organ utilization.

Organ matching is primarily based on ABO blood group compatibility and patient size. Other factors such as gender, allograft ischemia time, medical conditions prior to transplant, and human leukocyte antigen (HLA) mismatch have all been implied as risk factors for acute rejection but may not be used in the organ matching²⁻⁵. Scant information exists concerning predictors of long-term survival after heart transplantation⁶. The long-term outcome depends on several factors, and it is important to recognize that the influence from some of these varies over time. Because of the inherent complexity of coupled nonlinear biological systems, the development of computational models may be necessary for achieving a quantitative understanding of the outcome⁷. More complex analyses, including the interaction between several of the variables, are lacking and no study has to date created a personalized recipient donor matching model for identifying worst-case match, and to find best possible match in heart transplantation. Instead of using the traditional methodology based on standard linear model with the assumption of proportional hazards to predict the survival, a more flexible non-linear survival model based on artificial neural networks (ANNs) is preferable⁸. Despite computational learning approaches being well suited for medical application there are only a few examples within the field of transplantation⁹.

The simulated annealing (SA) algorithm can be found in various research fields for parameter optimization. The SA algorithm developed by Kirkpatrick et al.¹⁰ has been previously applied to a wide range of medical problems, including microbial engineering, classification of cancer gene expression data and gamma knife planning¹¹⁻¹³. SA is a random-search optimization technique for finding the global minimum of a cost function. SA is inspired by the physical process of controlled cooling of solid materials.

Here we show that SA could be used to 'customize' an optimal donor for the heart transplant recipients on the waiting list, which makes it possible to avoid poor recipient-donor match, and identify the best possible match.



Results

A total of 62,114 recipients of heart transplants from deceased donors were collected from the International Society for Heart and Lung Transplantation (ISHLT) Registry during the 19-year study period. After case records with incomplete mandatory data were excluded, the final study population comprised 59,698 patients. The mean age of the overall cohort was 51 ± 11 years and 20% were women. The patient material comprised 318,904 patient-years, with a mean follow-up duration of 5.3 ± 4.6 years (median 4.5, range 0–19.8 years). The most common indication for heart transplantation and cause of end-stage heart failure were ischemic cardiomyopathy in 26,266 patients (44%) and non-ischemic cardiomyopathy in 26,047 patients (44%). The average donor age was 32 ± 13 years. The majority of donors were men (69%). The study material was randomly divided in a derivation cohort ($N = 49,856$) and an

independent validation cohort ($N = 9,842$). The used variables in the model development were based on which information is available at the time of transplantation (Table 1A–B). The derivation and the validation cohorts were generally similar although a higher proportion of symptomatic peripheral vascular disease was registered in the validation group.

Calibration and discrimination of the ANN survival model. The applied ANN model (a generalization of the standard Cox proportional hazard model) is a flexible non-linear survival models. To improve the performance we used an ensemble (Committee Machine) of ANNs instead of a single prediction model^{14,15}. We optimized the model by ranking and minimizing the number of risk variables, similar to a stepwise backwards elimination procedure (Figure 1A). The final model included 30 of the 38 candidate

Table 1a | Demographics and clinical characteristics of the study population (1988–2006)

	N	Derivation Cohort N = 49,856	Validation Cohort N = 9,842	P-value
Recipient data				
Recipient's diagnosis	59,698			0.937
Non-ischemic cardiomyopathy		21,789 (44%)	4,258 (43%)	
Ischemic cardiomyopathy		21,911 (44%)	4,355 (44%)	
Graft failure		971 (2%)	203 (2%)	
Valvular heart disease		1,530 (3%)	296 (3%)	
Congenital		950 (2%)	191 (2%)	
Miscellaneous		2,705 (5%)	539 (5%)	
Age (year)	59,698	51 ± 11	51 ± 11	0.212
Female gender	59,698	10,052 (20%)	1,978 (20%)	0.884
Height (cm)	48,042	173 ± 9	173 ± 9	0.605
Weight (kg)	48,042	76 ± 15	76 ± 15	0.412
COPD	23,035	615 (3%)	136 (4%)	0.217
Hypertension	23,784	7,262 (38%)	1,447 (37%)	0.600
Peripheral vascular disease	23,783	648 (3%)	170 (4%)	<0.001
Unstable angina	29,089	2,373 (10%)	523 (11%)	0.010
History of cerebrovascular disease	23,791	714 (4%)	153 (4%)	0.360
Infection within two weeks	25,516	2,077 (10%)	442 (11%)	0.124
Cytomegalovirus status	31,998	18,823 (70%)	3,693 (70%)	0.504
Amiodarone prior to transplant	23,794	4,727 (24%)	888 (23%)	0.122
Antiarrhythmics	22,134	6,916 (37%)	1,364 (37%)	0.947
Previous transplant	47,311	1,263 (3%)	261 (3%)	0.412
Previous cardiac surgery	5,600	2,056 (44%)	391 (43%)	0.893
PVR (wood units)	21,689	$2.1 (1.4-3.2)$	$2.1 (1.4-3.2)$	0.718
Creatinine ($\mu\text{mol/l}$)	27,909	106 (88–132)	106 (88–132)	0.834
Serum bilirubin (mg/dl)	25,181	0.9 (0.6–1.4)	0.9 (0.6–1.4)	0.482
Dialysis pre-transplanted	2,033	28 (2%)	3 (1%)	0.334
Medical condition at transplant	59,698			0.549
Not hospitalized		31,507 (63%)	6,252 (64%)	
Hospitalized		4,903 (10%)	933 (10%)	
ICU		13,446 (27%)	2,657 (27%)	
Life support				
Inotropic support prior to transplant	39,128	12,901 (39%)	2,548 (40%)	0.754
Mechanical ventilation	36,421	938 (3%)	195 (3%)	0.435
Intra-aortic balloon pump	37,399	2,123 (7%)	387 (6%)	0.182
ECMO	36,542	92 (0%)	14 (0%)	0.377
Donor data				
Age (year)	59,698	32 ± 13	32 ± 13	0.278
Female gender	59,698	15,470 (31%)	3,096 (31%)	0.402
History of hypertension	28,421	2,636 (11%)	517 (11%)	0.981
Cytomegalovirus status	43,209	20,425 (57%)	4,015 (57%)	0.774
Ischemia time (minutes)	47,359	178 ± 63	178 ± 63	0.416
Era of transplantation				
2001–2006	59,698	13,933 (28%)	2,724 (28%)	0.824
1996–2000		14,088 (28%)	2,786 (28%)	
1991–1995		15,017 (30%)	3,005 (31%)	
1988–1990		6,818 (14%)	1,327 (13%)	

