SEX AND GENDER DIFFERENCES IN CKD EPIDEMIOLOGY

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Transplant Nephrologist, Westmead Hospital, Sydney Australia
DISCLOSURES

• None
Overview

• Life course approach to sex/gender differences in CKD
• Prevalence of CKD
• Prevalence of kidney failure
• Access to kidney care
• Outcomes of patients with CKD and kidney failure
• Impact of COVID-19
LIFE COURSE APPROACH TO SEX/GENDER DIFFERENCES IN CKD

• Critical stages, transitions, and settings where large differences can be made in promoting or restoring health and wellbeing.

• Understand that there are differences in factors that contribute to the gender differences/disparities over the life span

• Changing policies, societal norms, and the environment can affect the life course trajectory of the sex/gender differences over time
LIFE STAGES

Potential effect modifier and risk factor

A
Female sex
XX

B
Random X chromosome inactivation and escape

C
Testicular testosterone surge
Epigenetic programming of male cells

1 Pre-conception
2 Infancy
3 Childhood
4 Adolescence
5 Young adults
6 Middle age
7 Older adults

Chronic Kidney Disease (CKD)
Sex and gender

**GENDER**
Socially-constructed roles, behaviours, expressions and identities of girls, women, boys, men and gender-diverse people.

**SEX**
Biological attributes of humans and animals, including physical features, chromosomes, gene expression, hormones and anatomy.
Children and adolescents
Prevalence of CKD in children

- Boys have a higher prevalence of CKD compared to girls, largely due to congenital urinary tract disorders.
- Boys also have a higher prevalence of bed-wetting than girls.
- Girls have a higher preponderance of autoimmune-related glomerular disease such as Lupus.
- Boys are more likely to have advanced stage CKD (KRT and non-KRT dependent).
Advanced chronic kidney disease among UK children


Table 1: Demographic and clinical characteristics of UK children with advanced CKD, stratified by KRT status (n=1260)

<table>
<thead>
<tr>
<th>Variable</th>
<th>CKD (not KRT) cohort</th>
<th>KRT cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–&lt;16 years (N=199)</td>
<td>0–&lt;16 years (N=832)</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>128</td>
<td>64.3</td>
</tr>
<tr>
<td>Age band (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>57</td>
<td>28.6</td>
</tr>
<tr>
<td>6–10</td>
<td>60</td>
<td>30.2</td>
</tr>
<tr>
<td>11–15</td>
<td>82</td>
<td>41.2</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>114</td>
<td>57.3</td>
</tr>
<tr>
<td>Asian</td>
<td>47</td>
<td>23.6</td>
</tr>
<tr>
<td>Black</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>8.5</td>
</tr>
<tr>
<td>Missing</td>
<td>12</td>
<td>6.0</td>
</tr>
<tr>
<td>Area-level deprivation quintile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1—least deprived</td>
<td>25</td>
<td>12.6</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>15.1</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>17.1</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>23.1</td>
</tr>
<tr>
<td>5—most deprived</td>
<td>61</td>
<td>30.7</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Sex and Glomerular Filtration Rate Trajectories in Children

Stéphanie Bonnéric,1 Geeta Karadkhele,2 Cécile Couchoud,3 Rachel E. Patzer,2,4 Larry A. Greenbaum5, and Julien Hogan1,2

CJASN 15: 320–329, March, 2020

Table 4. Adjusted associations of clinical characteristics with eGFR trajectory groups in patients with glomerular and nonglomerular primary kidney diseases

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Nonglomerular Diseasesa</th>
<th>Glomerular Diseasesb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) of Moderate eGFR Decline</td>
<td>OR (95% CI) of Rapid eGFR Decline</td>
</tr>
<tr>
<td>Age (per 1-yr increase)</td>
<td>1.01 (0.97 to 1.05)</td>
<td>0.99 (0.82 to 1.20)</td>
</tr>
<tr>
<td>Male sex (versus female)</td>
<td>1.20 (1.00 to 1.44)</td>
<td>2.08 (0.70 to 6.20)</td>
</tr>
<tr>
<td>Baseline GFR (per 10 ml/min per 1.73 m² increase)</td>
<td>1.08 (0.97 to 1.18)</td>
<td>1.51 (1.10 to 1.92)</td>
</tr>
<tr>
<td>Urine protein-creatinine ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>0.5–2</td>
<td>0.96 (0.62 to 1.48)</td>
<td>n/a</td>
</tr>
<tr>
<td>≥2</td>
<td>1.89 (1.09 to 3.28)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

