

# Sex differences in COVID-19 mortality risk in patients on kidney function replacement therapy

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# Disclosures



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Unrestricted research grants were obtained from the European Renal Association, The Dutch Kidney Foundation, Baxter, and Sandoz.

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The funding organizations had no role in the design of the study, interpretation of results, or the presentation of findings.

# Background



- In the general population with COVID-19, male sex is an established risk factor for mortality.<sup>1</sup>
- A more robust immune response to COVID-19 in females has been suggested to be one of the factors explaining this sex difference.<sup>2</sup>
- Patients on kidney function replacement therapy (KFRT) have an impaired immune response, especially kidney transplant recipients due to their use of immunosuppressants.
- In this study, we, therefore, examined whether male sex is still a risk factor for mortality among patients on KFRT with COVID-19.

<sup>1</sup>Peckham et al. Nat Commun. 2020; <sup>2</sup>Takahashi et al. Nature 2020

# Study hypotheses and objectives

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## Hypotheses

- Sex differences in the risk of mortality are narrowed or eliminated among kidney transplant recipients
- Sex differences in the risk of mortality may be different among kidney transplant recipients and dialysis patients potentially due to differences in their use of immunosuppressants

## Objectives

- To investigate the association between sex and risk of mortality among kidney transplant recipients and dialysis patients
- To investigate whether the relationship between sex and the risk of mortality differs between kidney transplant recipients and dialysis patients

# Study design



**Data source:** the European Renal Association COVID-19 Database (ERACODA)

- Data voluntarily reported on outpatients and hospitalized patients by physicians responsible for their care
- Data recorded by approximately 225 physicians representing over 140 centers in about 35 countries, mostly in Europe

**Study population:** Adult (age  $\geq 18$  years) kidney transplant recipients and dialysis patients with COVID-19 who presented between February 1<sup>st</sup>, 2020 & April 30<sup>th</sup>, 2021

**Independent variable of interest:** Sex (female/male)

**Outcome:** Three-month mortality

# Statistical analyses

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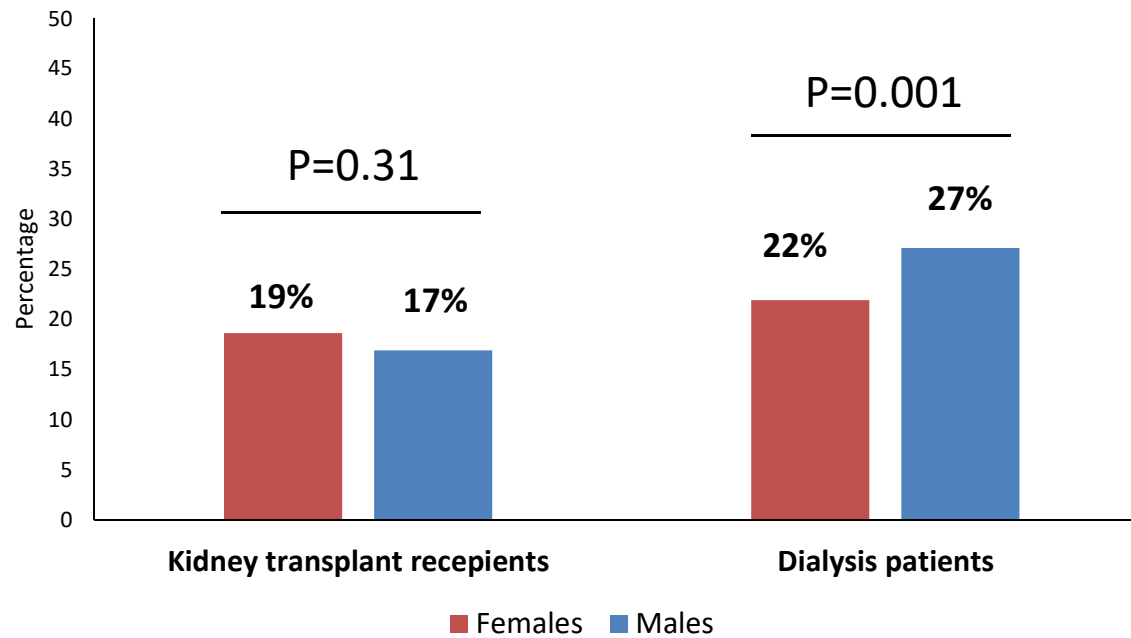
- Multivariable Cox proportional hazards regression
- Interaction investigated between sex and type of renal replacement therapy
- Diagnostic tests performed to investigate proportional hazards assumption

