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Distinct phenotypes of kidney transplant recipients aged 80 years or older in the USA by machine learning consensus clustering

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ABSTRACT

Objectives This study aimed to identify distinct clusters of very elderly kidney transplant recipients aged ≥80 and assess clinical outcomes among these unique clusters.

Design Cohort study with machine learning (ML) consensus clustering approach.

Setting and participants All very elderly (age ≥80 at time of transplant) kidney transplant recipients in the Organ Procurement and Transplantation Network/United Network for Organ Sharing database database from 2010 to 2019.

Main outcome measures Distinct clusters of very elderly kidney transplant recipients and their post-transplant outcomes including death-censored graft failure, overall mortality and acute allograft rejection among the assigned clusters.

Results Consensus cluster analysis was performed in 419 very elderly kidney transplant and identified three distinct clusters that best represented the clinical characteristics of very elderly kidney transplant recipients. Recipients in cluster 1 received standard Kidney Donor Profile Index (KDPI) non-extended criteria donor (ECD) kidneys from deceased donors. Recipients in cluster 2 received kidneys from older, hypertensive ECD deceased donors with a KDPI score ≥85%. Kidneys for cluster 2 patients had longer cold ischaemia time and the highest use of machine perfusion. Recipients in clusters 1 and 2 were more likely to be on dialysis at the time of transplant (88.3%, 89.4%). Recipients in cluster 3 were more likely to be preemptive (39%) or had a dialysis duration less than 1 year (24%). These recipients received living donor kidney transplants. Cluster 3 had the most favourable post-transplant outcomes. Compared with cluster 3, cluster 1 had comparable survival but higher death-censored graft failure, while cluster 2 had lower patient survival, higher death-censored graft failure and more acute rejection.

Conclusions Our study used an unsupervised ML approach to cluster very elderly kidney transplant recipients into three clinically unique clusters with distinct post-transplant outcomes. These findings from an ML clustering approach provide additional understanding towards individualised medicine and opportunities to improve care for very elderly kidney transplant recipients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Very elderly kidney transplant patients have diverse characteristics that can lead to variable outcomes.

WHAT IS THIS STUDY ADD

⇒ The machine clustering approach produced three phenotypic clusters of very elderly kidney transplant recipients aged ≥80 with differing posttransplant outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our approach identifies targets for individualised medicine and opportunities to improve care for very elderly kidney transplant recipients.

INTRODUCTION

In recent years, the number of elderly patients with end-stage kidney disease (ESKD) has increased substantially worldwide, paralleling the global ageing population and improved dialysis survival.[1–4] In the USA, there are currently over 120 000 patients with ESKD aged 75 years or older.[5] These patients account for more than 16% of the ESKD population.[6] Previous studies have consistently demonstrated kidney transplantation as the best treatment for ESKD, extending survival and improving quality of life across all age groups, including those aged older than 70.[7–13] There has consequently been an increase in the referral of older patients for kidney transplantation, and a general consensus is that age alone should not represent a barrier to kidney transplantation.[14–18]

In the recent decade, the number of very elderly (aged ≥80) patients with ESKD has risen substantially.[19 20] This has resulted in an increase in number of kidney transplant referrals and surgeries for octogenarians.[21] While overall post-transplant survival in very

elderly kidney transplant recipients aged ≥80 has been reported to be lower than younger patients, studies have demonstrated that survival is still improved compared with remaining dialysis dependent.[12 22] Octogenarians with ESKD experience a rapid loss of functional status and quality of life.[23] In addition, very elderly patients with ESKD have high mortality with a median survival after dialysis initiation in the USA of 15.6 months for patients aged 80–84 and 11.6 months for patients aged 85–89.[5] While several studies have demonstrated that kidney transplantation has excellent outcomes, including patient and graft survival, in carefully selected octogenarians,[12 22 24] there have been concerns regarding increased perioperative mortality, length of hospital stay, rates of graft loss in very elderly kidney transplant recipients aged ≥80 as well as the need to balance recipient benefit with the ongoing organ shortage.[25–28] A prior study of Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing database (UNOS) database of 471 octogenarians transplanted between 1988 and 2013 demonstrated increased risk of graft failure and decreased survival among this patient population.[25] However, kidney transplant patients, including the very elderly, have diverse characteristics that include recipient, donor and transplant-related factors that can lead to variable outcomes.[12 22 24 25]

Artificial intelligence and machine learning (ML) have been applied in medicine to develop clinical decision support tools that can improve and individualise healthcare, including organ transplantation.[29–36] Unsupervised consensus clustering is ML adopted to identify novel data patterns and distinct subtypes.[37–39] It can uncover similarities and differences in large heterogenous datasets of clinical variables and categorise them into meaningful clusters.[37 38] Recent studies have shown that unique subtypes identified by ML consensus clustering approach can predict distinct clinical outcomes.[40 41] Thus, ML consensus clustering approach may provide healthcare professionals with a novel understanding of distinct phenotypes of very elderly kidney transplant recipients with separate outcomes. This may translate to strategies that improves clinical outcomes.

In this study, UNOS/OPTN database from 2010 to 2019 was analysed using an ML unsupervised clustering approach to identify distinct clusters of very elderly kidney transplant recipients aged ≥80 and evaluate the clinical outcomes among these unique clusters.

MATERIALS AND METHODS

Data source and study population

We reviewed kidney transplant recipients in the USA from 2010 to 2019 in the OPTN/UNOS database to represent the current era of newer immunosuppressant agents.[31 42] We included patients aged 80 years or older at the time of kidney transplant. We excluded patients who received combined kidney transplant with other organs.

