

Preoperative Comorbidities and Outcomes of Medically Complex Living Kidney Donors



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Introduction: Recent reports have described an increased risk of renal disease in living kidney donors compared with the general population. However, these reports do not detail the outcomes of medically complex living donors (MCLDs) with preoperative comorbidities (PCs), such as hypertension, dyslipidemia, glucose intolerance, and obesity. Analysis of living donors with end-stage renal disease (ESRD) has shown that these PCs may contribute significantly to the development of ESRD. We aimed to evaluate the effect of PCs on postoperative renal function and mortality in MCLDs.

Methods: Between January 2008 and December 2016, 807 living-donor kidney transplants were performed in our unit. Of these, 802 donors completed postoperative follow-up of >5 months. Donors were stratified into 4 groups based on the number of PCs present: healthy living donors (HLDs) with no PCs ($n = 214$) or MCLDs with 1 PC ($n = 302$), 2 PCs ($n = 196$), or 3 PCs ($n = 90$) (denoted MCLD [PC 1], MCLD [PC 2], or MCLD [PC 3], respectively). We compared pathology observation data from baseline biopsy, postoperative estimated glomerular filtration rate (eGFR), postoperative urinary protein concentration, and mortality between HLD and MCLD groups.

Results: Interstitial fibrosis, tubular atrophy, glomerulosclerosis, and arteriosclerosis were more frequent in MCLDs (PC 3) than in HLDs. No significant differences were identified between HLDs and MCLDs in terms of postoperative eGFR and short-term mortality. Overt proteinuria and ESRD were not observed.

Conclusions: Appropriate postdonation management of MCLDs with PCs may result in similar outcomes as for HLDs.

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KEYWORDS: baseline biopsy; estimated glomerular filtration rate; kidney transplantation; medically complex living donor; preoperative comorbidities; proteinuria

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In 2009, a study by Ibrahim *et al.*¹ reported similar rates of ESRD and mortality for living kidney donors and controls from the general population. Furthermore, glomerular filtration rates were preserved after donation, with normal levels of albumin excretion.¹ More recent reports have described an increased risk of ESRD and mortality among living kidney donors compared with either matched or unmatched individuals from the general population.^{2,3} However, these reports do not detail the outcomes of MCLDs with PCs, such as hypertension (HT), dyslipidemia, glucose intolerance (GI), and obesity.

Analyses of living donors with ESRD have shown that these PCs may contribute heavily to ESRD development.^{4,5} Before nephrectomy, pathological findings of baseline biopsies can be useful for evaluating the presence of existing kidney disease as a consequence of PCs.^{6,7} However, the management of PCs after nephrectomy has not been investigated, and previous studies have been based on analysis of living donors with ESRD. Determining the consequences of organ donation in MCLDs requires detailed analysis of the outcomes of donors in relation to PCs. In this study, we aimed to compare MCLDs with PCs with HLDs (with no PCs) in terms of the pathological findings of baseline biopsies, postoperative renal function, ESRD, and mortality rates.

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METHODS

Study Design

This retrospective cohort study was approved by the institutional review board of the Nagoya Daini Red

Cross Hospital and was conducted according to the principles of the Declaration of Helsinki. Living-donor kidney transplantation was performed according to the Declaration of Istanbul. To evaluate the effect of PCs on postoperative renal function and short-term mortality in MCLDs, donors were stratified into 4 groups according to the number of PCs present: the HLD, MCLD (PC 1), MCLD (PC 2), or MCLD (PC 3) group. To assess the condition of the remaining kidney at baseline, a biopsy was obtained and was evaluated by a transplant pathologist. Postoperative renal function, eGFR, and protein content of urine collected over 24 hours were compared between MCLDs (PC 1–3) and HLDs. The rates of short-term ESRD and mortality of MCLDs (PC 1–3) were compared with those of HLDs. To determine the medical condition of donors during follow-up, we evaluated postoperative changes in low-density lipoprotein (LDL) cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and fasting blood glucose levels, as well as HbA1c, systolic blood pressure, diastolic blood pressure, and body mass index (BMI). This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

Follow-up Assessments

Postoperative assessments of HLDs were carried out at 1, 3, 6, and 12 months after transplantation, then annually thereafter. Follow-up of MCLDs was carried out every 1 to 3 months. During each visit, donors were educated on lifestyle changes by transplant coordinators. Systolic and diastolic blood pressure, LDL cholesterol levels, triglyceride levels, fasting glucose levels, and BMI were measured at each visit. Measurement of HbA1c was performed for donors who had been preoperatively treated for GI and whose fasting glucose levels reached >126 mg/dl during follow-up. Measurement of HDL levels was carried out only in donors whose postoperative LDL cholesterol and

triglyceride levels rose beyond the optimal ranges referred to in the guidelines.⁸ This was primarily because lipoprotein fraction tests are not covered by the National Insurance in Japan. When lifestyle changes failed to control HT, dyslipidemia, and GI, donors were treated with medication according to the Japanese guidelines for the treatment of chronic kidney disease.⁸

Participants

We recruited all consecutive living donors who underwent kidney transplant procedures at our hospital between January 2008 and December 2016. Patients were followed until December 2017. Patients with limited follow-up data (<5 months) were excluded. All donor data were retrospectively collected from their medical records. As such, the need for informed consent was waived.

Donor Selection

The selection and consent process for living kidney donors is described in the [Supplementary Methods](#).

Definition of Pathological Conditions From Baseline Biopsy

Baseline biopsies of the grafts were obtained 1 hour after reperfusion. Pathological conditions were identified from baseline biopsies by a transplant pathologist who evaluated the presence of interstitial fibrosis, tubular atrophy, glomerulosclerosis, and arteriosclerosis. Histological changes were scored according to the 2007 Banff classification system; positive changes were defined as presence of interstitial fibrosis, tubular atrophy of >5%, any arteriosclerosis, and any global glomerulosclerosis.^{9–11}

Preoperative Comorbidities

PCs included HT (defined as blood pressure >140/90 mm Hg or treatment with blood pressure-lowering medications), dyslipidemia (defined as LDL cholesterol

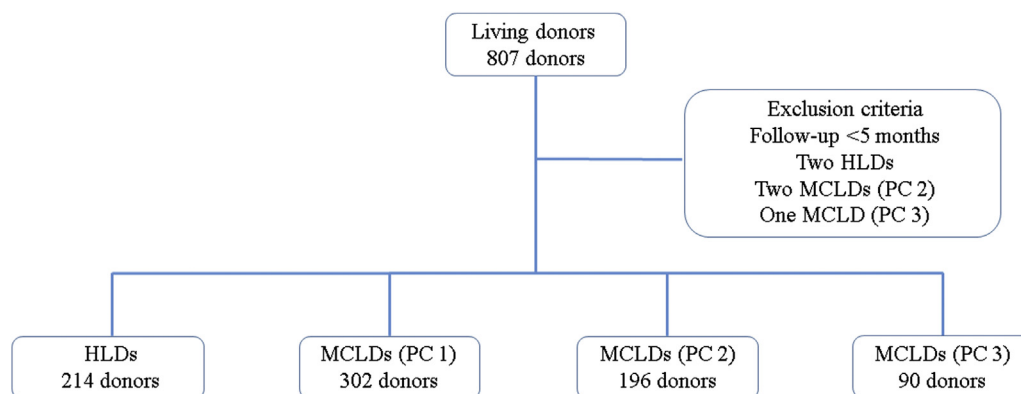


Figure 1. Study flowchart. Illustration of the flow of patients through the recruitment process. HLDs, healthy living donors; MCLDs, medically complex living donors; PC, preoperative comorbidity.

