Cognitive Impairment and Graft Loss in Kidney Transplant Recipients

Legend:

SDC, Material and Methods

Table S1. Risk of mortality for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on the internal study population.

Table S2. Risk of death-censored graft failure for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on the internal study population.

Table S3. Risk of all-cause graft loss (ACGL) for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on an external study population.

Table S4. Risk of mortality for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on an external study population.

Table S5. Risk of death-censored graft failure for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on an external study population.

Table S6. Risk of ACGL among Living Donor Transplant Recipients in the Registry Population (Step 1 of the Hybrid Registry-Augmented Regression).

Table S7. Risk of ACGL among Deceased Donor Transplant Recipients in the Registry Population (Step 1 of the Hybrid Registry-Augmented Regression).

SDC, Materials and Methods

Global Cognitive Function

The 3MS examination, a validated assessment of global cognitive function (1-3), was administered to study participants prior to KT. Scores for the 3MS examination range between 0-100 (lower scores indicate worse cognition) based on responses to 15 exam components including temporal and spatial orientation, multi-stage commands, and recall. In our primary analyses, we used internally-defined standard deviation (SD) cut-offs of 80 for cognitive impairment and 60 for severe cognitive impairment.

In sensitivity analyses, we considered cut-offs for cognitive impairment stratified by age and educational attainment based on normative data from an external population of community-dwelling adults (4). In these sensitivity analyses, the cut-offs for cognitive impairment were 80 for those >8 years of education and 74 for those with 0-8 years of education; likewise, the cut-offs for severe cognitive impairment were 60 for those with >8 years of education and 56 for those with 0-8 years of education or age≥80 in our sensitive analyses. These cut-offs were determined by mapping the normative data of our population to the external population.

Hybrid-augmented Cox Regression

In addition to traditional Cox regression, we used hybrid registry-augmented Cox proportional hazards regression to assess the independent association between cognitive impairment and post-KT graft loss and mortality defined as all-cause graft loss (ACGL) (5, 6). This statistically efficient method brings precisely estimated coefficients from the national registry model into the prospective cohort model. All analyses were stratified by donor type (living or deceased donor).

After calculating the association between the SRTR covariates and ACGL using national registry data, we introduced the national registry model coefficients into a multi-center cohort model using forced values. The Cox regression model for the prospective cohort estimated the coefficients for cognitive impairment and

comorbidities, as measured by the Charlson Comorbidity Index (CCI). Comorbidities are confounders that impact both cognitive impairment and ACGL, but the CCI is not captured in the national registry data (7, 8). Thus, we instead introduce this confounder in the prospective cohort model. The coefficients of theses covariates, other than the CCI, were constrained to be the coefficients from the national registry model, using a model offset. The resulting hybrid registry-augmented model can be expressed as:

$$\log\big(\lambda(t|X)\big) = \log(\lambda_0(t)) + \big(\beta_{impairment}X_{impairment} + \beta_{CCI}X_{CCI} + \beta_p X_p\big) + \varepsilon_{robust}$$

where λ_0 is the baseline hazard function, X_p is a matrix of participant characteristics for identified confounders, and β_p is a matrix of constrained coefficients from the national registry model. To correct for heteroscedastic errors, we calculated robust standard errors (ε_{robust}) using the Eicker-Huber-White sandwich estimator (9, 10).

In our primary analyses, we used Cox proportional hazards regression instead of the statistically efficient hybrid registry-augmented Cox regression. The Cox regression model can be expressed as:

$$\log\big(\lambda(t|X)\big) = \log(\lambda_0(t)) + \big(\beta_{impairment}X_{impairment} + \beta_C X_C\big) + \varepsilon_0$$

where λ_0 is the baseline hazard function, X_C is a matrix of participant characteristics for identified confounders, β_C is a matrix of confounder coefficients, and ε_0 are the standard error.

Unmeasured Confounding

We also report the E-value as a measure of robustness as described by VanderWeele and Ding (11); the E-value is joint minimum strength needed by unmeasured confounders, above and beyond the measured confounders, to explain away the observed relationship between the exposure and the outcome of interest.