Data collection

We abstracted a comprehensive list of clinically pertinent recipient-related, donor-related and transplant-related characteristics for inclusion in the cluster analysis. These factors included recipient age, sex, race, body mass index, kidney retransplant, dialysis vintage, ESKD aetiology, comorbidities, panel reactive antibody (PRA), hepatitis B, hepatitis C and HIV serostatus; Karnofsky performance status index, working income, insurance status, US residency status, education level, serum albumin, kidney donor type, ABO incompatibility, donor age, sex and race; donor history of hypertension, Kidney Donor Profile Index (KDPI), HLA mismatch, cold ischaemia time, kidney on pump, delayed graft function (DGF), allocation type, Epstein-Barr virus and cytomegalovirus status; and type of induction and maintenance immunosuppression. All of these extracted variables had less than 5% of missing data (online supplemental eTable 1). Any missing data were imputed using multivariable imputation by chained equation (MICE) method.[43]

Clustering analysis

ML was used via an unsupervised consensus clustering analysis to categorise kidney transplant recipients aged ≥80 into clinical phenotypes.[44] Due to the presence of mixed data, we computed pairwise distances between each observation using partitioning around medoids with Gower distance matrix.[37] We prescribed a prespecified subsampling parameter of 80% with 100 iterations and number of potential clusters (k) ranging from 2 to 10 in order to avoid generating an excessive number of clusters. The optimal number of clusters was established by appraising the consensus matrix (CM) heat map, cumulative distribution function (CDF), cluster-consensus plots with the within-cluster consensus scores, and the ambiguously clustered pairs (PAC) proportions. The within-cluster consensus score, ranging between 0 and 1, was defined as the average consensus value for all pairs of individuals belonging to the same cluster. A value closer to one indicates better cluster stability. PAC, ranging between 0 and 1, was calculated as the proportion of all sample pairs with consensus values falling within the predetermined boundaries.[37] A value closer to zero indicates better cluster stability.[37] For reproducibility, the details of the consensus cluster algorithms used in this study are provided in online supplemental eMethods.

Outcomes

Post-transplant outcomes included patient mortality, death-censored graft failure 5 years after kidney transplant, and acute allograft rejection within 1 year of kidney transplant. Death-censored graft failure was defined as need for dialysis or kidney retransplant. Patients were censored for death or at last follow-up date as per report to the OPTN/UNOS database.

Statistical analysis

After individual patients were assigned to a cluster using the ML consensus clustering analysis, we subsequently performed statistical analyses to compare the characteristics and outcomes of the assigned clusters. Differences in clinical characteristics between the assigned clusters were evaluated using analysis of variance for continuous variables and χ^2 test for categorical variables. We determined the key characteristics of each cluster by using the standardised mean difference with a cut-off of >0.3 between each cluster and the overall cohort. The Kaplan-Meier method was used to estimate the cumulative risk of death-censored graft failure and death after kidney transplant. We assessed the risk of death-censored graft failure and death among the assigned clusters by using Cox proportional hazard analysis. We did not adjust the HR for the clinical characteristic differences between the assigned clusters because the unsupervised consensus clustering approach intentionally created clinically distinct clusters. We used R, V.4.0.3 (RStudio, Boston, Massachusetts; http://www.rstudio.com/); ConsensusClusterPlus package (V.1.46.0) for consensus clustering analysis, and the MICE command in R for MICE.[43]

RESULTS

A total of 158 367 adult patients received kidney transplants from 2010 to 2019 in the USA. Of these, 419 (0.3%) were 80 years or older. Therefore, we performed ML consensus clustering analysis on a total of 419 very elderly kidney transplant recipients. Table 1 shows the recipient, donor and transplant-related characteristics of the patients. The median age was 81 (IQR 80–82) years.

Online supplemental eFigure 1A shows the UNOS regions for each clusters the CDF consensus distributions plot for each cluster of kidney transplant recipients aged ≥80; the delta area plot demonstrates the relative change in area beneath the CDF curves (online supplemental eFigure 1B). The greatest differences in area occurred between k=2 and k=4, where thereafter the relative increase in area became perceptibly smaller. Cluster 2 and cluster 3 had better distinct cluster boundaries than cluster 4 and cluster 5, indicative of good cluster stability over repeated iterations (CM heat map online supplemental eFigures 1C, 2–10). The mean cluster consensus scores of cluster 2 and cluster 3 were comparable (p=0.78) and higher than other clusters (figure 1). Cluster 3 had favourable low PAC compared with cluster 2 (online supplemental eFigure 11). Thus, using baseline variables at the time of transplant, the consensus clustering analysis identified three clusters that best represented the data pattern of kidney transplant recipients aged ≥80 in the USA.

Clinical characteristics of each very elderly kidney transplant cluster

Overall, very elderly kidney transplant recipients were more likely to be white (74%) and have glomerular kidney disease (43%). Comorbidities such as diabetes (28%) and peripheral vascular disease (11%) were less common. The majority of recipients had good functional status (Karnofsky Performance Scale score 80%–100%, 67%). In this cohort, consensus clustering analysis identified three clinically distinct clusters. Cluster 1 had 154 (37%) patients, cluster 2 had 152 (36%) patients and cluster 3 had 113 (27%) patients. These three clusters were clinically unique, as shown in table 1.