Table 1. Characteristics of the study population

	HLD	MCLD (PC 1)	MCLD (PC 2)	MCLD (PC 3)	ANOVA, Kruskal-Wallis test, or χ^2 test
	n = 214	n = 302	n = 196	n = 90	P value
Age, yr	52.3 ± 10.7	57.9 ± 9.2	60.6 ± 9.5	65.3 ± 7.9	<0.001
Male sex	54 (25.2)	114 (37.7)	88 (44.9)	41 (45.6)	<0.001
Asian	213 (99.5)	301 (99.7)	196 (100)	89 (98.9)	0.549
Hispanic	1 (0.5)	1 (0.3)	0	1 (1.1)	
Donation to first-degree relative of donor	93 (43.5)	153 (50.7)	93 (47.4)	55 (61.1)	0.057
Donation to child of donor	69 (32.2)	120 (39.7)	76 (38.8)	50 (55.6)	
Donation to sibling of donor	19 (8.9)	31 (10.3)	17 (8.7)	4 (4.4)	
Donation to parent of donor	5 (2.3)	2 (0.7)	0	0	
Smoking history	90 (42.1)	135 (44.7)	91 (46.4)	40 (44.4)	0.865
History of endoscopic surgery	206 (96.3)	291 (96.4)	188 (95.5)	88 (97.8)	0.889
Operative duration, min	214 ± 42.6	221.0 ± 49.1	222.8 ± 53.7	217.0 ± 52.0	0.259
Blood loss, ml	29.8 ± 39.3	36.9 ± 52.6	46.4 ± 121.3	38.6 ± 43.8	0.146
Duration of follow-up, mo	55.0 (24.0–83.0)	60.0 (33.0–83.0)	48.0 (25.3–83.0)	49.5 (23.0–72.0)	0.134

ANOVA, analysis of variance; HLD, healthy living donor; MCLD, medically complex living donor; PC, preoperative comorbidity. Categorical data are presented as number (%); continuous data are presented as mean ± SD or median (interquartile range).

>140 mg/dl, triglyceride level >150 mg/dl, and HDL cholesterol <40 mg/dl or treatment with lipid-lowering agents), GI (defined as impaired fasting glycemia, impaired glucose tolerance, or diabetes mellitus that was treated with medication to achieve an HbA1c <6.5% and an albumin/creatinine [Cr] ratio <30 mg/g Cr), and obesity (defined as BMI >30 kg/m²).

Statistical Analysis

Statistical analysis of donor characteristics was performed using analysis of variance, Kruskal-Wallis test, *t* test and Mann-Whitney *U* test for continuous variables and the χ^2

test and Fisher’s exact test for categorical variables. The normal distribution of eGFR and urinary protein level data was confirmed by histograms. Linear mixed model analysis was used to examine whether the number of PCs affected the eGFR and urinary protein levels over time, where “case” was a random factor, “time” was a repetitive factor, and “the number of PCs” and “interaction with time” (defined as “time × number of PCs”) were used as fixed factors. To adjust for confounding factors, age and sex were included as covariates. The repeated measures covariance structure was a compound symmetry. The estimated marginal means and their standard errors and

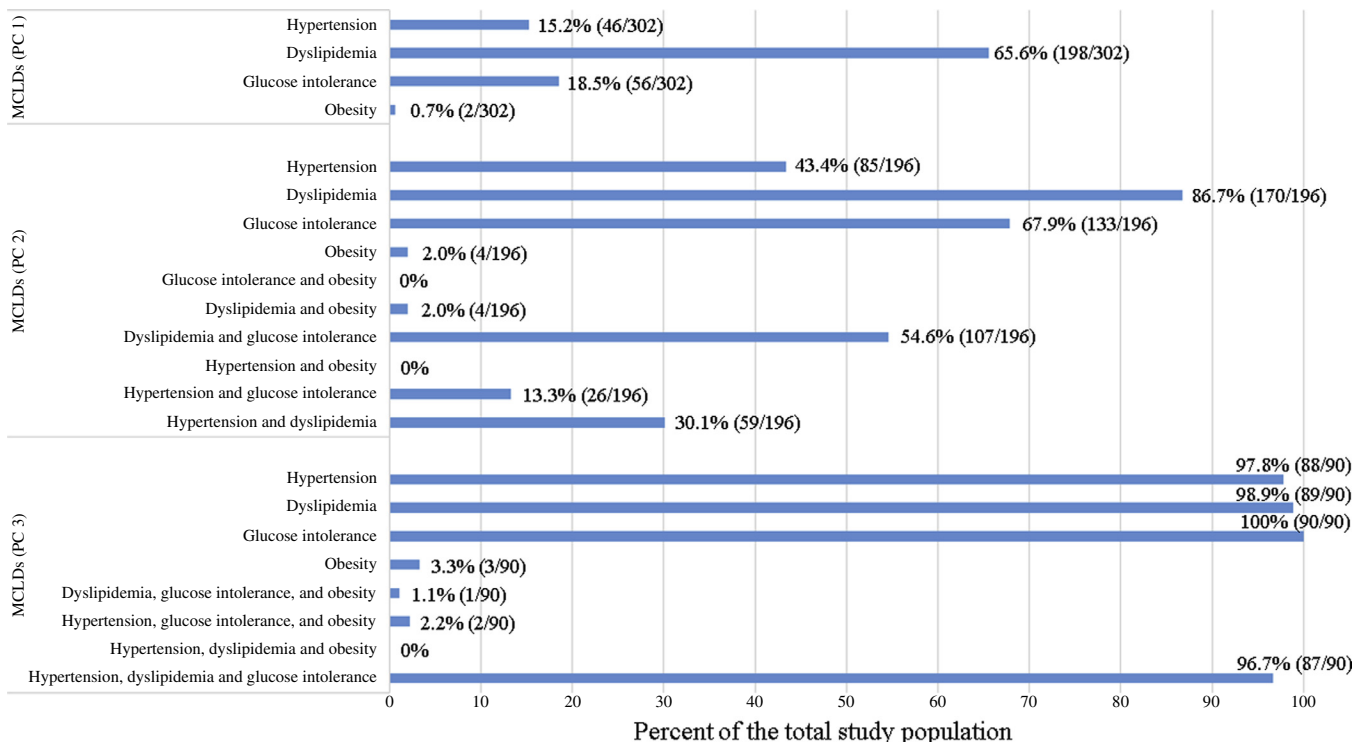


Figure 2. Preoperative morbidity rates for hypertension, dyslipidemia, glucose intolerance, and obesity stratified by preoperative comorbidities. Bar graph comparing preoperative data between the study groups. MCLDs, medically complex living donors; PC, preoperative comorbidity.

Table 2. Preoperative clinical data

	HLD	MCLD (PC 1)	MCLD (PC 2)	MCLD (PC 3)	HLD vs. MCLD (PC 1)		HLD vs. MCLD (PC 2)		HLD vs. MCLD (PC 3)	
					P value	95% CI	P value	95% CI	P value	95% CI
Systolic blood pressure, mm Hg	115.8 ± 11.0	121.6 ± 13.5	125.6 ± 13.9	131.8 ± 14.4	<0.001	-8.772 -2.667	<0.001	-13.010 -6.254	<0.001	-19.753 -11.169
Diastolic blood pressure, mm Hg	69.5 ± 10.4	75.8 ± 9.9	74.7 ± 10.6	76.7 ± 10.9	<0.001	-7.72 -2.870	<0.001	-7.850 -2.49	<0.001	-10.320 -3.510
LDL cholesterol, mg/dl	108.2 ± 19.6	128.9 ± 33.0	129.2 ± 32.5	123.0 ± 34.6	<0.001	-26.783 -12.831	<0.001	-28.609 -13.194	0.013	-21.504 -1.651
Triglyceride, mg/dl	88.2 ± 31.1	145.3 ± 79.8	169.4 ± 93.1	182.5 ± 88.0	<0.001	-75.050 -39.637	<0.001	-101.501 -62.212	<0.001	-121.560 -71.768
HDL cholesterol, mg/dl	70.0 ± 13.4	63.7 ± 16.6	60.9 ± 15.7	54.3 ± 12.7	0.032	0.350 12.280	0.001	2.949 15.232	<0.001	8.300 23.262
Fasting glucose, mm Hg	92.7 ± 7.5	96.0 ± 9.9	102.0 ± 13.8	104.9 ± 13.5	0.003	-5.984 -0.816	<0.001	-12.092 -6.341	<0.001	-16.188 -8.741
75-g oral glucose tolerance test results (blood glucose level 2 hours after glucose administration), mg/dl	106.7 ± 18.4	122.0 ± 30.0	146.3 ± 35.3	177.1 ± 46.3	<0.001	-22.616 -7.820	<0.001	-47.605 -31.137	<0.001	-80.718 -59.394
HbA1c, %	5.5 ± 0.3	5.7 ± 0.3	5.8 ± 0.4	6.1 ± 0.5	<0.001	-0.242 -0.067	<0.001	-0.362 -0.170	<0.001	-0.625 -0.385
BMI, kg/m ²	21.6 ± 2.6	22.8 ± 3.0	23.6 ± 3.0	24.4 ± 3.1	<0.001	-1.838 -0.473	<0.001	-2.747 -1.236	<0.001	-3.832 -1.912
Urine albumin/Cr ratio, mg/gCr	8.4 ± 12.0	9.8 ± 15.8	10.9 ± 15.4	14.3 ± 15.3	0.999	-5.174 2.329	0.647	-6.657 1.620	0.017	-11.142 -0.695

BMI, body mass index; CI, confidence interval; Cr, creatinine; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HLD, healthy living donor; LDL, low-density lipoprotein; MCLD, medically complex living donor; PC, preoperative comorbidity. Continuous data are presented as mean ± SD. The suffixes PC 1, PC 2, and PC 3 indicate donors with 1, 2, or, 3 comorbidities, respectively. Bold indicates statistically significant results. Bonferroni method was used for the multiplicity adjustment.