Multiple Imputation by Chained Equations

We used multiple imputation by chained equations (MICE) to handle missingness in model covariates. MICE was run separately for deceased donor KT recipients and living donor KT recipients.

For living donor KT recipients, the following variables were imputed with an augmented logit prediction model: recipient dialysis <2 years, recipient college education, 0 HLA mismatch, recipient employed, recipient public insurance, recipient HCV status, recipient HIV status, recipient CMV status, recipient PRA>80, and recipient preemptive transplant. For living donor KT recipients, the following were imputed using predictive mean matching (PMM) with 10 nearest neighbors: recipient BMI, donor BMI, CIT, and donor eGFR. Other covariates included in the MICE prediction models were recipient sex, recipient Black race, recipient Hispanic ethnicity, age (continuous with splines at 35 and 65), donor age (continuous), recipient diabetes, recipient hypertension, blood type incompatible, recipient previous transplant, donor sex, donor Black race, donor Hispanic ethnicity, biological recipient/donor relationship, date of transplant, an indicator of all-cause graft loss, and the Nelson-Aalen estimator of all-cause graft loss cumulative hazard function.

For deceased donor KT recipients, the following variables were imputed with an augmented logit prediction model: recipient dialysis <2 years, recipient college education, recipient employed, recipient public insurance, recipient HCV status, recipient HIV status, recipient CMV status, recipient PRA>80, and recipient preemptive transplant. For living donor KT recipients, the following were imputed using predictive mean matching (PMM) with 10 nearest neighbors: recipient BMI, donor BMI, and CIT. Other covariates included in the MICE prediction models were recipient sex, recipient Black race, recipient Hispanic ethnicity, age (continuous with splines at 35 and 65), donor age (continuous), recipient diabetes, recipient hypertension, recipient previous transplant, KDPI, date of transplant, an indicator of all-cause graft loss, and the Nelson-Aalen estimator of all-cause graft loss cumulative hazard function.

National Registry Population Study Population

KT recipients from the national registry contributed a total of 350,946 person-years at risk. Of the 101,718 KT recipients in the national registry population, 37,446 underwent LDKT and 64,272 underwent DDKT. Median (IQR) recipient age was 53 (42-62) years, median (IQR) BMI was 27.8 (24.1-31.9), median (IQR) time on dialysis prior to KT was 2.3 (0.4-4.8) years, 38.5% were female, 26.2% were African-American, 15.8% were Hispanic, 53.5% were college educated, 33.9% were employed, 64.8% had public insurance, 4.6% were positive for HCV, 26.4% had a history of diabetes, 22.2% had a history of hypertension, 13.8% had a history of previous transplant, and 12.9% had a PRA > 80 at the time of transplant. Median (IQR) donor age was 43 (31-52), median (IQR) BMI was 27.0 (23.7-30.7), 48.2% were female, 12.9% were African-American, and 14.2% were Hispanic. Deceased KT donors had a median (IQR) KDPI of 47.4 (26.2-68.9), and a median (IQR) CIT of 11.1 (1.9-18.9) hours. There were 7.3% recipient-donor pairs with zero HLA mismatches.

Table S1. Risk of mortality for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on the internal study population. Recipients with CI were compared to recipients without CI and recipients with severe CI were compared to recipients without severe CI. The 3MS score cut-offs for cognitive impairment was 80. The 3MS score cut-offs for severe cognitive impairment was 60.