Based on the standardised mean difference (figure 2), cluster 1 recipients received deceased donor kidney transplants from younger, male, non-hypertensive and non-extended criteria donor (ECD) donors with standard KDPI score (KDPI <85%). In contrast, cluster 2 recipients received deceased donor kidney transplants from older, hypertensive ECD deceased donors with a KDPI score ≥85%. Other identified key characteristics for cluster 2 included a greater number of HLA mismatches, longer cold ischaemia time and highest use of machine perfusion for the transplanted kidney. Recipients in clusters 1 and 2 were more likely to be on dialysis at the time of transplant (88.3%, 89.4%). By contrast, cluster 3 recipients were more likely to be preemptive (39%) or had dialysis duration less than 1 year (24%) prior to a kidney transplant. Cluster 3 recipients received living donor kidney transplants, had the shorted cold ischaemia time and the lowest incidence of DGF. Cluster 3 recipients had the lowest number of HLA mismatches and were more likely to receive non-depleting induction (basiliximab).

Online supplemental eFigure 12 and eTable 2 show the UNOS regions for each cluster. Region 6 (Alaska, Hawaii, Idaho, Montana, Oregon, Washington) had the highest proportion of cluster 1 recipients. Region 1 (Connecticut, Eastern Vermont, Maine, Massachusetts, New Hampshire, Rhode Island) had the highest proportion of cluster 2 recipients. Region 7 (Illinois, Minnesota, North Dakota, South Dakota and Wisconsin) had the highest proportion of cluster 3 recipients.

Post-transplant outcomes of each very elderly kidney transplant cluster

Table 2 shows cluster-based post-transplant outcomes. One-year patient survival for clusters 1, 2 and 3 was 93.3%, 88.5% and 96.9%; 5-year patient survival was 66.0%, 45.8%, 61.4%, respectively (p<0.001) (figure 3A). Cluster 1 had comparable mortality compared with cluster 3, but cluster 2 had higher 1-year and 5-year mortality with HR of 4.03 (95% CI 1.34 to 17.31) and 2.05 (95% CI 1.25 to 3.50), respectively. One-year and 5-year death-censored graft survival was 96.4%% and 91.5% in cluster 1, 89.9% and 80.6%% in cluster 2, and 100.0% and 98.3% in cluster 3 (p<0.001) (figure 3B). Both cluster 1 and cluster 2 had higher death-censored graft failures compared with cluster 3, with 5-year HRs of 6.38 (95% CI 1.20 to 117.58) and 16.39 (95% CI 3.43 to 293.65), respectively. The incidence of acute allograft rejection within 1 year after kidney transplant was 2.0% in cluster 1, 6.6% in cluster 2, and 0% in cluster 3 (p=0.01), (table 2).

Table 1 Clinical characteristics according to clusters of very elderly kidney transplant recipients

	All (n=419)	Cluster 1 (n=154)	Cluster 2 (n=152)	Cluster 3 (n=113)	P value
Recipient age (year)	81.4±1.7	81.6±1.8	81.5±1.8	81.0±1.4	0.01
Recipient male sex	336 (80)	120 (78)	122 (80)	94 (83)	0.57
Recipient race					<0.001
White	310 (74)	117 (76)	97 (64)	96 (85)	
Black	52 (12)	21 (14)	26 (17)	5 (4)	
Hispanic	38 (9)	11 (7)	15 (10)	12 (11)	
Other	19 (5)	5 (3)	14 (9)	0 (0)	
ABO blood group					0.14
A	162 (39)	55 (36)	62 (41)	45 (40)	
B	59 (14)	27 (17)	18 (12)	14 (12)	
AB	25 (6)	14 (9)	9 (6)	2 (2)	
O	173 (41)	58 (38)	63 (41)	52 (46)	
Body mass index (kg/m^2)	26.5±4.2	26.7±3.7	26.6±4.4	27.3±4.3	0.004
Kidney retransplant	9 (2)	6 (4)	2 (1)	1 (1)	0.17
Dialysis duration					<0.001
Preemptive	78 (19)	18 (11)	16 (10)	44 (39)	
<1 year	52 (12)	15 (10)	10 (7)	27 (24)	
13 years	161 (38)	72 (47)	72 (47)	17 (15)	
>3 years	128 (31)	49 (32)	54 (36)	25 (22)	
Cause of end-stage kidney disease					
Diabetes mellitus	96 (23)	32 (21)	34 (22)	30 (26)	0.53
Hypertension	47 (11)	16 (10)	13 (9)	18 (16)	0.2
Glomerular disease	182 (43)	70 (46)	71 (47)	41 (36)	0.16
PKD	19 (5)	8 (5)	8 (5)	3 (3)	0.53
Other	75 (18)	28 (18)	26 (17)	21 (19)	0.95
Comorbidity					
Diabetes mellitus	119 (28)	42 (27)	43 (28)	34 (30)	0.88
Malignancy	128 (31)	44 (29)	41 (27)	43 (38)	0.12
Peripheral vascular disease	47 (11)	19 (12)	15 (10)	13 (12)	0.79
PRA (%), median (IQR)	0 (0, 0)	0.0 (0, 6)	0.0 (0, 0)	0.0 (0, 3)	0.02
Positive HCV serostatus	8 (2)	5 (3)	0 (0)	3 (3)	0.09
Positive HBs antigen	5 (1)	3 (2)	0 (0)	2 (2)	0.24
Positive HIV serostatus	0 (0)	0 (0)	0 (0)	0 (0)	
Functional status					0.99
10%–30%	0 (0)	0 (0)	0 (0)	0 (0)	
40%–70%	140 (33)	51 (33)	51 (34)	38 (34)	
80%–100%	279 (67)	103 (67)	101 (66)	75 (66)	
Working income	55 (13)	23 (15)	13 (9)	19 (17)	0.1
Public insurance	356 (85)	134 (87)	131 (86)	91 (81)	0.3
US resident	416 (99)	153 (99)	152 (100)	111 (98)	0.24
Undergraduate education or above	272 (65)	101 (66)	90 (59)	81 (72)	0.11
Serum albumin (g/dL)	3.9±0.4	4.0±0.4	3.9±0.4	3.9±0.4	0.03
Kidney donor status					<0.001
Non-ECD deceased	181 (43)	145 (94)	14 (9)	22 (20)	