Data are mean \pm SD, number (%). The numbers are calculated on patients with available data. COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PVR, pulmonary vascular resistance. Test used: χ^2 -test; Wilcoxon test.



Table 1b | Blood groups and HLA for the study population

	Derivation Cohort N = 49,856	Validation Cohort N = 9,842	P-value
Recipient blood group			0.655
A	22,152 (44%)	4,369 (44%)	
B	6,238 (13%)	1,271 (13%)	
AB	2,990 (6%)	599 (6%)	
O	18,476 (37%)	3,603 (37%)	
Donor blood group			0.820
A	19,979 (40%)	3,943 (40%)	
B	4,985 (10%)	1,014 (10%)	
AB	1,333 (3%)	259 (3%)	
O	23,559 (47%)	4,626 (47%)	
Recipient-donor match			
HLA-A, 1 mismatch	11,417 (41%)	2,405 (41%)	0.994
HLA-A, 2 mismatch	15,372 (55%)	3,320 (56%)	0.161
HLA-B, 1 mismatch	7,471 (24%)	1,400 (23%)	0.095
HLA-B, 2 mismatch	22,894 (75%)	4,697 (76%)	0.0962
HLA-DR, 1 mismatch	9,543 (36%)	1,905 (36%)	0.997
HLA-DR, 2 mismatch	16,555 (62%)	3,246 (61%)	0.1712
Recipient-Donor Height ratio	0.997 ± 0.062	0.996 ± 0.061	0.403
Recipient-Donor Weight ratio	1.03 ± 0.21	1.03 ± 0.21	0.259

Data are mean ± SD, number (%). The numbers are calculated on patients with available data. HLA, Human Leukocyte Antigen. Test used: χ^2 -test; Wilcoxon test.

variables corresponding to 41 inputs. The hazard ratios (HR) for the top confounding risk factors, ranked in order of influence upon discriminatory power, are presented together with the mandatory variables in Table 2. The 12 mandatory variables (age, blood group, gender, height and weight ratio) were not included in the ranking because we wanted them incorporated in the ANN model regardless of discriminatory power. We validated the model by predicting the cumulative survival for each patient in the validation cohort. The Harrell's Concordance index for the ANN model was 0.59 (95% CI, 0.586–0.594) and the difference in area under the predicted survival curve was 1.4% compared with the Kaplan-Meier survival curve (Figure 1B).

Customize an optimal donor using simulated annealing. We used the SA to 'customize' an optimal and worst donor, respectively, for the recipients. The main feature of the SA algorithm is the ability to avoid being trapped in local minimum. This is done by letting the algorithm accept not only better solutions but also worse solutions, "uphill moves", with a given probability¹⁶. The SA algorithm is expressed by a flowchart in Figure 2A. We tested the SA algorithm for selecting best-case match (N = 36,696) and worst-case match (N = 34,638) using the five donor variables: age, gender, blood group, height and weight. The area under the predicted survival curve (AUPSC) was calculated for each recipient-donor match. Figure 2B shows how much the AUPSC changes as one of the five donor variables is altered. Figure 2C shows the monitoring of the SA function that is looking for a best recipient-donor match for one randomly selected patient from the registry. At approximately 7,000 iterations, the temperature was close to zero and an (approximate) optimum set of input values (the donor profile) was found. In Figure 3A, a plot of a random selection of 1,000 patients and their respective predicted survival curve from the experiment is drawn based on the best-case donor variables. The corresponding plot for worst-case match is shown in Figure 3B.

