Supplemental Table 1. Baseline characteristics according to the presence of missing TCO_2 or creatinine measurements.

	Total (n=2,318)	Complete cases (n=1,776)	Missing cases (n=542)	*p*-value
Age (years)	43.0 (34.0,51.0)	43.0 (33.0,51.0)	43.0 (34.0,50.0)	.427
Male recipient (%)	59.5	59.5	59.4	>.999
BMI (kg/m^2)				.796
<18.5 (%)	8.8	8.6	9.2	
≥18.5 and <25	72.1	72.0	72.5	
≥25	19.1	19.4	18.3	
Cause of ESRD (%)				<.001
Glomerulonephritis	22.5	24.4	16.4	
Diabetes	14.5	14.9	13.3	
Hypertension	7.8	8.4	5.5	
Cystic kidney disease	4.2	4.8	2.4	
Others	12.2	10.6	17.5	
Unknown	38.8	36.9	44.8	
Smoking (%)	22.5	22.9	21.4	.514
Diabetes (%)	18.9	19.4	17.2	.264
SBP (mmHg)	127.5 ± 15.7	127.1 ± 15.5	128.7 ± 16.4	.041
SBP (%)				.310
1^{st} quartile	24.7	25.4	22.5	
2^{nd} and 3^{rd} quartiles	49.3	49.2	49.6	
4^{th} quartile	26.0	25.5	27.9	
DBP (mmHg)	79.2 ± 10.9	78.9 ± 10.9	80.2 ± 10.9	.019
eGFR (mL/min/1.73 m²)	67.0 (55.4,80.7)	66.8 (55.7,80.0)	68.0 (53.8,83.8)	.249
Preemptive (%)		13.0	10.3	.122
Donor age (years)	41.0 (31.0,49.0)	41.0 (32.0,50.0)	40.0 (31.0,47.0)	.009
Male donor (%)	56.4	56.0	57.7	.510
Donor relationship (%)				.244
Living	76.5	77.1	74.5	
Deceased	23.5	22.9	25.5	
ABO incompatibility (%)	4.9	5.6	2.6	.006
HLA mismatch	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	.817
Positive cross-match (%)	3.5	4.2	1.5	.005
Positive DSA[a] (%)	0.9	1.2	0.2	.065

Delayed graft function (%)	1.2	1.5	0.2	.023
Calcineurin inhibitor				.027
Tacrolimus (%)	56.3	57.5	52.0	
Cyclosporine (%)	43.7	42.5	48.0	
Alkalinizing agent (%)	1.5	1.6	1.3	.783
Proteinuria (g/g creatinine)	0.7 (0.4,1.3)	0.7 (0.4,1.4)	0.3 (0.2,0.7)	<.001

[a]DSA, donor-specific antibody

[b]Compared within the subgroup of participants with available data. Total, n=887; complete cases, n=725; missing cases, n=162.

Supplemental Table 2. Analyses of associations of low TCO_2 (<22 mmol/L) with graft loss, mortality and DCGF according to subgroups of eGFR at 3 months post-transplant.

	Number of subjects	Conventional Cox model[a]		Time-varying Cox model[b]		Marginal structural Cox model[c]	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
eGFR ≥60 (mL/min/1.73 m²)	1,533						
Graft loss		1.58 (0.97-2.57)	.066	3.37 (2.01-5.63)	<.001	3.87 (2.15-6.98)	<.001
Mortality		2.08 (0.97-4.46)	.059	2.13 (0.86-5.27)	.100	1.99 (0.74-5.36)	.173
DCGF		1.22 (0.66-2.23)	.529	2.99 (1.72-5.22)	<.001	4.21 (2.37-7.47)	<.001
eGFR <60 (mL/min/1.73 m²)	785						
Graft loss		1.73 (1.08-2.76)	.023	4.46 (2.60-7.65)	<.001	5.39 (2.39-12.17)	<.001
Mortality		0.90 (0.39-2.09)	.804	3.82 (1.68-8.68)	.001	11.82 (4.67-29.90)	<.001
DCGF		1.95 (1.15-3.30)	.013	4.83 (2.57-9.09)	<.001	6.35 (2.51-16.06)	<.001

[a]Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection and calcineurin inhibitor.