	Cox PH			Hybrid Registry-Augmented Cox PH		
Exposure	**aHR Mortality**	**P value**	**E-value[5]**	**aHR Mortality**	**P-value**	**E-value (95% CI)[5]**
LDKT[1]						
Any CI[2]	$_{0.89}3.29_{12.17}$	0.07	-	$_{\mathbf{1.33}}\mathbf{3.01}_{\mathbf{6.80}}$	<0.01	3.67 (1.73)
Severe CI[3]	$_{0.30}3.00_{30.07}$	0.4	-	$_{0.29}2.65_{24.19}$	0.4	-
DDKT[4]						
Any CI	$_{0.42}0.88_{1.86}$	0.7	-	$_{0.42}0.82_{1.62}$	0.5	-
Severe CI	$_{0.82}2.31_{6.54}$	0.1	-	$_{0.99}2.22_{5.00}$	0.05	-

[1]LDKT Models adjusted for the recipient characteristics (continuous age with knots at 35 and 65, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and Carlson comorbidity index (CCI)), donor characteristics (age, BMI), and transplant characteristics (recipient and donor both male sex, zero HLA mismatches, blood type incompatibility, and date of transplant).

[2]3MS Score<80.

[3]3MS Score<60.

[4]DDKT Models adjusted for CCI and recipient factors (continuous age with knots at 35 and 65, sex, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and CCI), donor factors (KDPI), and transplant factors (CIT and date of transplant).

[5]E-value interpreted as the strength (relative risk) of an unmeasured confounder required to explain away the association between cognitive impairment and ACGL. An E-value of 1 would suggest that no unmeasured confounding is needed to explain away the observed association. Only the lower end of the 95% CI is shown.

Table S2. Risk of death-censored graft failure for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on the internal study population. Recipients with CI were compared to recipients without CI and recipients with severe CI were compared to recipients without severe CI. The 3MS score cut-offs for cognitive impairment was 80. The 3MS score cut-offs for severe cognitive impairment was 60.

	Cox PH			Hybrid Registry-Augmented Cox PH		
Exposure	**aHR DCGF**	**P value**	**E-value[5]**	**aHR DCGF**	**P value**	**E-value (95% CI)[5]**
LDKT[1]						
Any CI[2]	$_{0.57}2.87_{14.53}$	0.2	-	$_{0.71}2.28_{7.30}$	0.2	-
Severe CI[3]	$_{0.50}3.30_{21.63}$	0.2	-	$_{0.49}1.99_{8.11}$	0.3	-
DDKT[4]						
Any CI	$_{0.43}0.84_{1.63}$	0.6	-	$_{0.37}0.89_{2.15}$	0.8	-
Severe CI	$_{\mathbf{1.03}}\mathbf{2.61}_{\mathbf{6.62}}$	0.04	3.67 (1.73)	$_{0.51}2.38_{11.04}$	0.3	-

[1]LDKT Models adjusted for the recipient characteristics (continuous age with knots at 35 and 65, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and Carlson comorbidity index (CCI)), donor characteristics (age, BMI), and transplant characteristics (recipient and donor both male sex, zero HLA mismatches, blood type incompatibility, and date of transplant).

[2]3MS Score<80.

[3]3MS Score<60.

[4]DDKT Models adjusted for CCI and recipient factors (continuous age with knots at 35 and 65, sex, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and CCI), donor factors (KDPI), and transplant factors (CIT and date of transplant).

[5]E-value interpreted as the strength (relative risk) of an unmeasured confounder required to explain away the association between cognitive impairment and ACGL. An E-value of 1 would suggest that no unmeasured confounding is needed to explain away the observed association. Only the lower end of the 95% CI is shown.

Table S3. Risk of all-cause graft loss (ACGL) for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on an external study population. Recipients with CI were compared to recipients without CI and recipients with severe CI were compared to recipients without severe CI. The 3MS score cut-offs for cognitive impairment were 80 for those >8 years of education and 74 for those with 0-8 years of education. The 3MS score cut-offs for severe cognitive impairment were 60 for those with >8 years of education and 56 for those with 0-8 years of education or age≥80