Donor age was the variable that influenced outcome at most of the five evaluated donor variables. All patients received extreme values. For best-case match the optimal donor age was 15 ± 0.0 years compared with 32 ± 13 years, $P < 0.001$, for the original recipient-donor match. For the worst case match the donor age was 80 ± 0.0 years compared with 32 ± 13 years, $P < 0.001$, for the original recipient-donor match. Furthermore, in the best-case match only 57 female

hearts were given to 29,295 men while 1,568 (21%) female hearts were given to 7,384 women. Thus, not all women received a female donor organ. In the worst-case match, 27,652 (100%) female hearts were given to 27,668 men and 6,699 (96%) female hearts to 6,970 women, Table 3.

The blood group matching was analysed and differences between optimal and suboptimal outcomes were studied. Controversially, recipients with blood group B received identical matched blood group in only 18% of best-case match and 68% in worst-case match compared with 73%, $P < 0.001$ for the original recipient-donor match. We observed a similar finding for recipient with blood group AB. The SA algorithm avoided donor blood group B in the best-case match. Only 2% of these recipients were matched to donors with blood group B compared with 24%, $P < 0.001$, for the original recipient-donor match, Table 3.

The last of the five studied variables, weight ratio, showed a similar result as donor age for the best-case match. 65% of the recipients received an extreme value of a recipient-donor ratio of 0.5. For the recipients with non-extreme values (N = 12,682) the optimal recipient-donor weight ratio was 0.83 ± 0.24 . We could not see the same results for the recipient donor height ratio. In the best-case match none of the recipients achieved any extreme value. Instead, the optimum ratio was 1.08 ± 0.10 . However, in the worst-case match the recipient donor height ratio was 1.5 in 64% of the cases and 0.5 in 36% of the cases, Table 3.

Prediction of conditional failure after heart transplantation.

Figure 1B illustrates the mean value for all best-case and worst-case matches. By optimizing the donor profile, the survival could be improved with 33 months. In order to evaluate if the SA had been able to improve the survival compared to "real-life" donor profiles, we performed a virtual recipient-donor match (VRDM). The recipient was matched using all the different donor profiles from the registry. The recipient-donor combination with best-predicted survival was chosen. The procedure was repeated for all recipients and the mean predicted survival curve for all best-case matches was plotted. We identified the worst combination in a similar way. Of note, even if we created artificial combinations by changing the five variables, we could not improve survival compared to using VRDM combinations. On the other hand, we could identify much worse combinations using SA, Figure 1B.