Continued

Table 1 Continued

	All (n=419)	Cluster 1 (n=154)	Cluster 2 (n=152)	Cluster 3 (n=113)	P value
ECD deceased	138 (33)	0 (0)	133 (88)	5 (4)	
Living	100 (24)	9 (6)	5 (3)	86 (76)	
ABO incompatibility	1 (0)	0 (0)	0 (0)	1 (1)	0.26
Donor age (year)	50.1±14.8	36.4±12.4	61.7±6.5	53.0±10.3	<0.001
Donor male sex	220 (53)	112 (73)	62 (41)	46 (41)	<0.001
Donor race					<0.001
White	311 (74)	106 (69)	106 (70)	99 (88)	
Black	44 (11)	25 (16)	17 (11)	2 (2)	
Hispanic	50 (12)	17 (11)	21 (14)	12 (11)	
Other	14 (3)	6 (4)	8 (5)	0 (0)	
History of hypertension in donor	163 (39)	35 (23)	111 (73)	17 (15)	<0.001
KDPI					<0.001
Living donor	100 (24)	9 (6)	5 (3)	86 (76)	
KDPI <85%	212 (51)	141 (92)	46 (30)	25 (22)	
KDPI ≥85%	107 (26)	4 (3)	101 (66)	2 (2)	
HLA mismatch, median (IQR)	4 (35)	5 (45)	5 (45)	3 (24)	<0.001
Cold ischaemia time (hours)	15.0±10.9	17.7±9.7	19.5±9.1	5.2±8.2	<0.001
Kidney on pump	179 (43)	75 (49)	96 (63)	8 (7)	<0.001
Delay graft function	107 (26)	44 (29)	53 (35)	10 (9)	<0.001
Allocation type					<0.001
Local	331 (78)	121 (79)	102 (67)	108 (96)	
Regional	44 (11)	14 (9)	29 (19)	1 (1)	
National	44 (11)	19 (12)	21 (14)	4 (3)	
EBV status					0.42
Low risk	6 (1)	4 (3)	0 (0)	2 (2)	
Moderate risk	377 (90)	136 (88)	139 (91)	102 (90)	
High risk	36 (9)	14 (9)	13 (9)	9 (8)	
CMV status					0.09
D-/R-	49 (12)	21 (14)	12 (8)	16 (14)	
D-/R+	103 (25)	40 (26)	32 (21)	31 (27)	
D+/R+	194 (46)	62 (40)	86 (57)	46 (41)	
D+/R-	73 (17)	31 (20)	22 (15)	20 (18)	
Induction immunosuppression					
Thymoglobulin	159 (38)	67 (44)	65 (43)	27 (24)	0.002
Alemtuzumab	12 (3)	6 (4)	3 (2)	3 (3)	0.59
Basiliximab	204 (49)	57 (37)	73 (48)	74 (65)	<0.001
Other	18 (4)	10 (7)	7 (5)	1 (1)	0.08
No induction	47 (11)	22 (14)	13 (9)	12 (11)	0.28
Maintenance Immunosuppression					
Tacrolimus	376 (90)	133 (86)	135 (89)	108 (96)	0.04
Cyclosporine	3 (1)	1 (1)	2 (1)	0 (0)	0.45
Mycophenolate	370 (88)	133 (86)	135 (89)	102 (90)	0.6
Azathioprine	1 (0)	0 (0)	0 (0)	1 (1)	0.26
mTOR inhibitors	2 (1)	0 (0)	2 (1)	0 (0)	0.17

Continued

Table 1 Continued

	All (n=419)	Cluster 1 (n=154)	Cluster 2 (n=152)	Cluster 3 (n=113)	P value
Steroid	254 (61)	98 (64)	94 (62)	62 (55)	0.33

SI conversion: serum albumin: g/dL × 10 = g/L.
CMV, cytomegalovirus; D, donor; EBV, Epstein-Barr virus; ECD, extended criteria donor; HBs, hepatitis B surface; HCV, hepatitis C virus; KDPI, Kidney Donor Profile Index; mTOR, mammalian target of rapamycin; PKD, polycystic kidney disease; PRA, panel reactive antibody; R, recipient.

DISCUSSION

Previous studies analysing the UNOS dataset of kidney transplant recipients ≥80 years old described the overall patient characteristics as primarily white males (>80%) who received a kidney (from donors approximately 50 years in age) with a mean cold ischaemia time of 16.72 hours.[24 25] By applying an ML approach, our present study demonstrates greater heterogeneity among this patient population, and our ML consensus cluster analysis successfully identified three clusters of very elderly kidney transplant recipient with unique clinical characteristics and associated post-transplant outcomes.

Cluster 1 recipients were more likely to be on dialysis at the time of transplant, and receive a deceased donor kidney transplant from a younger non-ECD KDPI <85% male donor without hypertension. Recipients in cluster 2 were also more likely to be on dialysis at the time of transplant. Cluster 2 recipients however received deceased donor kidneys from older, hypertensive, ECD donors with KDPI scores ≥85%. Cluster 2 recipients had a greater number of HLA mismatches, the longest cold ischaemia time and the highest use of machine perfusion for the transplanted kidney. In contrast, cluster 3 recipients were more likely to either be preemptive or be on dialysis for less than 1 year prior to kidney transplant. Cluster 3 recipients received living donor kidney transplants, had the lowest number of HLA mismatches and were more likely to receive nondepleting induction therapy. Glomerular disease was the most common indication for transplant in all clusters (43%). Recipients in all clusters also had good functional status with an overall low incidence of diabetes and peripheral vascular disease. Acute rejection events were low in all clusters. Among the three clusters, cluster 3 had the most favourable post-transplant outcomes specific to patient survival and death-censored graft failure.