OR, odds ratio; n/a, not applicable.
aReference group for nonglomerular diseases: slow eGFR decline group.
bReference group for glomerular diseases: moderate eGFR decline group.
Sex-based differences in access to KRT care in children with kidney failure

Female gender was associated with a slower access to transplantation compared with male gender (HR 0.88, 95% confidence interval [CI] 0.83–0.94) after adjustment for age.
Also less likely to receive pre-emptive transplant …

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Univariate analysis</th>
<th>Multivariate analysis I</th>
<th>Multivariate analysis II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)^1</td>
<td>OR (95% CI)^2</td>
</tr>
<tr>
<td>Overall population</td>
<td>0.70 (0.61–0.79)</td>
<td>0.64 (0.56–0.73)</td>
<td>0.77 (0.66–0.88)</td>
</tr>
<tr>
<td>Age at RRT (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 &lt; 1</td>
<td>1.82 (0.36–9.22)</td>
<td>—</td>
<td>1.38 (0.24–7.83)</td>
</tr>
<tr>
<td>1 &lt; 2</td>
<td>0.38 (0.15–0.97)</td>
<td>—</td>
<td>0.54 (0.21–1.45)</td>
</tr>
<tr>
<td>2 &lt; 6</td>
<td>0.49 (0.34–0.71)</td>
<td>—</td>
<td>0.66 (0.45–0.97)</td>
</tr>
<tr>
<td>6 &lt; 10</td>
<td>0.45 (0.32–0.61)</td>
<td>—</td>
<td>0.62 (0.45–0.86)</td>
</tr>
<tr>
<td>10 &lt; 14</td>
<td>0.77 (0.60–0.98)</td>
<td>—</td>
<td>0.80 (0.63–1.01)</td>
</tr>
<tr>
<td>&gt;14</td>
<td>0.77 (0.61–0.97)</td>
<td>—</td>
<td>0.86 (0.68–1.09)</td>
</tr>
<tr>
<td>Type of donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased donor</td>
<td>0.63 (0.50–0.79)</td>
<td>0.59 (0.47–0.74)</td>
<td>0.71 (0.56–0.90)</td>
</tr>
<tr>
<td>Living donor</td>
<td>0.70 (0.56–0.87)</td>
<td>0.65 (0.52–0.82)</td>
<td>0.73 (0.58–0.93)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.59 (0.42–0.84)</td>
<td>0.57 (0.40–0.81)</td>
<td>0.72 (0.49–1.06)</td>
</tr>
</tbody>
</table>
Similar patterns are observed in India.
But not in Australia and New Zealand
Sex-based differences in cardiovascular outcomes among children treated with KRT

Findings from 4C-T Study demonstrate an increased cardiovascular burden in girls with end stage kidney disease and kidney transplantation


Kidney International (2022) 101, 585–596;
• Interaction with time, sex and PWVz was observed for girls with CKD.

• Girls in general have higher PYVz scores across all stages of CKD, compared with boys.

• Girls were more likely to experience higher PWVz scores in the pre-KRT, KRT and post-transplant over time. However, the slope of incline appears to decrease post transplant.