	Cox PH			Hybrid Registry-Augmented Cox PH		
Exposure	**aHR ACGL**	**P value**	**E-value[5]**	**aHR ACGL**	**P value**	**E-value (95% CI)[5]**
LDKT[1]						
Any CI[2]	$_{1.61}$**4.22**$_{11.06}$	<0.01	4.74 (2.13)	$_{1.30}$**2.94**$_{6.64}$	<0.01	3.60 (1.69)
Severe CI[3]	$_{0.96}$3.80$_{14.96}$	0.06	-	$_{0.53}$2.09$_{8.22}$	0.3	-
DDKT[4]						
Any CI	$_{0.43}$0.84$_{1.63}$	0.6	-	$_{0.44}$0.82$_{1.54}$	0.5	-
Severe CI	$_{1.03}$**2.61**$_{6.62}$	0.04	3.27 (1.17)	$_{1.10}$**2.47**$_{5.55}$	0.03	3.13 (1.34)

[1]LDKT Models adjusted for the recipient characteristics (continuous age with knots at 35 and 65, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and Carlson comorbidity index (CCI)), donor characteristics (age, BMI), and transplant characteristics (recipient and donor both male sex, zero HLA mismatches, blood type incompatibility, and date of transplant).

[2]3MS Score<80.

[3]3MS Score<60.

[4]DDKT Models adjusted for CCI and recipient factors (continuous age with knots at 35 and 65, sex, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and CCI), donor factors (KDPI), and transplant factors (CIT and date of transplant).

[5]E-value interpreted as the strength (relative risk) of an unmeasured confounder required to explain away the association between cognitive impairment and ACGL. An E-value of 1 would suggest that no unmeasured confounding is needed to explain away the observed association. Only the lower end of the 95% CI is shown.

Table S4. Risk of mortality for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on an external study population. Recipients with CI were compared to recipients without CI and recipients with severe CI were compared to recipients without severe CI. The 3MS score cut-offs for cognitive impairment were 80 for those >8 years of education and 74 for those with 0-8 years of education. The 3MS score cut-offs for severe cognitive impairment were 60 for those with >8 years of education and 56 for those with 0-8 years of education or age≥80

	Cox PH			Hybrid Registry-Augmented Cox PH		
Exposure	**aHR Mortality**	**P value**	**E-value[5]**	**aHR Mortality**	**P value**	**E-value (95% CI)[5]**
LDKT[1]						
Any CI[2]	$_{0.89}3.29_{12.17}$	0.07	-	$_{\mathbf{1.06}}\mathbf{2.75}_{\mathbf{7.11}}$	0.04	3.41 (1.25)
Severe CI[3]	$_{0.30}3.00_{30.07}$	0.4	-	$_{0.29}2.65_{24.20}$	0.4	-
DDKT[4]			-			
Any CI	$_{0.42}0.88_{1.86}$	0.7	-	$_{0.42}0.82_{1.62}$	0.6	-
Severe CI	$_{0.82}2.31_{6.54}$	0.1	-	$_{\mathbf{1.003}}\mathbf{2.26}_{\mathbf{5.09}}$	0.049	2.90 (1.05)

[1]LDKT Models adjusted for the recipient characteristics (continuous age with knots at 35 and 65, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and Carlson comorbidity index (CCI)), donor characteristics (age, BMI), and transplant characteristics (recipient and donor both male sex, zero HLA mismatches, blood type incompatibility, and date of transplant).

[2]3MS Score<80.

[3]3MS Score<60.

[4]DDKT Models adjusted for CCI and recipient factors (continuous age with knots at 35 and 65, sex, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and CCI), donor factors (KDPI), and transplant factors (CIT and date of transplant).

[5]E-value interpreted as the strength (relative risk) of an unmeasured confounder required to explain away the association between cognitive impairment and ACGL. An E-value of 1 would suggest that no unmeasured confounding is needed to explain away the observed association. Only the lower end of the 95% CI is shown.