Patients in all clusters were unlikely to be sensitised (low PRA). The number of HLA mismatches was highest in clusters 1 and 2 and lowest in cluster 3, which is likely a reflection of living-related kidney donation. Despite the low PRA in clusters 1 and 2, depleting induction (thymoglobulin, alemtuzumab) was used in a significant number of recipients (table 1). Overall rates of acute rejection were low in all clusters ranging from 0% in cluster 3 to 6.6% in cluster 2. Cluster 2 patients had the highest acute rejection rates at 1 year. It can be hypothesised that this may be due to the higher number of HLA mismatches, longer cold ischaemia time and higher occurrence of DGF compared with the other clusters. Cluster 3 recipients had the lowest incidence of acute rejection (0%) at 1 year among all clusters despite more patients receiving non-depleting induction (basiliximab) and steroid-sparing regimens. These recipients had the lowest number of

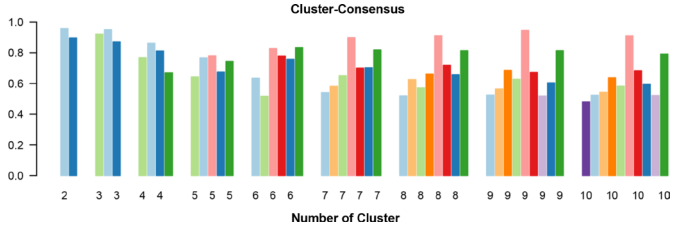

Figure 1 Mean cluster consensus score.

Figure 2 Mean standardized difference across 3 clusters for each baseline characteristics. CMV, cytomegalovirus; DGF, delayed graft function; EBV, Epstein-Barr virus; ECD, extended criteria donor.

Table 2 Post-transplant outcomes according to the clusters

	Cluster 1	Cluster 2	Cluster 3
1-year death	6.7%	11.5%	3.1%
HR for 1-year death	2.23 (0.66–10.04)	4.03 (1.34–17.31)	1 (ref)
5-year death	33.9%	54.2%	38.6%
HR for 5-year death	0.96 (0.55–1.71)	2.05 (1.25–3.50)	1 (ref)
1-year death-censored graft failure	3.6%	10.2%	0%
HR for 1-year death-censored graft failure	N/A*	N/A*	1 (ref)
5-year death-censored graft failure	8.5%	19.4%	1.7%
HR for 5-year death-censored graft failure	6.38 (1.20–117.58)	16.39 (3.43–293.65)	1 (ref)
1-year acute rejection	2.0%	6.6%	0%

*HR was be calculated due to no event in the reference group.
N/A, not available.

HLA mismatches and DGF, and these factors may have contributed to the low incidence of rejection. It has been suggested that the risk for acute rejection is lower in older kidney transplant recipients due to immunosenescence. Recent evidence suggests that lower-intensity immunosuppression regimens (steroid-sparing) offer beneficial outcomes in older kidney transplant recipients by balancing risk for rejection and also helping to minimise immunosuppression side effects.[45] Among very elderly kidney transplant recipients aged ≥80, the findings of our ML consensus cluster analysis confirms that lower-intensity immunosuppression regimens appears safe with low risk of rejection for patients with clinical characteristics shown in clusters 1 and 3.

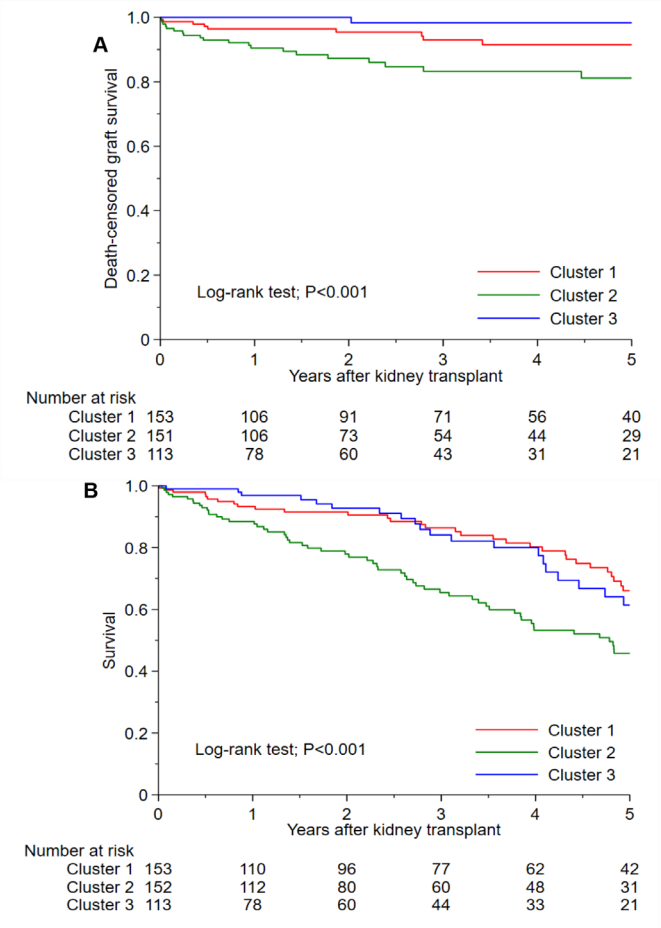

Figure 3 Kaplan-Meier plots for (A) death-censored graft survival and (B) patient survival.