95% confidence intervals were calculated and compared with respect to the number of PCs at each time point. The Bonferroni method was used to adjust for multiple comparisons.

Logistic regression analysis was used to examine whether the number of PCs affected biopsy results at 1 hour after transplant. To adjust for confounding factors, age and sex were incorporated into the model as independent variables. Survival analysis was used to determine whether the number of PCs influenced overall survival. The cumulative survival rate was calculated using the Kaplan-Meier method. To adjust for confounding factors, the effect of number of PCs was tested using log-rank tests stratified by age (≥60 years or <60 years) and sex. All statistical analyses were performed using SPSS software, version 23.0 for Windows (IBM Corporation, Armonk, NY). For all analyses, a P < 0.05 was considered significant.

RESULTS

Study Population

A total of 807 living donors underwent kidney transplant procedures at our hospital during the study

period. All 807 were recruited for this study. Five of the 807 donors (0.6%) did not attend the >5 months of follow-up, so were excluded from the analysis. The remaining 802 donors were followed for more than 5 months between January 2008 and December 2017 (median duration of follow-up: 56.0 months [interquartile range 26.8–83.0]), were enrolled in the study, and were included in the final analysis.

Follow-up Rate

Of the remaining 802 enrolled participants, 214 were categorized as HLD, 302 as MCLD (PC 1), 196 as MCLD (PC 2), and 90 as MCLD (PC 3) (Figure 1). In total, 751 donors (93.1%) were followed for >5 months and assessed at least once after January 2016, whereas 51 (6.3%) were followed for >5 months but were not assessed after January 2016.

Descriptive Data

Table 1 presents the characteristics of the study population. No significant differences were observed between HLDs and MCLDs (PC 1–3) in terms of donations to first-degree relatives, smoking history, number of endoscopic operations, operative duration, blood loss,

Table 3. Logistic regression analysis of biopsy results 1 hour after implantation

	Unadjusted				Adjusted for age and sex			
	n	OR	95% CI	P value	n	OR	95% CI	P value
HLD	211	1.000			211	1.000		
MCLD (PC 1)	296	1.945	1.344 2.816	<0.001	296	1.260	0.834 1.905	0.272
MCLD (PC 2)	192	2.947	1.960 4.432	<0.001	192	1.484	0.934 2.358	0.095
MCLD (PC 3)	89	5.323	3.097 9.150	<0.001	89	1.862	1.012 3.425	0.046

CI, confidence interval; HLD, healthy living donor; MCLD, medically complex living donor; OR, odds ratio; PC, preoperative comorbidity. Bold indicates statistically significant results. Interstitial fibrosis or tubular atrophy of >5% was considered significant. Any arteriosclerosis or glomerulosclerosis was considered significant.

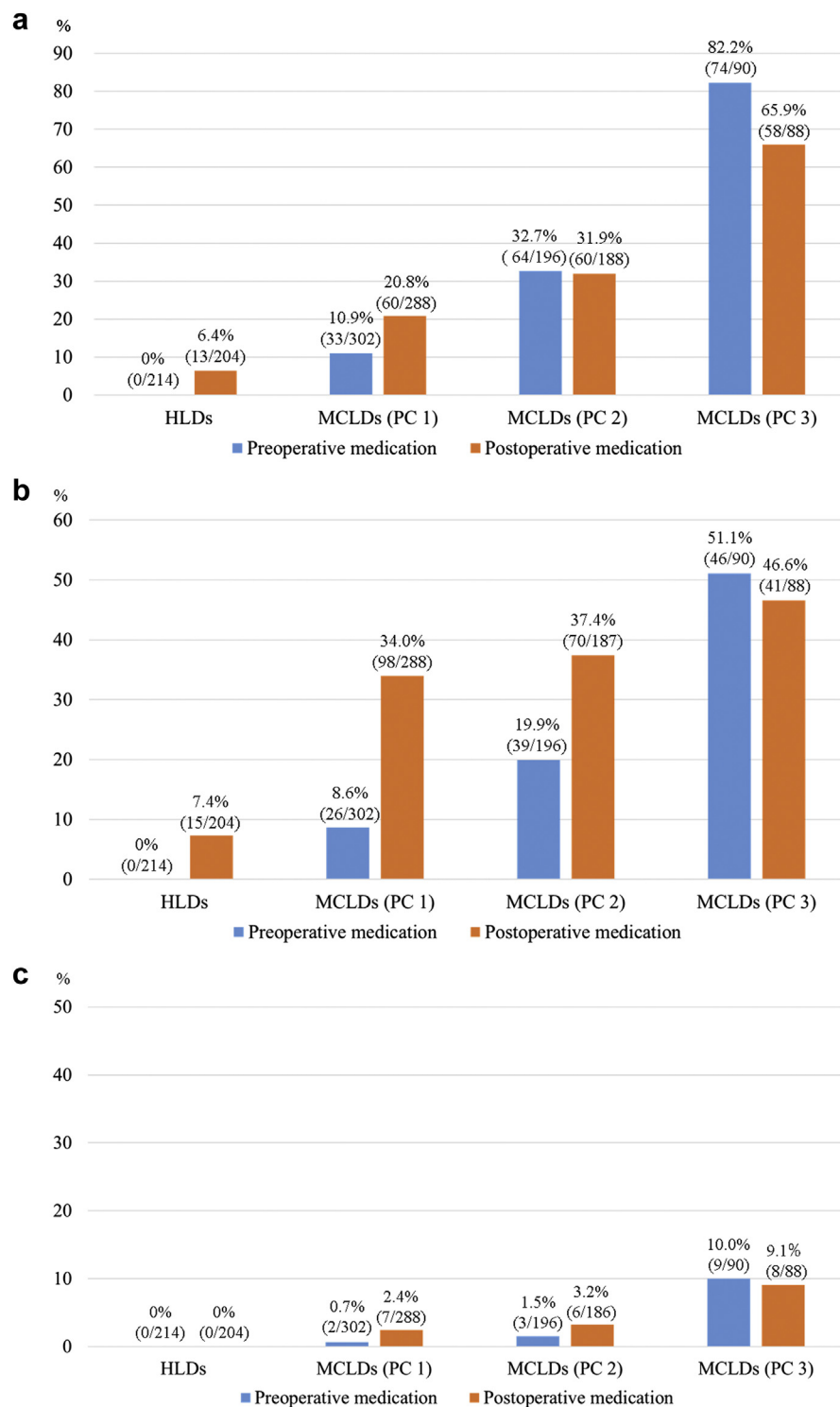


Figure 3. Rates of administration of pre- and postoperative medication according to group. Bar graph comparing rates of administration of medication for (a) hypertension, (b) dyslipidemia, and (c) glucose intolerance among groups. HLDs, healthy living donors; MCLDs, medically complex living donors; PC, preoperative comorbidity.

and duration of follow-up. Significant differences were observed in mean age and sex.

Preoperative Morbidity Rates and Clinical Data

Preoperative morbidity rates associated with HT, dyslipidemia, GI, and obesity in HLDs and MCLDs (PC 1–3)

are shown in [Figure 2](#). Preoperative clinical data are shown in [Table 2](#). Significant differences were identified between HLDs and all MCLDs for all clinical parameters except for urine albumin/Cr ratio in MCLDs (PC 1 and 2). Detailed numerical values are shown in [Table 2](#).