# Baseline characteristics



	Kidney transplant recipients (N=1,204)			Dialysis patients (N=3,206)		
	Female (N=457)	Male (N=747)	p-value	Female (N=1,225)	Male (N=1,981)	p-value
<b>Patient characteristics</b>						
Age, (years)	55.7 (14.1)	56.9 (13.7)	0.16	67.5 (14.6)	67.8 (14.2)	0.67
Clinical frailty scale, AU	3.2 (1.6)	2.8 (1.4)	<0.001	4.2 (1.8)	3.9 (1.8)	<0.001
Comorbidities, n (%)						
Hypertension	352 (77.0)	631 (84.5)	0.001	969 (79.2)	1607 (81.1)	0.18
Diabetes Mellitus	130 (28.6)	249 (33.4)	0.08	494 (40.4)	871 (44.0)	0.04
Coronary artery disease	49 (10.8)	162 (21.7)	<0.001	354 (28.9)	742 (37.6)	<0.001
Immunosuppressants			0.58			
Monotherapy	14 (3.1)	19 (2.6)		-	-	-
Dual therapy	152 (33.6)	232 (31.4)		-	-	-
Triple therapy	286 (63.3)	489 (66.1)		-	-	-
Disease characteristics, n (%)						
Cough	265 (60.2)	438 (61.5)	0.66	471 (47.0)	765 (48.9)	0.36
Shortness of breath	168 (38.1)	297 (41.9)	0.20	318 (31.6)	502 (32.0)	0.81
Fever	281 (63.3)	497 (69.5)	0.03	506 (50.3)	873 (55.6)	0.01
O2 saturation room air, %	94.3 (6.4)	93.9 (6.6)	0.36	94.1 (5.1)	93.7 (5.8)	0.16
Lymphocytes, x1000/ $\mu$ L	0.8 (0.5, 1.3)	0.8 (0.5, 1.3)	0.60	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	0.46
CRP, mg/L	72 (25, 147)	83 (33, 187)	0.05	68 (20, 190)	82 (27, 240)	0.03

# Mortality by sex and type of KFRT



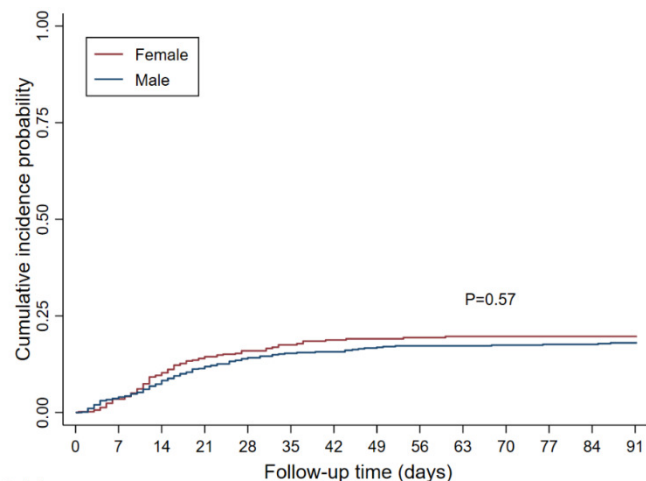


# Cumulative incidence of mortality by sex and type of KFRT



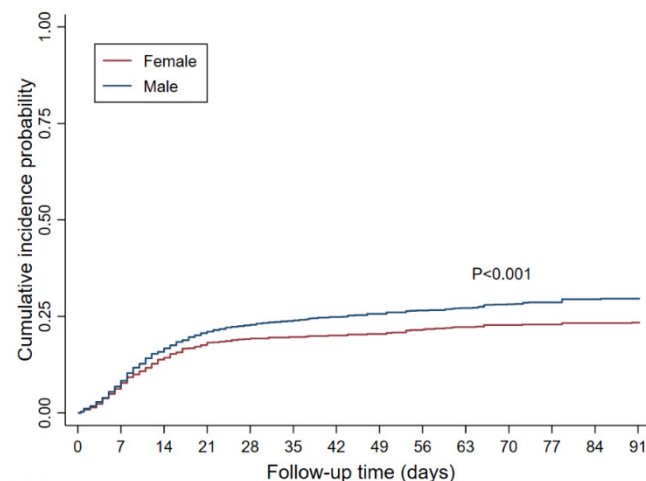
## Kidney transplant recipients

## Dialysis patients



Number at risk

Female	457	441	413	393	384	265	261	260	259	258	258	258	258	258
Male	747	720	692	662	643	441	439	434	431	431	430	429	429	427



Number at risk

Female	1225	1149	1056	1010	991	622	619	616	608	602	598	597	594	593
Male	1981	1846	1668	1572	1532	945	932	922	911	903	891	885	875	873

# Association of sex with mortality by type of KFRT



Presented are hazard ratios (95% Confidence interval)