Key features for cluster 3 recipients included preemptive kidney transplantation or dialysis duration for less than 1 year prior kidney transplant. The majority of recipients in cluster 3 received living donor kidney transplants from non-hypertensive donors. Transplantation in the elderly, particularly for those beyond the age of 80 years, is often a strongly debated topic that takes into account benefit to the recipient and judicious use of a scare resource.[25–28] For elderly recipients, there can be additional controversy over the use of a living donor kidney due to overall lower survival as a general limitation of age and comorbidities.[28] In this study, cluster 3 recipients had the best survival, 96.9% at 1 year, and the lowest risk for graft loss. Hypertension and diabetes, generally account for a significant proportion of kidney transplants in the elderly.[16 46] In our analysis, glomerular disease was the most common kidney disease aetiology (43%) for all three clusters. Moreover, comorbidities such as diabetes (28%) and peripheral vascular disease (11%) were less common and the majority of recipients had a Karnofsky functional score ranging from 80%–100%. These data suggest that the recipient profile for kidney transplant recipients greater than 80 years of age differs to that of all kidney transplant recipients aged greater than 65 years of age. Overall, 1-year and 5-year patient survival was 93% and 66% in cluster 1, 88% and 46% in cluster 2, and 97% and 61% in cluster 3. Recipients in clusters 1 and 3 had comparable patient survival, and cluster 2 patients had the highest mortality, despite comparable factors between cluster 1 and 2 for post-transplant patient survival in older kidney transplant recipients such as recipients age, dialysis vintage, comorbidities and functional status.[47 48]

One-year and five year death-censored graft survival was 96% and 91% in cluster 1, 90% and 81% in cluster 2, and

100% and 98% in cluster 3, respectively. Cluster 2 patients had the highest death-censored graft failure at 5 years among the clusters. The highest of proportion of cluster 2 recipients were in UNOS Region 1. Lower graft survival in cluster 2 may be explained by donor quality as these recipients were more likely to receive deceased donor kidney transplants from hypertensive ECD deceased donors with a KDPI score ≥85%. Kidneys from donor with a KDPI score greater than >85%, so-called high KDPI kidneys, are known to have shorter graft survival, and are often reserved for older recipients who have comorbidities, like diabetes and cardiovascular disease, that otherwise limit their long-term survival.[16] In this study, the overall incidence of diabetes and peripheral vascular disease was lower for recipients above the age of 80 years and the primary indication for transplant was glomerular disease. As such, patients above the age of 80 years who meet criteria to qualify for a transplant may be less likely to have other common comorbidities, such as diabetes, and be self-selected to have better survival that extends beyond the standard survival for an elderly kidney transplant recipient and a high KDPI kidney. In our ML clustering analysis, both cluster 3 recipients who were more likely to received preemptive living donor kidney transplants and cluster 1 recipients receiving standard non-ECD deceased donor kidney transplants had better death-censored graft survival than cluster 2 recipients.

Our study has several limitations. The UNOS database has inherent limitations including lack of granular data regarding cause of patient death and graft loss. In addition, we applied ML cluster analysis on a retrospectively reported multicentre database. All very elderly kidney transplant recipients have undergone a comprehensive pretransplant evaluation, however, each transplant programme has differing criteria for the management of patients prior, during and after transplant.[49] Furthermore, some transplant programmes currently offer kidney transplantation only to older candidates with living donors due to concern of waitlist mortality and perioperative morbidity and mortality.[50 51] Third, while it is possible that missing data were not completely random, all variables in our study had missing data <5%. Therefore, it is unlikely that missing data imputation would substantially alter the result of our analysis. In addition, unlike supervised ML that data model bias is a challenge, an unsupervised learning clustering algorithm has parameters that control the model's flexibility to fit the data and can learn bias from dataset. Nevertheless, unsupervised models can still encounter particular biases in data composition. Thus, the potential gender and racial bias based on populations' ethnic backgrounds or geographical locations should be noted. Lastly, data on quality-of-life post-transplant are limited in the UNOS database.[52 53] While cluster 2 had the worst post-transplant outcomes among all clusters, future studies assessing the quality of life in this cluster of very elderly kidney transplant recipients aged ≥80 are needed.

Despite limitations, our study using an unsupervised ML clustering approach identifies distinct clusters within kidney transplant recipients aged ≥80 years. While the survival benefits of kidney transplant in octogenarians have previously been compared with remaining on dialysis,[7 12 22 24 54] the findings of our study provide further insights into the different allograft and patient outcomes among the unique phenotypic subtypes of very elderly kidney transplant recipients. Glomerular disease was the most common kidney disease aetiology (43%) for all clusters and comorbidities such as diabetes (28%) and peripheral vascular disease (11%) were less common. The majority of recipients in all clusters had a Karnofsky functional score ranging from 80% to 100%. Despite advanced age, cluster 3 recipients, who were largely preemptive and received living donor kidney transplants, had favourable outcomes (both allograft and patient survival) comparable to younger kidney transplant recipients. Compared with cluster 3, cluster 1 recipients had comparable survival but higher death-censored graft failure, while recipients in cluster 2 had the worst post-transplant outcomes specific to patient survival and death-censored graft failure. Cluster 2 recipients also had the highest incidence of acute rejection (6.6% vs 2.0% and 0%). Future studies are required to better identify specific differences between cluster 2 recipients, who had less than 50% survival at 5 years post-transplant, compared with recipients in clusters 1 and 3 so as to better guide clinical and patient decision making specific to transplant. In addition, while the findings of unsupervised ML clustering approach in this study provide detailed information on distinct phenotypes of kidney recipients aged ≥80 in the USA and associated outcomes with differing post-transplant outcomes, ML clustering algorithms have their limitations that do not directly generate risk prediction for each individual. Thus, future studies assessing the utilisation of supervised ML prediction models for transplant outcomes among kidney transplant recipients ≥80 in the USA are required.