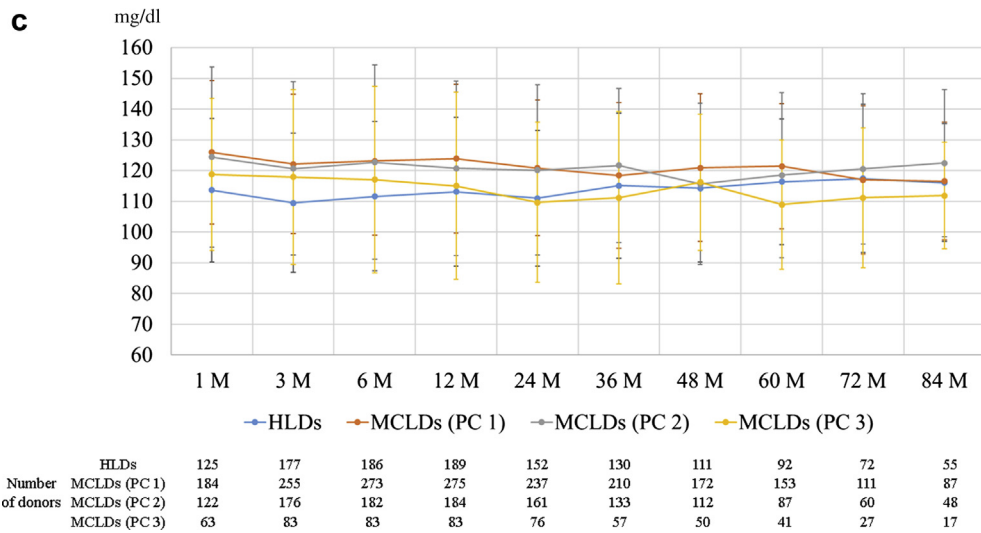
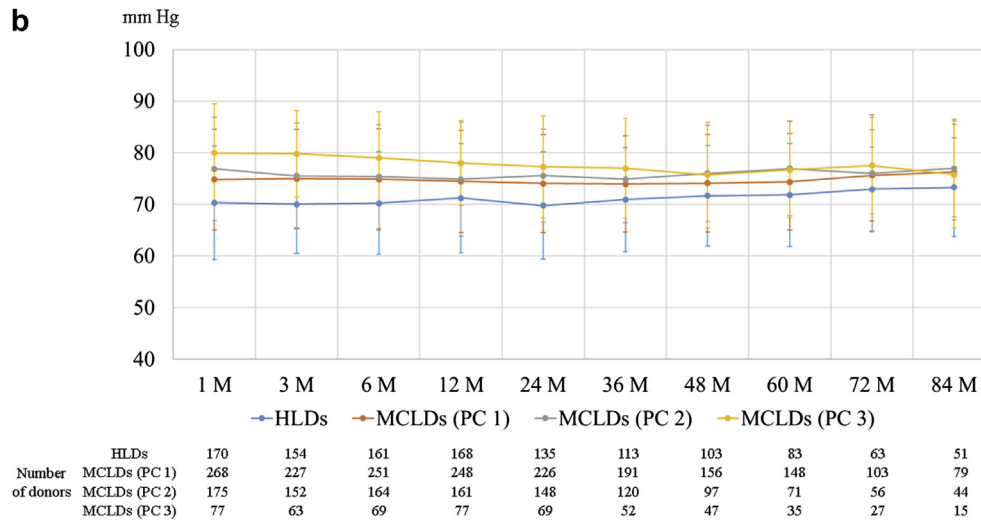
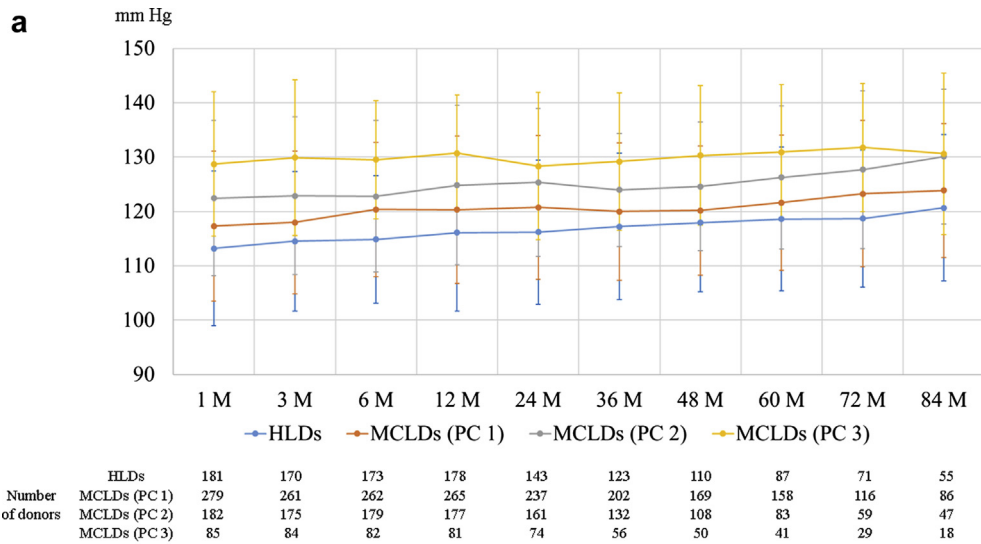


Figure 4. Postoperative clinical changes over time according to group. Graphical representation of (a) systolic blood pressure, (b) diastolic blood pressure, (c) low-density lipoprotein cholesterol levels, (continued)

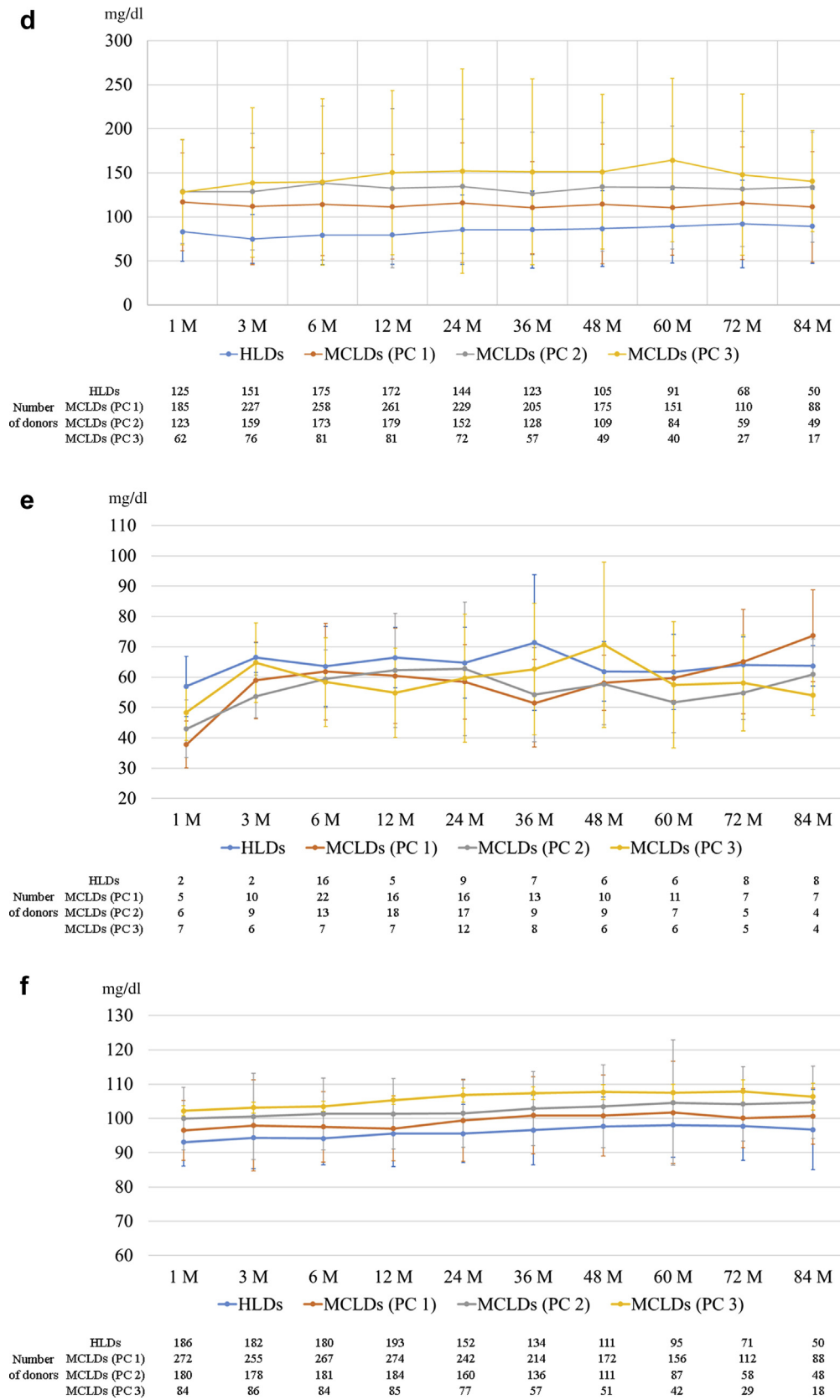


Figure 4. (continued) (d) triglyceride levels, (e) high-density lipoprotein cholesterol levels, (f) fasting glucose levels, (continued)