Transplant recipients (N=1,204)	Females (N=457)	Males (N=747)	p-value
<b>Event, n (%)</b>	<b>85 (18.6)</b>	<b>126 (16.9)</b>	
Model 1	Ref.	0.90 (0.68, 1.18)	0.43
Model 2	Ref.	0.97 (0.73, 1.29)	0.86
Model 3	Ref.	0.96 (0.73, 1.28)	0.80
Model 4	Ref.	0.87 (0.63, 1.19)	0.37
<b>Model 5</b>	<b>Ref.</b>	<b>0.89 (0.65, 1.23)</b>	<b>0.49</b>
Dialysis patients (N=3,206)	Females (N=1,225)	Males (N=1,981)	p-value
<b>Event, n (%)</b>	<b>268 (21.9)</b>	<b>536 (27.1)</b>	
Model 1	Ref.	1.27 (1.10, 1.47)	0.001
Model 2	Ref.	1.41 (1.21, 1.64)	<0.001
Model 3	Ref.	1.40 (1.20, 1.63)	<0.001
Model 4	Ref.	1.32 (1.13, 1.56)	0.001
<b>Model 5</b>	<b>Ref.</b>	<b>1.33 (1.13, 1.56)</b>	<b>0.001</b>

Model 1: crude

Model 2: Model 1 + age (continuous), clinical frailty score (continuous)

Model 3: Model 2 + the reason for COVID-19 screening (symptoms-based screening, positive COVID-19 contact or routine screening)

Model 4: Model 3 + smoking (never, current, former), obesity (yes/no), hypertension (yes/no), diabetes (yes/no), heart failure (yes/no), chronic lung disease (yes/no), coronary artery disease (yes/no), and auto-immune disease (yes/no)

Model 5: Model 4 + duration of kidney function replacement therapy (years) and estimated glomerular filtration rate (continuous)

**(p-for interaction between sex and type of kidney function replacement therapy=0.02 in fully adjusted model for three-month mortality)**

# Association of KFRT type with mortality by sex



Presented are hazard ratio (95% Confidence interval)

Males (N=2,728)	Dialysis patients (N=1,981)	Kidney transplant recipients (N=747)	p-value
<b>Event, n (%)</b>	<b>536 (27.1)</b>	<b>126 (16.9)</b>	
Model 1	Ref.	0.57 (0.47, 0.69)	<0.001
Model 2	Ref.	1.25 (1.01, 1.55)	0.04
Model 3	Ref.	1.19 (0.96, 1.47)	0.13
Model 4	Ref.	1.20 (0.97, 1.50)	0.09
<b>Model 5</b>	<b>Ref.</b>	<b>1.39 (1.02, 1.89)</b>	<b>0.04</b>
Females (N=1,682)	Dialysis patients (N=1,225)	Kidney transplant recipients (N=457)	p-value
<b>Event, n (%)</b>	<b>268 (21.9)</b>	<b>85 (18.6)</b>	
Model 1	Ref.	0.81 (0.63, 1.03)	0.09
Model 2	Ref.	1.63 (1.25, 2.13)	<0.001
Model 3	Ref.	1.54 (1.17, 2.01)	0.002
Model 4	Ref.	1.64 (1.24, 2.17)	0.001
<b>Model 5</b>	<b>Ref.</b>	<b>2.04 (1.40, 2.97)</b>	<b>&lt;0.001</b>

Model 1: crude

Model 2: Model 1 + age (continuous), clinical frailty score (continuous)

Model 3: Model 2 + the reason for COVID-19 screening (symptoms-based screening, positive COVID-19 contact or routine screening)

Model 4: Model 3 + smoking (never, current, former), obesity (yes/no), hypertension (yes/no), diabetes (yes/no), heart failure (yes/no), chronic lung disease (yes/no), coronary artery disease (yes/no), and auto-immune disease (yes/no)

Model 5: Model 4 + duration of kidney function replacement therapy (years) and estimated glomerular filtration rate (continuous)

(p-for interaction between type of kidney function replacement therapy and sex=0.02 in fully adjusted model for three-month mortality)

# Conclusions

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- Among patients on KFRT with COVID-19
  - male sex is not a risk factor for mortality in kidney transplant recipients
  - but remains a risk factor in dialysis patients
- The use of immunosuppressants in kidney transplant recipients
  - may have contributed to a narrowed difference in the immune response to COVID-19 between males and females
  - whereby especially females may have suffered from the deleterious effect of transplantation related immunosuppression

# Acknowledgement



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We thank all contributors for entering information in the ERACODA database and for their participation. We especially thank all healthcare workers that have taken care of the included COVID-19 patients.

# Thank you



For information about ERACODA visit: [www.eracoda.org](http://www.eracoda.org)