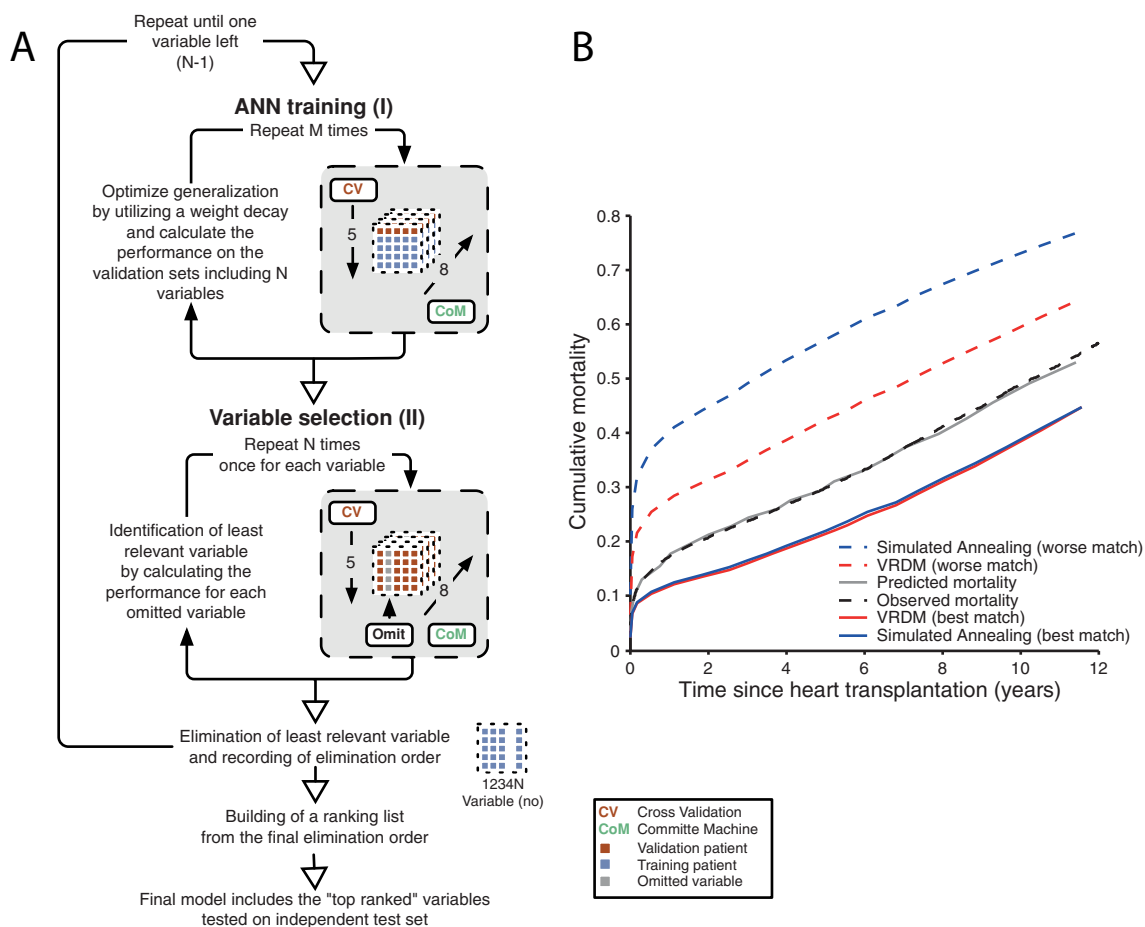


Figure 1 | Schematic illustration of the variable-ranking process for ANN training and validation. Panel (A): Step I: training of the survival model using fivefold cross-validation and a committee machine with 8 members. Step II: variable ranking using the trained survival model from step I. Each variable is omitted from the model and the decrease in performance is recorded. The variable resulting in the least reduction in performance is removed. Steps I–II are repeated until only one variable is left. A ranking list is constructed using the elimination order. To evaluate whether the final ANN risk prediction model was applicable in a patient cohort that had not been used in the development of the ANNs, the validation set ($N = 9,842$) was used as a blind test. Panel (B): Heart transplantation prediction of conditional failure probability. The solid grey line presents the predicted mortality in the validation cohort using the ANN survival model. The dashed black line presents the observed mortality for the validation cohort (Kaplan-Meier estimate). The predicted mortality obtained with our pilot Simulated Annealing (SA) model is presented with a blue line, Virtual Recipient Donor Match (VRDM) model with a red line. Best match is presented with solid line and worse match with dashed line.

Discussion

Heart transplantation remains the therapy of choice for end-stage heart failure. There is shortage of donors and many candidates die awaiting transplantation. Simulation-based analysis offers a practical way to make informed decisions by predicting likely outcomes from different choices¹⁷. To our knowledge, this study represents the first to show how to utilize SA in heart transplantation. SA is a stochastic optimization technique for non-linear modeling. SA has been used in medical research to solve optimization problems and has gained renewed interest since its introduction in the 1980s^{10–13}. Furthermore, ANNs have become a very powerful and practical method to model very complex non-linear systems. However, the published experience with ANNs within transplantation research is limited. Only a few studies have been published in kidney, liver and heart transplantation⁹. In this study, we demonstrated that by combining SA and ANNs, a customize optimal donor using simulated annealing (CODUSA) model for patients requiring heart transplantation can be developed that is accurate and highly reproducible, allowing for identification of optimal and even more important worst-case recipient-donor match.

In the present study, after the selection of influential variables by the SA model, some variables remained different between the

optimal and sub-optimal matches. This finding suggests that best-case and worst-case matches are governed by different sets of factors. Thus, some recipient-donor combinations must be avoided at all times while some combinations of characteristics must be considered in every transplantation attempt. The strength of our SA model lies in the identification of unsuitable donors for a specific recipient. To our knowledge, this is the first study of its kind and a step towards so called ‘personalized medicine’ in the field of heart transplantation. Future studies, should include more donor variables, but may also include genomic and proteomic data to increase the predictive ability of the SA model.

During the last decades, several studies have evaluated the importance of the matching criteria age, ischemia time, ABO blood group, and body size. The influence of age on survival is well established. Older donors and recipients are associated with atrial fibrillation, cardiac allograft vasculopathy, and higher mortality^{18,19}. The importance of donor age was confirmed in the present study, and all recipients in the CODUSA model were matched to a low age donor.