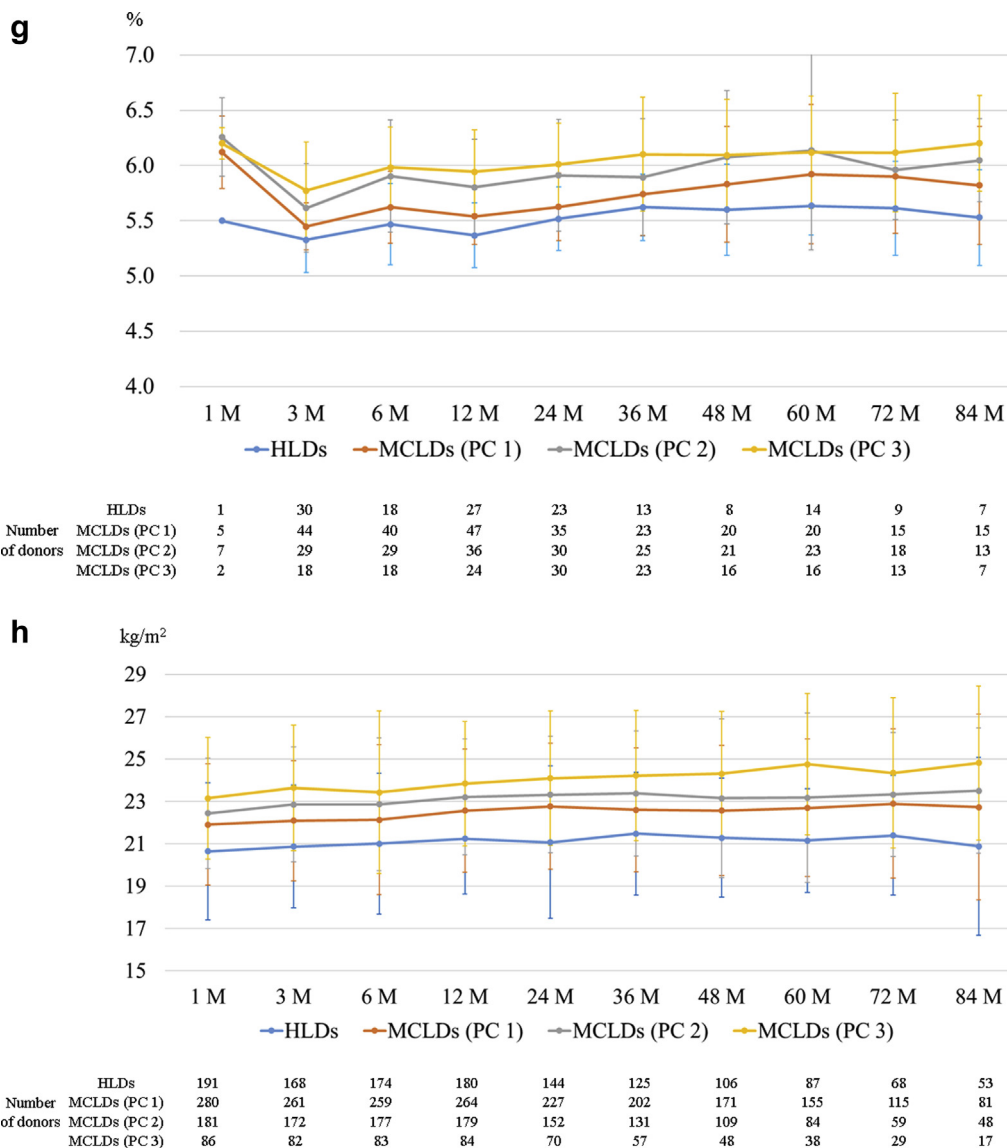


Figure 4. (continued) (g) glycated hemoglobin levels, and (h) body mass index values over the 84-month follow-up period. Error bars show the SD. HLDs, healthy living donors; M, months postoperatively; MCLDs, medically complex living donors; PC, preoperative comorbidity.

Pathological Findings From Baseline Biopsies

Based on observations from baseline biopsies that were obtained 1 hour after reperfusion, interstitial fibrosis, tubular atrophy, glomerulosclerosis, and arteriosclerosis were identified more frequently in MCLDs (PC 3) than in HLDs (Table 3).

Preoperative and Postoperative Medication

Preoperative and postoperative medications for HT, dyslipidemia, and GI of HLDs and MCLDs (PC 1–3) are shown in Figure 3.

Postoperative Data Changes

Postoperative changes in donors' systolic and diastolic blood pressure, LDL cholesterol levels, triglyceride levels, HDL cholesterol levels, fasting glucose levels, HbA1c, and BMI are shown in Figure 4.

Postoperative Renal Function

Supplementary Table S1 (unadjusted data), Supplementary Table S2 (adjusted data), and Figure 5 show the pre- and postoperative changes in eGFR over time. In the adjusted data, no significant differences were observed between HLDs and MCLDs (PC 1–3).

The decline in the Δ eGFR between preoperative and postoperative day (POD) 6 eGFR differed slightly between HLDs and MCLDs (PC 1–3), but this was not statistically significant (Table 4). The difference in Δ eGFR from POD 6 (when eGFR was lowest) to each time point was not significant between HLDs and MCLDs (PC 1–3) (Table 4).

Supplementary Table S3 (unadjusted data), Supplementary Table S4 (adjusted data), and Figure 6 show the changes in 24-hour urinary protein in HLDs and MCLDs (PC 1–3) during follow-up. Changes

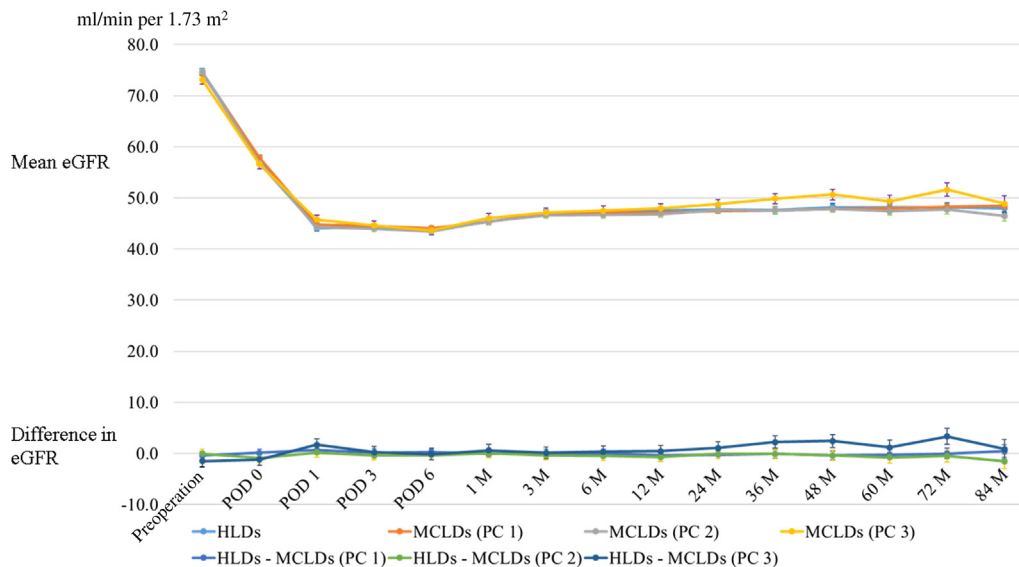


Figure 5. Preoperative and postoperative changes in estimated glomerular filtration rate (eGFR) adjusted for age and sex. Graphical representation illustrating the changes in eGFR for all groups throughout the 84-month follow-up period. Error bars show the SD. HLDs, healthy living donors; M, months postoperatively; MCLDs, medically complex living donors; PC, preoperative comorbidity; POD, postoperative day.

of <0.2 g/24 hours were observed in HLDs and MCLDs (PC 1–3). No significant differences in 24-hour urinary protein were identified between HLDs and MCLDs (PC 1–3), except when comparing the HLD and MCLD (PC 2) groups at 60 months.