[b]Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection and calcineurin inhibitor. TCO_2, acute rejection and eGFR were considered as time-varying variables.

[c]Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection and calcineurin inhibitor. TCO_2 considered as a time-varying variable was the exposure of interest. We considered acute rejection and eGFR as time-varying confounders.

Supplemental Table 3. Association of high anion gap (>14 mmol/L) and low TCO_2 (<22 mmol/L) with graft loss, mortality and DCGF using conventional, time-varying and marginal structural Cox proportional hazards models.

	Conventional Cox model[a]		Time-varying Cox model[b]		Marginal structural Cox model[c]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Graft loss						
Low TCO_2	1.90 (1.35-2.68)	<.001	3.09 (2.16-4.42)	<.001	2.76 (1.47-5.17)	.002
High anion gap	1.33 (0.49-3.64)	.579	1.25 (0.38-4.15)	.715	1.06 (0.29-3.93)	.926
Low TCO_2 & high anion gap	0.47 (0.12-1.85)	.280	1.78 (0.50-6.40)	.374	2.94 (0.44-19.72)	.264
Mortality						
Low TCO_2	1.54 (0.84-2.80)	.170	2.59 (1.34-5.02)	.005	4.46 (1.81-11.02)	.001
High anion gap	3.31 (1.00-10.99)	.051	3.39 (0.99-11.62)	.052	2.34 (0.67-8.14)	.180
Low TCO_2 & high anion gap	0.44 (0.08-2.60)	.367	0.77 (0.15-4.03)	.752	0.77 (0.13-4.52)	.776
DCGF						
Low TCO_2	1.85 (1.25-2.74)	.002	3.09 (2.03-4.72)	<.001	3.39 (1.70-6.77)	.001
High anion gap	1.16 (0.36-3.72)	.798	0.56 (0.08-3.99)	.558	0.67 (0.08-5.76)	.717
Low TCO_2 & high anion gap	0.40 (0.08-2.13)	.286	3.41 (0.45-26.07)	.237	4.43 (0.35-55.93)	.249

[a]Model 1: Conventional Cox regression models for graft loss, mortality and DCGF. Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection and calcineurin inhibitor. Fixed TCO_2 and anion gap values measured at 3 months post-transplant were used. Interaction term between TCO_2 and anion gap was included.

[b]Model 2: Time-varying Cox regression models for graft loss, mortality and DCGF. Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection and calcineurin inhibitor. TCO_2, anion gap, acute rejection and eGFR were considered as time-varying variables. Interaction term between TCO_2 and anion gap was included.

[c]Model 3: Marginal structural Cox regression models for graft loss, mortality and DCGF. Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection and calcineurin inhibitor. Time-varying TCO_2, anion gap and their interaction were evaluated for the association of three outcomes. Acute rejection and eGFR were considered as time-varying confounders.

Supplemental Table 4. Proportion (%) of KTRs prescribed alkalinizing agents post-transplant according to serum TCO_2.

	Time since transplant (months)								
	3	6	9	12	18	24	36	48	60
Number of subjects	2,318	2,299	2,285	2,262	2,180	2,082	1,801	1,518	1,304
TCO_2									
Low (<22 mmol/L)	5.4	5.9	7.0	9.5	8.8	8.3	7.3	9.7	11.2
Normal (22-29.9 mmol/L)	0.8	0.5	0.4	0.7	1.6	0.8	0.8	0.9	0.8
High (≥30 mmol/L)	0.0	0.0	0.0	0.4	0.6	0.5	0.0	0.9	1.2
Total	1.5	1.1	1.0	1.3	1.6	1.3	1.3	1.8	1.9

Supplemental Table 5. Associations of the use of alkalinizing agents and low TCO_2 (<22 mmol/L) with graft loss, mortality and DCGF using conventional, time-varying and marginal structural Cox proportional hazards models.