The long-term effect of gender is a matter of controversy. Our data showed that female hearts should not be given to men, but the SA model did also prefer male donor to female recipients. Generally, heart transplant patients with donor-recipient sex mismatch have



Table 2 | Hazard ratio for the risk factors included in the ANN model. Confounding variables ranked in order of importance for the ANN model

Mandatory risk variable		HR mean (95% CI)
	Donor age	1.107 (1.107–1.107)
	Recipient age	1.126 (1.125–1.126)
	Donor blood group O	0.979 (0.979–0.980)
	Donor blood group B	1.055 (1.055–1.056)
	Donor blood group AB	1.024 (1.023–1.025)
	Recipient blood group A	1.008 (1.008–1.009)
	Recipient blood group B	1.027 (1.027–1.028)
	Recipient blood group O	1.084 (1.083–1.084)
	Donor female gender	1.034 (1.034–1.035)
	Recipient female gender	1.025 (1.024–1.025)
	Recipient-donor height match	0.998 (0.998–0.999)
	Recipient-donor weight match	1.013 (1.013–1.013)
Rank no.	Confounding risk variables	
1	Diagnosis: Non-ischemic cardiomyopathy	0.882 (0.881–0.882)
2	Life support: Ventilator	1.152 (1.150–1.153)
3	Transplantation era: 2001–2006	0.946 (0.946–0.947)
4	Creatinine ($\mu\text{mol/l}$)	1.019 (1.018–1.019)
5	Duration of ischemia (min)	1.020 (1.020–1.020)
6	Diagnosis: Ischemic cardiomyopathy	1.011 (1.010–1.012)
7	Transplantation era: 1988–1990	1.451 (1.449–1.452)
8	Transplantation era: 1991–1995	1.227 (1.226–1.228)
9	Medical condition at transplant: In ICU	1.192 (1.191–1.193)
10	Previous transplantation	1.136 (1.136–1.137)
11	Height (cm)	0.977 (0.977–0.977)
12	Infection (within 2 weeks of transplant)	1.051 (1.050–1.051)
13	Diagnosis: Graft failure	1.756 (1.752–1.759)
14	Weight (kg)	1.027 (1.027–1.027)
15	Bilirubin (mg/dl)	1.003 (1.003–1.003)
16	Diagnosis: congenital heart disease	0.912 (0.912–0.913)
17	Medical condition at transplant: Hospitalized	1.159 (1.158–1.160)
18	Diagnosis: Valvular heart disease	0.844 (0.844–0.845)
19	Life support: Intra-aortic balloon pump	1.015 (1.015–1.016)
20	HLA-DR mismatch	0.940 (0.939–0.940)
21	Life support: ECMO	1.179 (1.177–1.180)
22	Drug-treated hypertension	1.018 (1.018–1.018)
23	Peripheral vascular disease	1.131 (1.130–1.132)
24	PVR (wood units)	1.004 (1.004–1.004)
25	Prior cardiac surgery	0.987 (0.986–0.987)
26	HLA-B mismatch	0.944 (0.944–0.945)
27	COPD	1.086 (1.085–1.086)
28	Cerebrovascular disease	1.064 (1.063–1.065)
29	Life support: Inotropic support	0.965 (0.964–0.965)

ANN, artificial neural network; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; HLA, Human Leukocyte Antigen; HR, hazard ratio; ICU, intensive care unit; PVR, pulmonary vascular resistance.

inferior survival^{3,20,21}. But, for female recipient this is controversial. Weiss et al showed, analyzing the UNOS registry, that no survival advantage was seen for women receiving organ with same sex²². Many mechanisms explaining these discrepancies have been proposed, but remain to be fully elucidated. For example, it has been suggested that there may be immunologic or hormonal factors involved²⁰. Gender differences in the susceptibility to ischemia reperfusion injury have also been suggested, and at any given duration of cold ischemia, heart transplants coming from female donors had consistently worse graft survival compared with male donors²⁰.

We found no significant difference in survival following compatible versus identical ABO matching. Similar findings have been reported in previous studies using donor hearts with compatible, but non-identical, blood group match^{23–25}. However, our results indicate that donor blood group B is not selected and these patients are instead given donor blood group O. A similar finding was seen for the recipients with blood group AB. Also here donors with blood group B were avoided. Already in the series from Barnard's group²⁶, reduced

survival in recipients with the B antigen was seen. It has been hypothesized that patients with blood group B may elicit a greater immune response but this remains controversial²⁷.

The present study demonstrated that weight and height have been handled differently depending on if it is best-case match or worst-case match. Previous data suggest that the donor-recipient weight match criteria may be extended to increase the donor pool^{28,29}. However, height has been proposed to be a better predictor of heart size as estimated by left ventricular end-diastolic diameter, as well as a novel measurement from the superior vena cava-right atrium junction to inferior vena cava-right atrium junction³⁰. Here we show that the optimal recipient-donor weight ratio is around 0.8, but a recipient-donor height ratio should be 1.08. Both extreme undersize and oversize in height were correlated with reduced survival.