The difference between preoperative and postoperative 24-hour urinary protein was significantly different between the HLD and MCLD (PC 2 and 3) groups (Table 5). However, the mean 24-hour urinary protein did not show overt proteinuria at any time point for any group (Figure 6).

End-Stage Renal Disease

None of the donors developed ESRD during the follow-up period.

Mortality

No significant differences in short-term mortality rates were identified between HLDs and MCLDs (PC 1–3) following stratification of the groups according to age or sex (Figure 7). Six donors died; deaths were due to prostate cancer in 1 HLD, colon cancer in 1 MCLD (PC 1), brain cancer in 1 MCLD (PC 2), amyotrophic lateral sclerosis in 1 MCLD (PC 2), multiple organ failure in 1 MCLD (PC 3), and abdominal aortic aneurysm rupture in 1 MCLD (PC 3).

Comparison Between HLDs and MCLDs With Hypertension and GI

Supplementary Table S5 presents the characteristics of HLDs and MCLDs with HT and GI (denoted MCLD [HT and GI]). No significant differences were observed in smoking history, number of endoscopic operations,

operative duration, blood loss, or duration of follow-up between the 2 groups. However, significant differences were observed in the number of donations to first-degree relatives, mean age, and sex. Preoperative clinical data are shown in Supplementary Table S6. Significant differences were identified between HLDs and MCLDs (HT and GI) for all parameters. The urine albumin/Cr ratio of both groups was <30 mg/gCr, although this was significantly higher in MCLDs (HT and GI). Based on the pathological observations of baseline biopsies, interstitial fibrosis, tubular atrophy, glomerulosclerosis, and arteriosclerosis were identified more frequently in the MCLD (HT and GI) group than in the HLD group (Supplementary Table S7). Supplementary Table S8 and Supplementary Figure S1 show the preoperative and postoperative eGFR changes over time. In the adjusted data, no significant differences were observed between HLDs and MCLDs (HT and GI). The Δ eGFR between preoperative and POD 6 rates was not significantly different between HLDs and MCLDs (HT and GI) (Supplementary Table S9). The improvement in Δ eGFR from the lowest rate (observed on POD 6) at each time point was not significantly different between the 2 groups (Supplementary Table S9). Supplementary Table S10 and Supplementary Figure S2 show the changes in 24-hour urinary protein during follow-up. Changes of <0.2 g/24 hours were observed for all donors, with significant differences identified between the groups, from the adjusted data, at 60 and 72 months only. The values of Δ 24-hour urinary protein were significantly different between HLDs and MCLDs (HT and GI) (Supplementary Table S11), although overt proteinuria

Table 4. Comparison of Δ eGFR adjusted for age and sex
 Δ eGFR (adjusted for age and sex)
(ml/min per 1.73 m²)

	MCLD (PC 1)			MCLD (PC 2)			MCLD (PC 3)			HLD vs. MCLD (PC 1)			HLD vs. MCLD (PC 2)			HLD vs. MCLD (PC 3)				
	HLD	MCLD (PC 1)	MCLD (PC 2)	MCLD (PC 3)	Difference (ml/min per 1.73 m ²)	SD	P value	95% CI	Difference (ml/min per 1.73 m ²)	SD	P value	95% CI	Difference (ml/min per 1.73 m ²)	SD	P value	95% CI	Difference (ml/min per 1.73 m ²)	SD	P value	95% CI
Δ Pre operation-POD 6	-30.88	-30.21	-31.19	-29.50	0.67	0.55	>0.999	-0.41	1.75	-0.31	>0.999	-1.50	0.89	1.38	0.77	0.755	-0.14	2.90		
Δ POD 6-3 M	3.24	2.99	3.17	3.49	-0.25	0.58	>0.999	-1.39	0.89	-0.07	>0.999	-1.32	1.18	0.25	0.81	>0.999	-1.33	1.83		
Δ POD 6-6 M	3.41	3.17	3.23	3.87	-0.23	0.59	>0.999	-1.38	0.92	-0.18	>0.999	-1.44	1.08	0.46	0.82	>0.999	-1.14	2.06		
Δ POD 6-12 M	3.75	3.07	3.36	4.31	-0.68	0.59	>0.999	-1.84	0.67	-0.39	>0.999	-1.66	0.87	0.56	0.83	>0.999	-1.06	2.18		
Δ POD 6-24 M	3.91	3.36	4.15	5.11	-0.55	0.62	>0.999	-1.78	0.67	0.24	>0.999	-1.11	1.60	1.20	0.88	>0.999	-0.53	2.93		
Δ POD 6-36 M	3.88	3.51	4.13	6.24	-0.36	0.67	>0.999	-1.67	0.95	0.25	>0.999	-1.19	1.70	2.36	0.94	1.109	0.52	4.20		
Δ POD 6-48 M	4.44	3.73	4.39	7.02	-0.71	0.71	>0.999	-2.10	0.68	-0.06	>0.999	-1.61	1.49	2.57	1.00	0.089	0.62	4.53		
Δ POD 6-60 M	4.39	3.87	3.95	5.71	-0.52	0.78	>0.999	-2.06	1.01	-0.45	>0.999	-2.18	1.29	1.32	1.16	>0.999	-0.95	3.58		
Δ POD 6-72 M	4.47	4.15	4.28	7.94	-0.32	0.89	>0.999	-2.07	1.43	-0.18	>0.999	-2.20	1.84	3.48	1.36	0.093	0.82	6.14		
Δ POD 6-84 M	4.24	4.39	3.00	5.22	0.15	1.09	>0.999	-1.99	2.29	-1.24	>0.999	-3.62	1.14	0.98	1.67	>0.999	-2.31	4.26		

CI, confidence interval; eGFR, estimated glomerular filtration rate; Δ eGFR, the difference in eGFR between preoperative and POD 6 and between POD 6 to each time point; HLD, healthy living donor; M, months postoperatively; MCLD, medically complex living donor; PC, preoperative comorbidity; POD, postoperative day. Bonferroni method was used for the multiplicity adjustment. The suffixes PC 1, PC 2, and PC 3 indicate donors with 1, 2, or 3 comorbidities, respectively. "Difference" was calculated by the mean value for MCLDs (PC 1, 2, or 3) minus that for HLDs.

was not detected at any point in either group (Supplementary Figure S2). No significant differences were identified in the short-term mortality rates of HLDs and MCLDs (HT and GI) following stratification of the groups according to age or sex (Supplementary Figure S3).

DISCUSSION

Recently, Kidney Disease: Improving Global Outcomes guidelines, as well as other guidelines, have recommended that kidney donations from MCLDs be allowed if they meet strict criteria both before and after donation.¹²⁻¹⁴ The Japanese guidelines allow for a broader range of MCLDs compared with Kidney Disease: Improving Global Outcomes guidelines.^{12,13} This is because Japan has a low number of deceased donors; only 10% of kidney transplants originate from deceased people.¹⁵ To enable a broader range of individuals to become living donors and to prevent the risk of ESRD, the Japanese guidelines include additional criteria to the Kidney Disease: Improving Global Outcomes guidelines and the criteria of the Amsterdam Forum.^{12,13,16,17} In this study, we included living kidney donors who met the Japanese criteria. Donors were categorized based on the number of PCs present, which included HT, dyslipidemia, GI, and obesity.