Table S5. Risk of death-censored graft failure for kidney transplant recipients with cognitive impairment (CI) using cut-offs based on an external study population. Recipients with CI were compared to recipients without CI and recipients with severe CI were compared to recipients without severe CI. The 3MS score cut-offs for cognitive impairment were 80 for those >8 years of education and 74 for those with 0-8 years of education. The 3MS score cut-offs for severe cognitive impairment were 60 for those with >8 years of education and 56 for those with 0-8 years of education or age≥80

	Cox PH			Hybrid Registry-Augmented Cox PH		
Exposure	**aHR DCGF**	**P value**	**E-value[5]**	**aHR DCGF**	**P value**	**E-value (95% CI)[5]**
LDKT[1]						
Any CI[2]	$_{0.57}2.87_{14.53}$	0.2	-	$_{0.75}2.41_{7.75}$	0.1	-
Severe CI[3]	$_{0.50}3.30_{21.63}$	0.2	-	$_{0.49}1.99_{8.10}$	0.3	-
DDKT[4]						
Any CI	$_{0.43}0.84_{1.63}$	0.6	-	$_{0.44}1.13_{2.89}$	0.8	-
Severe CI	$_{\mathbf{1.03}}\mathbf{2.61}_{\mathbf{6.62}}$	0.04	3.27 (1.17)	$_{0.60}2.80_{13.01}$	0.2	-

[1]LDKT Models adjusted for the recipient characteristics (continuous age with knots at 35 and 65, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and Carlson comorbidity index (CCI)), donor characteristics (age, BMI), and transplant characteristics (recipient and donor both male sex, zero HLA mismatches, blood type incompatibility, and date of transplant).

[2]3MS Score<80.

[3]3MS Score<60.

[4]DDKT Models adjusted for CCI and recipient factors (continuous age with knots at 35 and 65, sex, African-American race, Hispanic ethnicity, years on dialysis, diabetes status, PRA at transplant, college education, BMI, hypertension status, history of transplantation, and CCI), donor factors (KDPI), and transplant factors (CIT and date of transplant).

[5]E-value interpreted as the strength (relative risk) of an unmeasured confounder required to explain away the association between cognitive impairment and ACGL. An E-value of 1 would suggest that no unmeasured confounding is needed to explain away the observed association. Only the lower end of the 95% CI is shown.

Table S6. Risk of ACGL among Living Donor Transplant Recipients in the Registry Population (Step 1 of the Hybrid Registry-Augmented Regression). During the first step of hybrid registry-augmented regression, a full model of all confounders is run against the outcome of ACGL. These coefficients are then brought into the second stage, which is estimated in the prospective cohort, as model offsets.

	aHR ACGL	P Value
Recipient Black Race	$_{1.10}1.21_{1.32}$	<0.001
Recipient Hispanic Ethnicity	$_{0.67}0.74_{0.82}$	<0.001
Recipient Age (by 1 year)	$_{1.00}1.01_{1.01}$	<0.01
Recipient Age<35	$_{1.44}1.66_{1.91}$	<0.001
Recipient Age>65	$_{1.23}1.38_{1.56}$	<0.001
Donor Age (by 1 year)	$_{1.01}1.01_{1.01}$	<0.001
Recipient >2 years on Dialysis	$_{1.12}1.21_{1.31}$	<0.001
Recipient Diabetes	$_{1.41}1.53_{1.66}$	<0.001
Recipient PRA>80	$_{0.95}1.10_{1.27}$	0.2
Recipient College Education	$_{0.82}0.88_{0.94}$	<0.001
Recipient BMI (by 1 Unit)	$_{1.01}1.01_{1.02}$	<0.001
Recipient Hypertension	$_{1.05}1.15_{1.26}$	0.003
0 HLA mismatch	$_{0.54}0.63_{0.74}$	<0.001
Blood Type Incompatible	$_{1.24}1.53_{1.90}$	<0.001
Recipient Previous Transplant	$_{1.22}1.35_{1.49}$	<0.001
Donor BMI (by 1 Unit)	$_{1.00}1.01_{1.02}$	0.03
Both Male	$_{0.85}0.92_{0.99}$	0.03
Transplant Year (by 1 year)	$_{0.91}0.93_{0.95}$	<0.001
Recipient HCV	$_{1.16}1.39_{1.67}$	<0.001
Recipient on Public Insurance	$_{1.11}1.19_{1.29}$	<0.001
Recipient Employed	$_{0.72}0.78_{0.84}$	<0.001