	Conventional Cox model[a]		Time-varying Cox model[b]		Marginal structural Cox model[c]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Graft loss						
Low TCO_2 & alkalinizing agent		.623		.290		.160
Low TCO_2[d]	1.78 (1.28-2.47)	.001	3.04 (2.13-4.34)	<.001	2.84 (1.74-4.61)	<.001
Alkalinizing agent[d]	1.23 (0.44-3.46)	.691	3.75 (2.35-5.97)	<.001	15.75 (6.09-40.70)	<.001
Mortality						
Low TCO_2 & alkalinizing agent		.998	0.10 (0.02-0.52)	.006		.220
Low TCO_2[d]	1.54 (0.88-2.69)	.133	3.10 (1.62-5.95)	.001	2.98 (1.45-6.13)	.003
Alkalinizing agent[d]	1.31 (0.28-6.07)	.732	16.80 (5.39-52.39)	<.001	20.71 (7.61-56.38)	<.001
DCGF						
Low TCO_2 & alkalinizing agent		.755		.421		.258
Low TCO_2[d]	1.70 (1.17-2.48)	.006	3.04 (2.00-4.62)	<.001	2.78 (1.60-4.85)	<.001
Alkalinizing agent[d]	0.90 (0.21-3.74)	.879	4.26 (2.58-7.03)	<.001	22.39 (8.42-59.53)	<.001

[a]Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection, and calcineurin inhibitor. Fixed TCO_2 and use of alkalinizing agents measured at 3 months post-transplant were used.

[b]Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection, and calcineurin inhibitor. TCO_2, acute rejection, eGFR and use of alkalinizing agents were considered as time-varying variables.

[c]Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection, and calcineurin inhibitor. Time-varying TCO_2 and use of alkalinizing agents were evaluated for the association of three outcomes. Acute rejection, eGFR, and use of alkalinizing agents were considered as time-varying confounders.

[d]The results were described without considering interaction effects due to their insignificance.

Supplemental Table 6. Associations of proteinuria and low TCO_2 (<22 mmol/L) with graft loss, mortality and DCGF using conventional, time-varying and marginal structural Cox proportional hazards models.

	Conventional Cox model[a]		Time-varying Cox model[b]		Marginal structural Cox model[c]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Graft loss						
TCO_2 <22 mmol/L	2.64 (1.39-5.00)	.003	3.34 (1.67-6.68)	.001	5.16 (1.96-13.54)	.001
Proteinuria (g/g creatinine)	1.18 (0.86-1.61)	.300	1.06 (0.80-1.39)	.703	1.08 (0.77-1.51)	.660
Mortality						
TCO_2 <22 mmol/L	2.25 (0.80-6.33)	.126	3.13 (1.00-9.81)	.508	4.85 (1.34-17.54)	.016
Proteinuria (g/g creatinine)	0.75 (0.38-1.44)	.383	0.77 (0.39-1.51)	.440	0.78 (0.39-1.55)	.475
DCGF						
TCO_2 <22 mmol/L	2.40 (1.11-5.16)	.025	2.73 (1.14-6.56)	.024	4.93 (1.38-17.64)	.014
Proteinuria (g/g creatinine)	1.32 (0.92-1.88)	.135	1.11 (0.81-1.52)	.513	1.13 (0.71-1.81)	.597

[a]Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection, calcineurin inhibitor, and urine protein-to-creatinine ratio at 3 months post-transplant. Fixed TCO_2 values at 3 months post-transplant were used.

[b]Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection, calcineurin inhibitor, and urine protein-to-creatinine ratio at 3 months post-transplant. TCO_2, acute rejection, and eGFR were considered as time-varying variables.

[c]Adjusted for age, gender, BMI, cause of ESRD, smoking, diabetes, SBP category, eGFR, preemptive transplantation, donor age, donor gender, donor status (deceased vs. living), ABO incompatibility, HLA mismatch, cross-match, donor-specific antibody, delayed graft function, acute rejection, calcineurin inhibitor, and urine protein-to-creatinine ratio at 3 months post-transplant. TCO_2 considered as a time-varying variable was the exposure of interest. Acute rejection and eGFR were considered as time-varying confounders.