The mortality and ESRD risks are thought to be similar for living kidney donors as for the general population^{1,18,19}; however, findings from studies published in 2014 suggest that the risks of ESRD and mortality among living kidney donors are in fact higher than among the general population.^{2,3} The first of these studies, based on a Norwegian cohort, excluded MCLDs with PCs.² In the second study, based on an American cohort, the investigators matched living kidney donors with individuals from the general population. However, they were matched only for blood pressure and BMI as PCs.³ In both reports, the risks of ESRD and mortality were described without extensive donor follow-up, consideration of administered medications, or management of PCs. Reports from other studies investigating the effects of metabolic syndrome on eGFR have not included details about follow-up duration or changes in metabolic syndrome over time.^{6,7,20-23} The Japanese guidelines recommend that living kidney donors are assessed regularly, and their health and comorbidities must be well managed.^{6,7,14,15} Without detailed investigations into donor management and treatment adherence during follow-up, evaluation of ESRD risk, mortality, and renal function cannot provide insight into the true effects of PCs in the context of kidney donation. Detailed investigations and powerful evidence (regardless of study size) can be obtained only

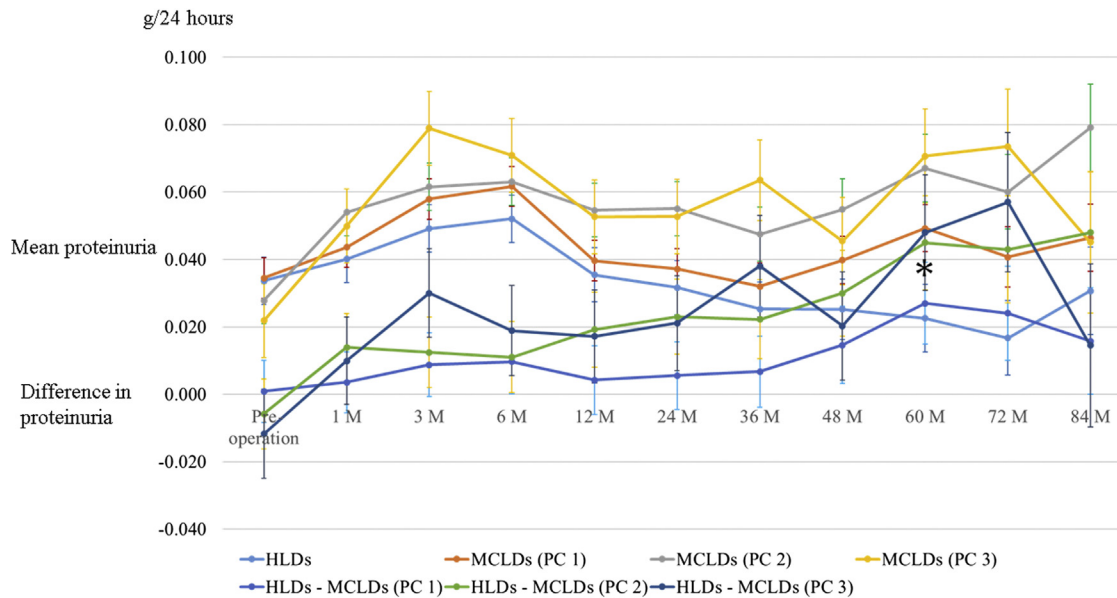


Figure 6. Changes in urine protein content over a 24-hour period adjusted for age and sex. Graphical representation illustrating the changes in protein content of urine collected over 24 hours for all groups throughout the 84-month follow-up period. Error bars show the SD. *Statistical significance ($P < 0.05$). HLDs, healthy living donors; M, months postoperatively; MCLDs, medically complex living donors; PC, preoperative comorbidity.

with regular follow-up and the implementation of appropriate donor management protocols. The effects of individual PCs on the risks of chronic kidney disease, ESRD, and mortality in living kidney donors have been reported.^{24–26} Coexisting PCs are often observed in clinical practice and it is known that coexisting, as well as individual, comorbidities contribute to chronic kidney disease risk in the general population.^{27,28} However, few studies have investigated the effects of multiple PCs on the risks of ESRD and mortality in living kidney donors.⁷ For such investigations, we believe it is more appropriate to categorize living kidney donors according to the numbers of PCs to enable comparisons of the risks between groups rather than in relation to individual PCs.

This study included 802 consecutive living kidney donors, with a median follow-up period of 5 years. Unlike studies from Norway² and the United States,³ this study did not involve large numbers of donors. Nevertheless, this represents the largest study investigating the effects of the number of PCs on postoperative eGFR, ESRD risk, and mortality in living kidney donors.^{6,7,23} Providing these donors with the option to attend follow-up meetings at local hospitals and private clinics (as well as at our hospital) may have contributed to the excellent follow-up rate. Data from living kidney donors who were followed up at other local hospitals and private clinics were sent to our hospital annually.

Our findings on the number of coexisting PCs in relation to age and sex suggest that female living kidney donors present with fewer PCs than male living

kidney donors. Our data on systolic blood pressure, diastolic blood pressure, BMI, LDL cholesterol levels, HDL cholesterol levels, triglyceride levels, fasting glucose levels, and HbA1c values are presented as means without statistical adjustment, and groups were compared in terms of eGFR, urinary protein level, and mortality. Pathology findings from baseline biopsies as well as eGFR results and mortality rates were compared between HLDs and MCLDs (PC 1–3) after adjustment for sex and age due to the significant differences among the groups with respect to these variables. Findings from the pathology assessments of baseline biopsies provide insights into the condition of the grafts and the remaining kidney. Pathology findings were also statistically adjusted for age and sex, as biopsy results may have been influenced by these factors.

Some reports have described relationships between pathology findings from baseline biopsies and postoperative eGFR in living kidney donors with PCs^{6,7,29}; however, the numbers of patients included in these studies were small. We did not identify significant differences between HLDs and MCLDs (PC 1 and 2) with respect to pathology findings from baseline biopsies. In contrast, compared with HLDs, interstitial fibrosis, tubular atrophy, glomerulosclerosis, and arteriosclerosis were more frequently identified in baseline biopsies from MCLDs (PC 3). This implies that PCs may cause pathological renal changes in MCLDs (PC 3) and lead to significant changes in the preoperative urine albumin/Cr ratio.³⁰ The significant differences observed in the kidney biopsies between HLDs and MCLDs (PC 3) are still suggestive of the increased

Table 5. Comparison of Δ urinary protein content over 24 hours (adjusted for age and sex)

	HLD vs. MCLD (PC 1)				HLD vs. MCLD (PC 2)				HLD vs. MCLD (PC 3)									
	HLD	MCLD (PC 1)	MCLD (PC 2)	MCLD (PC 3)	Difference, g/24 hours	SD	P value	95% CI	Difference, g/24 hours	SD	P value	95% CI	Difference, g/24 hr	SD	P value	95% CI		
Δ Pre operation-1 M	0.006	0.009	0.026	0.028	0.003	0.011	>0.999	-0.018	0.024	0.020	0.012	0.980	-0.004	0.043	0.015	>0.999	-0.008	0.051
Δ Pre operation-3 M	0.015	0.023	0.034	0.057	0.008	0.011	>0.999	-0.014	0.030	0.018	0.012	>0.999	-0.006	0.042	0.015	0.062	0.012	0.071
Δ Pre operation-6 M	0.018	0.027	0.035	0.049	0.009	0.011	>0.999	-0.013	0.031	0.017	0.012	>0.999	-0.007	0.041	0.015	0.463	0.001	0.061
Δ Pre operation-12 M	0.002	0.005	0.027	0.031	0.003	0.012	>0.999	-0.020	0.026	0.025	0.013	0.513	0.000	0.050	0.016	0.660	-0.002	0.060
Δ Pre operation-24 M	-0.002	0.003	0.027	0.031	0.005	0.012	>0.999	-0.018	0.027	0.029	0.013	0.223	0.004	0.054	0.016	0.384	0.002	0.064
Δ Pre operation-36 M	-0.008	-0.003	0.020	0.042	0.006	0.012	>0.999	-0.018	0.029	0.028	0.013	0.343	0.002	0.054	0.017	0.029	0.017	0.083
Δ Pre operation-48 M	-0.008	0.005	0.027	0.024	0.014	0.013	>0.999	-0.011	0.039	0.035	0.014	0.121	0.008	0.063	0.018	0.696	-0.003	0.067
Δ Pre operation-60 M	-0.011	0.015	0.039	0.049	0.026	0.013	0.524	0.000	0.052	0.050	0.015	0.010	0.020	0.080	0.019	0.014	0.023	0.097
Δ Pre operation-72 M	-0.017	0.006	0.032	0.052	0.023	0.015	>0.999	-0.006	0.053	0.049	0.017	0.039	0.016	0.083	0.022	0.017	0.026	0.111
Δ Pre operation-84 M	-0.003	0.012	0.051	0.023	0.015	0.017	>0.999	-0.018	0.048	0.054	0.019	0.041	0.017	0.091	0.025	>0.999	-0.023	0.076

CI, confidence interval; HLD, healthy living donor; MCLD, medically complex living donor; POD, postoperative day; PC, preoperative comorbidity. Bonferroni method was used for the multiplicity adjustment. The suffixes PC 1, PC 2, and PC 3 indicate donors with 1, 2, or 3 comorbidities, respectively. "Difference" was calculated by the mean value for MCLDs (PC 1, 2, or 3) minus that for HLDs. Bold indicates statistically significant results.

long-term risk for the MCLDs, especially for the development of progressive chronic kidney disease, although eGFR changes were similar between the HLDs and MCLDs (PC 3). This implies that strict and robust follow-up with proactive management of PCs after donation are necessary.