Table S7. Risk of ACGL among Deceased Donor Transplant Recipients in the Registry Population (Step 1 of the Hybrid Registry-Augmented Regression). During the first step of hybrid registry-augmented regression, a full model of all confounders is run against the outcome of ACGL. These coefficients are then brought into the second stage, which is estimated in the prospective cohort, as model offsets.

	aHR ACGL	P Value
Recipient Female	$_{0.86}0.90_{0.93}$	<0.001
Recipient Black Race	$_{1.02}1.07_{1.11}$	<0.001
Recipient Hispanic Ethnicity	$_{0.74}0.78_{0.83}$	<0.001
Recipient Age (by 1 year)	$_{1.01}1.01_{1.01}$	<0.001
Recipient Age<35	$_{1.46}1.60_{1.76}$	<0.001
Recipient Age>65	$_{1.19}1.26_{1.34}$	<0.001
Recipient >2 years on Dialysis	$_{1.19}1.24_{1.30}$	<0.001
Recipient Diabetes	$_{1.31}1.37_{1.44}$	<0.001
Recipient PRA>80	$_{1.07}1.13_{1.20}$	<0.001
Recipient College Education	$_{0.95}0.99_{1.03}$	0.7
Recipient BMI (by 1 unit)	$_{1.01}1.01_{1.01}$	<0.001
Recipient Hypertension	$_{1.08}1.14_{1.20}$	<0.001
Recipient Previous Transplant	$_{1.14}1.22_{1.29}$	<0.001
CIT (by 1 hour)	$_{1.00}1.01_{1.01}$	<0.001
KDPI (by 1 unit)	$_{1.01}1.01_{1.01}$	<0.001
Transplant Year (by 1 year)	$_{0.93}0.94_{0.95}$	<0.001
Recipient HCV	$_{1.20}1.28_{1.38}$	<0.001
Recipient on Public Insurance	$_{1.07}1.12_{1.18}$	<0.001
Recipient Employed	$_{0.76}0.80_{0.84}$	<0.001

REFERENCES

1. Teng E, Chui H. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987;48(8):314-318.

2. McDowell I, Kristjansson B, Hill GB, Hébert R. Community screening for dementia: The Mini Mental State Exam (MMSE) and modified Mini-Mental State Exam (3MS) compared. *J Clin Epidemiol.* 1997;50(4):377-383.

3. Kurella M, Luan J, Yaffe K, Chertow GM. Validation of the Kidney Disease Quality of Life (KDQOL) Cognitive Function subscale. *Kidney International.* 2004;66(6):2361-2367.

4. Tombaugh TN, McDowell I, Kristjansson B, Hubley AM. Mini-Mental State Examination (MMSE) and the modified MMSE (3MS): A psychometric comparison and normative data. *Psychol Assessment*. 1996;8(1):48-59.

5. McAdams-DeMarco MA, King EA, Luo X, Haugen C, DiBrito S, Shaffer A et al. Frailty, Length of Stay, and Mortality in Kidney Transplant Recipients: A National Registry and Prospective Cohort Study. *Ann Surg.* 2016.

6. McAdams-DeMarco MA, Law A, King E, Orandi B, Salter M, Gupta N et al. Frailty and mortality in kidney transplant recipients. *Am J Transplant*. 2015;15(1):149-154.

7. Miskulin D, Martin A, Brown R, Fink N, Coresh J, Powe NR et al. Predicting 1 year mortality in an outpatient haemodialysis population: a comparison of comorbidity instruments. *Nephrol Dial Transplant.* 2004;19(2):413-420.

8. van Manen JG, Korevaar JC, Dekker FW, Boeschoten EW, Bossuyt PMM, Krediet RT. How to adjust for comorbidity in survival studies in ESRD patients: A comparison of different indices. *Am J Kidney Dis.* 2002;40(1):82-89.

9. White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. *Econometrica*. 1980;48(4):817-838.

10. Lin D, Wei L-J. The robst inference for the Cox proportional hazards model. *J Am Stat Assoc.* 1989;84(408):1074-1078.

11. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med*. 2017.