The limitations of the present study deserve further discussion. The complexity between different risk variables from two individuals is extreme. Certain variables have historically been considered more important than others and we have therefore focused on these (blood

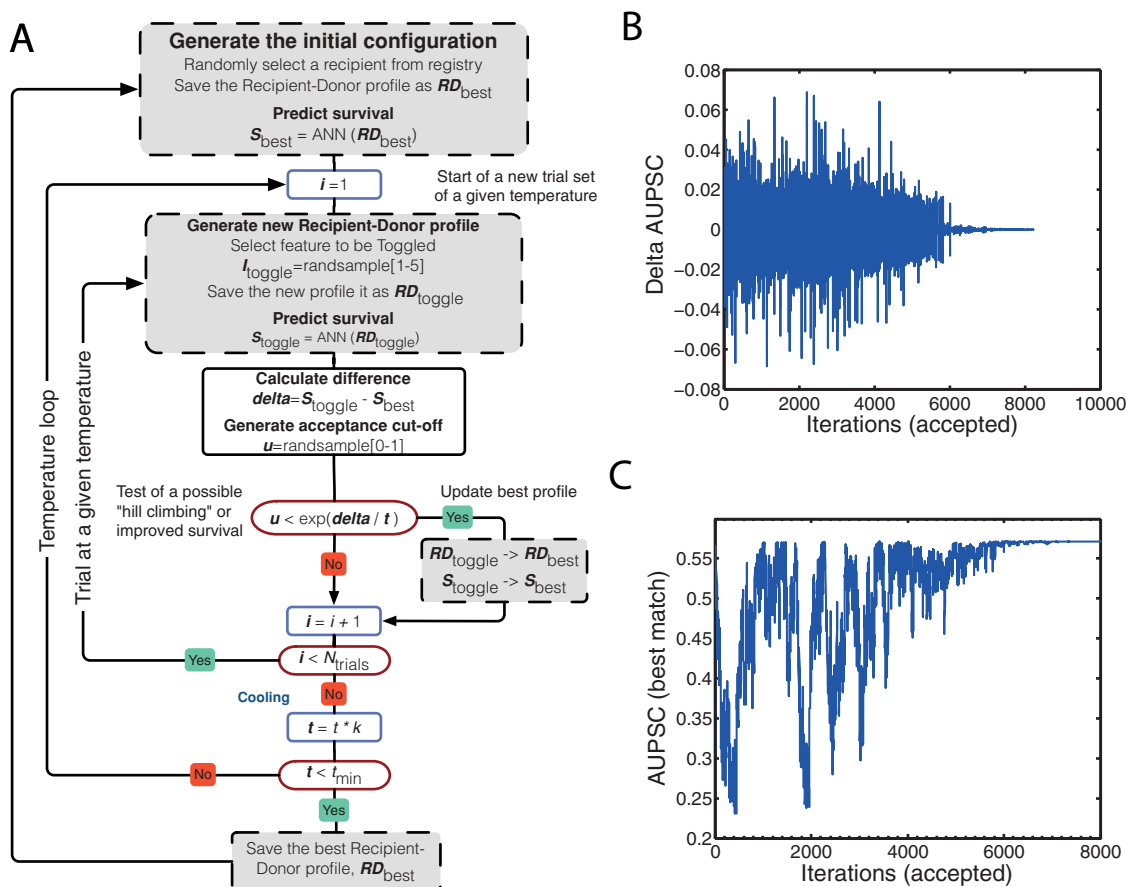


Figure 2 | Recipient donor match using simulation annealing (SA). Panel (A): The simulated annealing (SA) Monte Carlo algorithm: A recipient is randomly selected from the recipient registry. The predicted survival is calculated and the existed recipient-donor profile and the data are recorded. Then the simulation process is started. A donor variable and the value for this variable are selected at random. The difference (delta) between the predicted survival for this new recipient donor profile and the earlier best survival is calculated. If the predicted survival is better than the previous, the best recipient-donor profile and the best-predicted survival are updated. If not the test for allowance "uphill" moves are performed. The allowance for "uphill" moves saves the method from becoming stuck at local minima, which means that a worse value can be accepted in some cases. This procedure is repeated 50 times and then the temperature is decreased with 4%. The whole procedure is started with 50 new trials at this new temperature. When the temperature has gone below 0.000025 the simulation for this patient is ended and a new is selected. The waiting list is updated with a new recipient, and the procedure is repeated. Panel (B): Area under predicted survival curve (AUPSC) related to change in one of the SA variables. Panel (C): Monitoring of the simulated annealing (SA) function as it is looking for a best-case match.