In this study, kidney donors were assessed after organ donation. Because MCLDs (PC 3) had received medication before donation, their lifestyle changes and treatment regimens may have already been well established, which may explain the similar rates of pre- and postoperative drug administration. Patients in the MCLD (PC 1) and MCLD (PC 2) groups had not received medication before donation and were younger than those in the MCLD (PC 3) group. Morbidity rates increased with age as expected; however, the rates of postoperative medication administration were lower in MCLDs (PC 1 and 2) than the preoperative rate in MCLDs (PC 3), which may have been a result of regular follow-up and lifestyle education.^{31,32} The average systolic and diastolic blood pressure, BMI, LDL cholesterol levels, HDL cholesterol levels, triglyceride levels, fasting glucose levels, and HbA1c values of all donors were maintained within optimal ranges,¹³ indicating that PCs were well managed during the follow-up period.

Although ESRD was not identified in any donor during the follow-up period, it is possible that this is because the follow-up period was very short. The lack of significant differences in decline in Δ eGFR between HLDs and any MCLDs may imply that rapid changes in eGFR after hemi-nephrectomy were not associated with baseline biopsy results. Furthermore, the results of improvement in Δ eGFR, which might be influenced by baseline biopsy results and the management of PCs after donation in the absence of overt proteinuria, may imply that appropriate management of comorbidities can contribute to the maintenance of renal function. After kidney donation, eGFR increases and postoperative urinary protein level tends to increase gradually after a temporary decrease¹; however, in this study, the average postoperative urine protein levels were notably lower than the diagnostic range for proteinuria. This may imply that the significant differences in Δ 24-hour urinary protein that we identified between HLDs and MCLDs (PC 2 and 3) were not clinically important.

The deaths of donors due to prostate cancer, colon cancer, brain cancer, and amyotrophic lateral sclerosis are unlikely to have been related to organ donation; however, deaths from multiple organ failure and abdominal aortic aneurysm rupture may have been associated with donation. A previous study found that the cardiovascular-related mortality rate in kidney

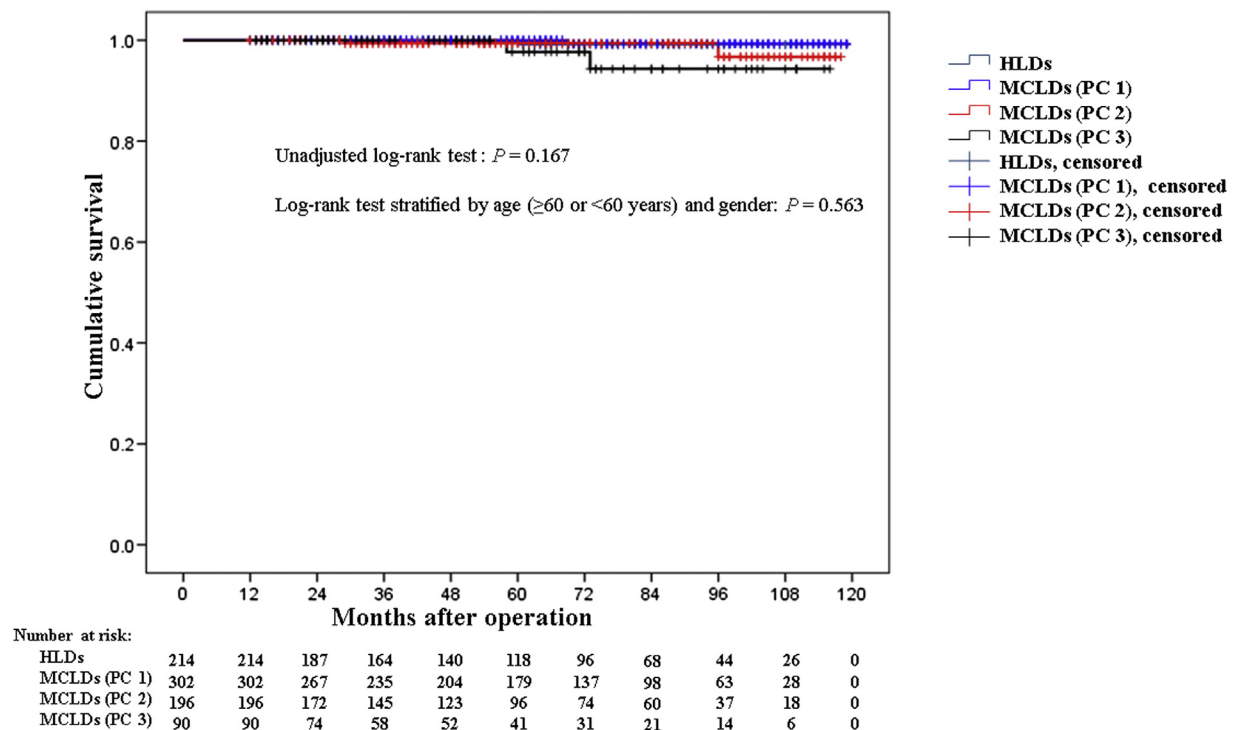


Figure 7. Mortality rates of each group. Kaplan-Meier curves comparing the mortality rates between study groups. HLDs, healthy living donor; MCLDs, medically complex living donor; PC, preoperative comorbidity.

donors was significantly higher than in the general population³³; however, in this study, only 1 donor died of cardiovascular disease.

This study has some limitations. First, this was a retrospective cohort study that investigated only the living donors. Second, the follow-up period was very short to sufficiently identify the significant differences and trends of mortality and ESRD. However, the findings do suggest that optimal management of comorbidities after donation may mean similar outcomes will be observed for MCLDs (PC 3) as for HLDs with no PCs. In addition, the impact of PCs on MCLDs with HT and GI was investigated. Further prospective randomized studies are required, investigating the differences in outcomes of living donors with PCs and the general population over an extended period, as significant differences in morbidity and mortality associated with ESRD are primarily observed after follow-up periods of ≥ 15 years.^{2,3,34}

In conclusion, appropriate management of MCLDs with PCs can result in renal function and short-term mortality rates that are similar to those observed for HLDs with no PCs.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Supplementary References.

Figure S1. Preoperative and postoperative changes in estimated glomerular filtration rate in healthy and medically complex (hypertension and glucose intolerance) living donors (adjusted for age and sex).

Figure S2. Changes in urine protein content over a 24-hour period in healthy and medically complex (hypertension and glucose intolerance) living donors (adjusted for age and sex).

Figure S3. Mortality rates in healthy and medically complex (hypertension and glucose intolerance) living donors.

Table S1. Difference in preoperative and postoperative estimated glomerular filtration rate changes (unadjusted for age and sex).

Table S2. Difference in preoperative and postoperative estimated glomerular filtration rate changes (adjusted for age and sex).

Table S3. Difference in urinary protein content over 24 hours (unadjusted for age and sex).

Table S4. Difference in urinary protein content over 24 hours (adjusted for age and sex).

Table S5. Characteristics of healthy and medically complex (hypertension and glucose intolerance) living donors.

Table S6. Preoperative clinical data of healthy and medically complex (hypertension and glucose intolerance) living donors.

Table S7. Logistic regression analysis of the biopsy results 1 hour after implantation.

Table S8. Difference in preoperative and postoperative estimated glomerular filtration rate changes in healthy and medically complex (hypertension and glucose intolerance) living donors.

Table S9. Comparison of Δ estimated glomerular filtration rate in healthy and medically complex (hypertension and glucose intolerance) living donors (adjusted for age and sex).

Table S10. Difference in urinary protein content over 24 hours in healthy and medically complex (hypertension and glucose intolerance) living donors.

Table S11. Comparison of Δ urinary protein content over 24 hours in healthy and medically complex (hypertension and glucose intolerance) living donors (adjusted for age and sex).

The STROBE Statement.

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