The ML clustering approach produced three phenotypic clusters of very elderly kidney transplant recipients aged ≥80 in the USA. Post-transplant outcomes differed among the clusters including variability in allograft rejection, allograft loss and patient mortality. Our study also demonstrated a varying geographical distribution of kidney recipients aged ≥80 in the USA in the different UNOS Regions in the USA. Our approach identifies targets for individualised medicine and opportunities to improve care for very elderly kidney transplant recipients, particularly those within cluster 2 subtype.

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REFERENCES

1 Danovitch GM, Gill J, Bunnapradist S. Immunosuppression of the elderly kidney transplant recipient. *Transplantation* 2007;84:285–91.
2 Stevens LA, Viswanathan G, Weiner DE. Chronic kidney disease and end-stage renal disease in the elderly population: current prevalence, future projections, and clinical significance. *Adv Chronic Kidney Dis* 2010;17:293–301.
3 Saran R, Robinson B, Abbott KC, *et al*. US renal data system 2018 annual data report: epidemiology of kidney disease in the united states. *Am J Kidney Dis* 2019;73:A7–8.
4 Knoll GA. Kidney transplantation in the older adult. *Am J Kidney Dis* 2013;61:790–7.
5 Saran R, Robinson B, Abbott KC, *et al*. US renal data system 2017 annual data report: epidemiology of kidney disease in the united states. *Am J Kidney Dis* 2018;71:A7.
6 Roberts AW, Ogunwole SU, Blakeslee L, *et al*. *The population 65 years and older in the united states 2016*. US: US Department of Commerce, Economics and Statistics Administration, 2018.
7 Wolfe RA, Ashby VB, Milford EL, *et al*. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725–30.
8 Tonelli M, Wiebe N, Knoll G, *et al*. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 2011;11:2093–109.
9 National Institute of Diabetes and Digestive and Kidney Diseases. United states renal data system: 2018 USRDS annual data report: epidemiology of kidney disease in the united states B, MD, national institutes of health. 2018. Available: https://www.usrds.org/2018/view/Default.aspx
10 Heldal K, Hartmann A, Grootendorst DC, *et al*. Benefit of kidney transplantation beyond 70 years of age. *Nephrol Dial Transplant* 2010;25:1680–7.
11 Knoll GA. Is kidney transplantation for everyone? the example of the older dialysis patient. *Clin J Am Soc Nephrol* 2009;4:2040–4.
12 Lønning K, Midtvedt K, Leivestad T, *et al*. Are octogenarians with end-stage renal disease candidates for renal transplantation? *Transplantation* 2016;100:2705–9.
13 Sørensen VR, Heaf J, Wehberg S, *et al*. Survival benefit in renal transplantation despite high comorbidity. *Transplantation* 2016;100:2160–7.
14 Johnson DW, Herzig K, Purdie D, *et al*. A comparison of the effects of dialysis and renal transplantation on the survival of older uremic patients. *Transplantation* 2000;69:794–9.
15 Oniscu GC, Brown H, Forsythe JLR. Impact of cadaveric renal transplantation on survival in patients listed for transplantation. *J Am Soc Nephrol* 2005;16:1859–65.
16 Jay CL, Washburn K, Dean PG, *et al*. Survival benefit in older patients associated with earlier transplant with high KDPI kidneys. *Transplantation* 2017;101:867–72.
17 Chadban SJ, Ahn C, Axelrod DA, *et al*. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. *Transplantation* 2020;104:S11–103.
18 Segall L, Nistor I, Pascual J, *et al*. Criteria for and appropriateness of renal transplantation in elderly patients with end-stage renal disease: a literature review and position statement on behalf of the European renal association-european dialysis and transplant association Descartes Working group and European renal best practice. *Transplantation* 2016;100:e55–65.
19 Kurella M, Covinsky KE, Collins AJ, *et al*. Octogenarians and nonagenarians starting dialysis in the United States. *Ann Intern Med* 2007;146:177–83.
20 Sutherland AI. Renal transplantation in OCTOGENARIANS-A real proposition? *Transplantation* 2016;100:2519–20.
21 Gheith O, Halim MA, Al-Otaibi T, *et al*. Elderly kidney transplant recipients: single-center experience in the middle east. *Exp Clin Transplant* 2019;17:135–41.
22 Ravichandran BR, Sparkes TM, Masters BM, *et al*. Survival benefit of renal transplantation in octogenarians. *Clin Transplant* 2020;34:e14074.
23 Kurella Tamura M, Covinsky KE, Chertow GM, *et al*. Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med* 2009;361:1539–47.
24 Huang E, Poommipanit N, Sampaio MS, *et al*. Intermediate-Term outcomes associated with kidney transplantation in recipients 80 years and older: an analysis of the OPTN/UNOS database. *Transplantation* 2010;90:974–9.
25 Ravinuthala A, Mei X, Daily M, *et al*. Perioperative and long-term outcomes in octogenarians after kidney transplantation: the US perspective . *Clin Nephrol* 2017;87 (2017):69–75.
26 Chumfong I, Brown D, Keune J, *et al*. Distributing a limited resource: ethical allocation of deceased donor kidneys. *Surgery* 2014;156:198–203.
27 Heilman RL, Mathur A, Smith ML, *et al*. Increasing the use of kidneys from unconventional and high-risk deceased donors. *Am J Transplant* 2016;16:3086–92.
28 Cooper M, Forland CL. The elderly as recipients of living donor kidneys, how old is too old? *Curr Opin Organ Transplant* 2011;16:250–5.
29 Kampaktsis PN, Tzani A, Doulamis IP, *et al*. State-Of-The-Art machine learning algorithms for the prediction of outcomes after contemporary heart transplantation: results from the UNOS database. *Clin Transplant* 2021;35:e14388.
30 Killian MO, Payrovnaziri SN, Gupta D, *et al*. Machine learning-based prediction of health outcomes in pediatric organ transplantation recipients. *JAMIA Open* 2021;4:ooab008.
31 Ershoff BD, Lee CK, Wray CL, *et al*. Training and validation of deep neural networks for the prediction of 90-day post-liver transplant mortality using UNOS registry data. *Transplant Proc* 2020;52:246–58.
32 Wadhwani SI, Hsu EK, Shaffer ML, *et al*. Predicting ideal outcome after pediatric liver transplantation: an exploratory study using machine learning analyses to leverage studies of pediatric liver transplantation data. *Pediatr Transplant* 2019;23:e13554.
33 Schwantes IR, Axelrod DA. Technology-enabled care and artificial intelligence in kidney transplantation. *Curr Transplant Rep* 2021;8:235–40.