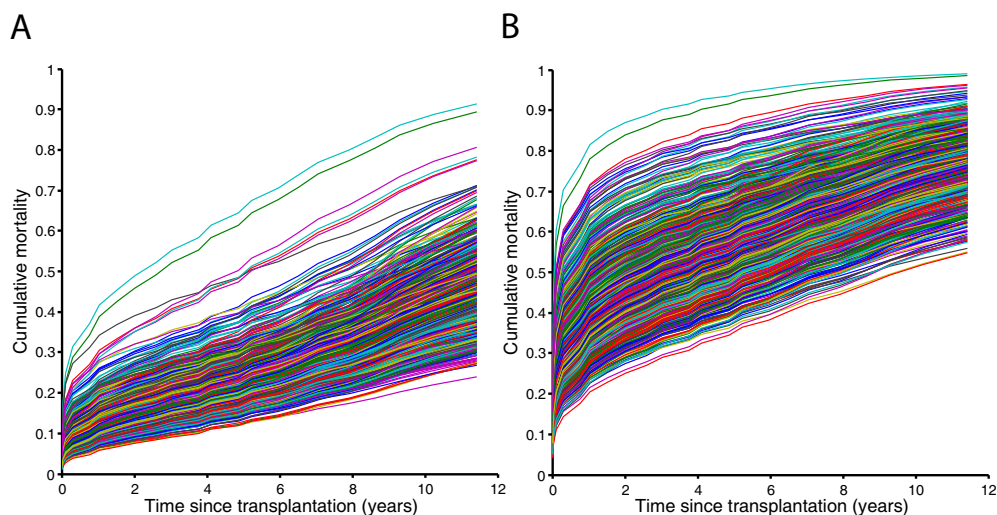


Figure 3 | Customize Optimal Donor Using Simulated Annealing (CODUSA). Panel (A): Random selection of 1,000 patients and their respective survival curve based on the best case customized donor profile. Panel (B): Random selection of 1,000 patients and their respective survival curve based on the worst case customized donor profile.



Table 3 | SA variables

	a			
	Best match		Worse match	
	SA match N = 36,679	Original match N = 36,679	SA match N = 34,638	Original match N = 34,638
Donor data				
Age (year)	15 15 1.15 (1.5 ± 0.001)	21 30 42 (32 ± 13)	80 80 80 (80 ± 0.02)	21 30 42 (32 ± 13)
Female gender	1,625 (4%)	11,377 (31%)	34,351 (99%)	10,778 (31%)
Height quota	1.01 1.08 1.15 (1.08 ± 0.10)	0.96 1.00 1.03 (1.00 ± 0.06)	0.50 1.50 1.50 (1.14 ± 0.48)	0.96 1.00 1.03 (1.00 ± 0.06)
Weight quota	0.50 0.50 0.66 (0.62 ± 0.22)	0.89 1.02 1.16 (1.04 ± 0.21)	1.50 1.50 1.50 (1.50 ± 0.04)	0.89 1.02 1.16 (1.03 ± 0.21)
Donor blood group				
A	13,798 (38%)	14,668 (40%)	9,032 (26%)	13,830 (40%)
B	879 (2%)	3,713 (10%)	3,709 (11%)	3,516 (10%)
AB	1,604 (4%)	994 (3%)	1,030 (3%)	955 (3%)
O	20,398 (56%)	17,304 (47%)	20,875 (60%)	16,337 (47%)
		b		
	Best match		Worse match	
	SA match N = 36,679	Original match N = 36,679	SA match N = 34,638	Original match N = 34,638
Gender match				
Male-Male	29,238 (100%)	21,823 (74%)	16 (0%)	20,592 (74%)
Female-Female	1,568 (21%)	3,905 (53%)	6,699 (96%)	3,702 (53%)
Blood group match				
A-A versus A-O	13,605 (84%)	13,824 (85%)	8,840 (58%)	13,041 (85%)
B-B versus B-O	845 (18%)	3,396 (73%)	3,007 (68%)	3,213 (73%)
AB-O versus AB-AB	366 (19%)	168 (15%)	176 (15%)	164 (15%)
AB-A versus AB-AB	193 (11%)	732 (43%)	192 (16%)	685 (42%)
AB-B versus AB-AB	34 (2%)	308 (24%)	694 (40%)	293 (24%)
AB-O versus AB-A	366 (65%)	168 (19%)	176 (48%)	164 (19%)
AB-O versus AB-B	399 (92%)	168 (35%)	176 (20%)	164 (36%)
AB-B versus AB-A	34 (15%)	308 (30%)	694 (78%)	293 (30%)

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. x ± s represents $\bar{x} \pm 1$ SD. Numbers after percentage are frequencies. The numbers are calculated on patients with available data. SA, simulated annealing.



group, gender, age, weight, height) due to temporal constraints. Each simulation usually spanned several hours, which limited the study. It took 30 days à 24 hours for the cluster to calculate the results of approximately 35,000 patients. In one experiment, we identified best-case match and in another experiment worst-case match. Ischemia time was not included. Ideally we would have included more donor variables than the 5 utilized in our study.

In conclusion, by applying ANNs, we have designed an effective model for predicting long-term outcomes in patients undergoing heart transplantation that can incorporate multiple recipient and donor-related variables. A CODUSA model based on SA shows strong potential to enhance the prediction of patient survival and to identify important variables that have an impact on individual matching outcome. Information provided by our CODUSA model may improve the ability to select optimal match and avoid worst-case match in the clinical setting, functioning as an alternative to prospective cross-matching.

Methods

Data source. In this registry study, we used the International Society for Heart and Lung Transplantation (ISHLT) registry (www.isHLT.org), the largest repository of heart transplant data in the world².

The registry includes data since 1983 and at present, over 223 centers from 18 countries submit data to this registry. Heart donors and the corresponding recipient transplanted between January 1, 1988 and December 31, 2006 were included in the study population. The latest yearly follow up was on January 19, 2008. We excluded patients if they were younger than 18 years at transplantation or have incomplete mandatory data (diagnosis, blood group, age, gender, follow up duration and/or cause of death). A subset of 38 clinically relevant variables, of the registered 293, were selected, Table 1. The Ethics Committee for Clinical Research at Lund University, Sweden approved the study protocol.

Design of ANN. The applied ANN survival model follows the principles described by Biganzoli et al., with the extension of using an ensemble of ANNs instead of a single prediction model³¹ (Supplementary Methods). The number of hidden nodes was determined based on experiments starting with a single node and increasing the number of nodes until the highest accuracy was found for the development set. The selection of risk variables to use as inputs was achieved using a backward elimination technique removing low ranking risk variables, Figure 1A. To improve the generalization performance weight-decay regularization, optimized using a 5-fold cross-validation technique, was used in the model building process. The number of ANN models used in the ensemble was 8 and no effort was made to tune this number. The ensemble output was the mean of the 8 individual ANN model³².

Time dependent hazard ratio. The time dependent hazard ratios for the risk variables were determined in a similar way as described by Lippmann and co-workers³³ (Supplementary Methods). By changing the risk variable in a patient from absent to present and calculating the hazard for the two conditions at each time interval, a time dependent hazard ratio for the specific risk variable of each patient could be determined. A hazard ratio for the specific variable was then obtained by computing the geometric mean of the hazard ratio from all patients. The 95% confidence intervals hazard ratio was calculated using the bootstrap technique (N = 10,000).

SA algorithm. The SA is the metallurgical process of heating up a solid material and cooling it slowly until it crystallizes. Atoms have high energies at very high temperatures, which give them freedom in their ability to restructure themselves. When the temperature is reduced the energy decreases, until a state of minimum energy for the atom is achieved. SA seeks to emulate this process. SA begins at a high temperature where the input values are allowed to have a pronounced range of variation. As algorithm progresses temperature is allowed to fall, which restricts the inputs to vary. The algorithm will progress to a better solution, just as a metal achieves a better crystal structure through the annealing process. The main feature of SA algorithm is the ability to avoid being trapped in local minima by allowing for uphill moves of the cost function. SA begins at a high temperature, allowing for almost all uphill moves, and new solutions are generated given a pre-defined range of variation for each input variable. A new solution is always accepted if it improves the cost function (downhill move) and with a certain probability if it worsens the cost function (uphill move). As the SA algorithm is running the temperature is gradually lowered, thereby making it harder and harder for uphill moves to occur. Finally, when a very low temperature has been reached the best obtained solution is extracted, which then, hopefully, is close to the optimal one.

The SA simulation started with selection of a starting temperature ($t = 1$). Five donor features were used to toggle (age, gender, blood group, weight and height). Which of the donor variables to be changed were randomly selected in each of the trial loops at a given temperature. For each temperature 50 trials were performed. The best recipient-donor combination was selected using the SA with acceptance of

dis-improvements, or “uphill moves”. In the next step the temperature was decreased with 4% ($k = 0.96$) and the procedure was repeated. When the temperature was below 0.000025 the procedure was ended and a new recipient was chosen, Figure 2A.

Statistics. Values are reported as mean (s.d.) or median (i.q.r) for continuous variables and as percentages for categorical variables. Participant characteristics were compared using χ^2 -test for categorical variables and Wilcoxon test for continuous variables. Kaplan-Meier survival analysis was performed to demonstrate whether survival predictions from ANNs trained by the outcome data in a particular time point was capable of predicting survival for the entire follow-up period. Harrell’s Concordance index³⁴ was used to measure prediction performance in the survival analysis. Multiple and probability imputation was used to deal with missing data^{35,36} (Supplementary Methods).

High-performance computing clusters were used to train and evaluate the ANNs, and performing the SA. The ANN calibration and analyses were performed with MatLab Distribution Computing Server 2010a, Neural Network Toolbox (MathWorks, Natick, Mass). Graphs and statistical analyses were performed using the Stata MP version 12.1 (2012) statistical package (StataCorp LP, College Station, TX) and R version 2.15.1 (2012, The R Foundation for Statistical Computing).

Data and materials availability. Requests for the data should be directed to the ISHLT Transplant Registry (<https://www.isHLT.org/registries/registriesDataRequest.asp>). The developed neural network model, including weights (Matlab® net files), can be obtained from the corresponding author.

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Author contributions

All authors contributed to the study design and data interpretation. J.N. and M.O., undertook the analysis and validation of the data. J.N. performed the computer programming. D.A. and J.N. drafted the initial report, and all authors contributed to the final draft. Data was provided from the ISHLT registry by staff at the US, United Network for Organ Sharing, and compiled by J.N.

Additional information

Supplementary information accompanies this paper at <http://www.nature.com/scientificreports>

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