34 Connor KL, O'Sullivan ED, Marson LP, *et al*. The future role of machine learning in clinical transplantation. *Transplantation* 2021;105:723–35.
35 Thongprayoon C, Jadlowiec CC, Kaewput W, *et al*. Distinct phenotypes of kidney transplant recipients in the United States with limited functional status as identified through machine learning consensus clustering. *J Pers Med* 2022;12:859.
36 Thongprayoon C, Mao SA, Jadlowiec CC, *et al*. Machine learning consensus clustering of morbidly obese kidney transplant recipients in the united states. *J Clin Med* 2022;11:3288.
37 Wilkerson MD, Hayes DN. ConsensusClusterPlus: a class discovery tool with confidence assessments and item tracking. *Bioinformatics* 2010;26:1572–3.
38 MacEachern SJ, Forkert ND. Machine learning for precision medicine. *Genome* 2021;64:416–25.
39 Alyousef AA, Nihtyanova S, Denton C, *et al*. Nearest consensus clustering classification to identify subclasses and predict disease. *J Healthc Inform Res* 2018;2:402–22.
40 Zheng Z, Waikar SS, Schmidt IM, *et al*. Subtyping CKD patients by consensus clustering: the chronic renal insufficiency cohort (CRIC) study. *J Am Soc Nephrol* 2021;32:639–53.
41 Thongprayoon C, Kattah AG, Mao MA, *et al*. Distinct phenotypes of hospitalized patients with hyperkalemia by machine learning consensus clustering and associated mortality risks. *QJM* 2022;115:442–9.
42 Thongprayoon C, Vaitla P, Jadlowiec CC, *et al*. Use of machine learning consensus clustering to identify distinct subtypes of black kidney transplant recipients and associated outcomes. *JAMA Surg* 2022;157:e221286.
43 Van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw* 2011;45:1–67.
44 Monti S, Tamayo P, Mesirov J. Consensus clustering: a resampling-based method for class discovery and visualization of gene expression microarray data. *Mach Learn* 2003;52:91–118.
45 Lentine KL, Cheungpasitporn W, Xiao H, *et al*. Immunosuppression regimen use and outcomes in older and younger adult kidney transplant recipients: a national registry analysis. *Transplantation* 2021;105:1840–9.
46 Heilman RL, Smith ML, Smith BH, *et al*. Long-Term outcomes following kidney transplantation from donors with acute kidney injury. *Transplantation* 2019;103:e263–72.
47 Sutherland AI, IJzermans JNM, Forsythe JLR, *et al*. Kidney and liver transplantation in the elderly. *Br J Surg* 2016;103:e62–72.
48 Heldal K, Hartmann A, Leivestad T, *et al*. Clinical outcomes in elderly kidney transplant recipients are related to acute rejection episodes rather than pretransplant comorbidity. *Transplantation* 2009;87:1045–51.
49 Axelrod DA, Cheungpasitporn W, Bunnapradist S, *et al*. Posttransplant diabetes mellitus and immunosuppression selection in older and obese kidney recipients. *Kidney Med* 2022;4:100377.
50 Wu C, Shapiro R, Tan H, *et al*. Kidney transplantation in elderly people: the influence of recipient comorbidity and living kidney donors. *J Am Geriatr Soc* 2008;56:231–8.
51 Massie AB, Luo X, Lonze BE, *et al*. Early changes in kidney distribution under the new allocation system. *J Am Soc Nephrol* 2016;27:2495–501.
52 Pinter J, Hanson CS, Chapman JR, *et al*. Perspectives of older kidney transplant recipients on kidney transplantation. *Clin J Am Soc Nephrol* 2017;12:443–53.
53 Wlodarczyk E, Wlodarczyk Z, Paczek L, *et al*. Holistic long-term care over elderly kidney transplant recipients. *Transplant Proc* 2018;50:1900–3.
54 Rao PS, Merion RM, Ashby VB, *et al*. Renal transplantation in elderly patients older than 70 years of age: results from the scientific registry of transplant recipients. *Transplantation* 2007;83:1069–74.