• This interactive effect with time was not observed in boys except post transplant.
Sex based differences in quality of life outcomes in children with CKD

Longitudinal assessment of the health-related quality of life of children and adolescents with chronic kidney disease

Table 1 | Mixed model for MAU scores with interaction term between baseline CKD stage and follow-up time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.77</td>
<td>0.68 to 0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time (per year of follow-up)</td>
<td>0.001</td>
<td>-0.01 to 0.02</td>
<td>0.93</td>
</tr>
<tr>
<td>Male</td>
<td>0.07</td>
<td>0.01 to 0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>CKD stage (ref: transplant)</td>
<td>-0.02</td>
<td>-0.08 to 0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Dialysis</td>
<td>-0.14</td>
<td>-0.25 to -0.03</td>
<td></td>
</tr>
<tr>
<td>Global SES index, quartile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ref: SES quartile 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (lowest)</td>
<td>-0.13</td>
<td>-0.22 to -0.05</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-0.07</td>
<td>-0.15 to 0.01</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-0.05</td>
<td>-0.13 to 0.03</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (ref: Caucasian)</td>
<td>-0.02</td>
<td>-0.08 to 0.04</td>
<td>0.52</td>
</tr>
<tr>
<td>Time* CKD stage</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Effect of time of follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>on:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant</td>
<td>ref</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Stages 1–5</td>
<td>-0.003</td>
<td>-0.02 to 0.02</td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.05</td>
<td>0.02 to 0.09</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; CKD, chronic kidney disease; MAU, multi-attributive utility; ref, referent; SES, socioeconomic status.

*All the CKD stages are at baseline; e.g., the interaction term of time with the dialysis cohort (time*dialysis) refers to the baseline dialysis cohort.
Sex-based differences in post-transplant outcomes

Association of Sex with Risk of Kidney Graft Failure Differs by Age

Fanny Lepeytre,1 Mourad Dafihou,1 Xun Zhang,1 Julie Boucquemont,1 Ruth Sepi-Pichhadze,6 Heloise Cardinal,6 and Bethany J. Foster11


- Three-way interactions between donor sex, recipient sex and recipient age.

- If the donor is male, a higher risk of death-censored allograft loss was observed in younger female transplant recipients. This association was not observed in older female recipients.

- This relationship attenuates when the donor is female.
Differences in kidney graft survival by recipient sex vary by recipient age and by donor-sex


<table>
<thead>
<tr>
<th>SRTR: Scientific Registry of Transplant Recipients (USA)</th>
<th>N=231,673</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTS: The Collaborative Transplant Study (Europe/International)</td>
<td>N=193,530</td>
</tr>
<tr>
<td>ANZDATA: Australia and New Zealand Dialysis and Transplant Registry (Australia/New Zealand)</td>
<td>N=13,382</td>
</tr>
</tbody>
</table>

Multivariable Cox regression analyses in each cohort separately

Individual Patient Data Meta-Analysis: Relative hazards of death-censored graft loss in Female versus Male Kidney Transplant Recipients

When the donor was male, young female recipients had a ↑ risk of graft loss than young males.

Older female recipients had a ↓ risk of graft loss than males of the same age.

Conclusion: The association between recipient sex and death-censored graft loss is modified by donor sex and recipient age.

Vinson AJ et al. Transplantation. Dec 2021 @TransplantJrnl

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Adulthood

ADULTHOOD DEVELOPMENT
Classification of Adulthood

- Early Adulthood
  - 18-40 years

- Middle Adulthood
  - 41-60 years

- Late Adulthood or Old Age
  - 61 years & extends until death
Prevalence of CKD in adulthood

Sex and gender differences in chronic kidney disease and access to care around the globe

Guillermo Garcia Garcia, MD, Arpana lyengar, MD, FPN, FRCP, Francois Kaze, MD, Clara Kierans, PhD, Cesar Padilla-Altamir, PhD, and Valerie A. Luyckx, MD, MSc, PhD.
Prevalence of kidney failure
Sex-Specific Differences in Mortality and Incident Dialysis in the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps)

**Cohort** | At baseline | On follow-up (2.57 yr) hazard ratio in Men vs Women
--- | --- | ---
CKDopps | eGFR (ml/min/1.73m²) |
N = 8237
| **Men** |
| | **28.9 ± 11.5** |

| **Women** |
| | **27.0 ± 10.8** |

- ** CKD stage 3-5 |

| Dialysis initiation | aHR [95% CI] | **1.50 [1.25 – 1.80]** |
| Transplantation | aHR [95% CI] | **1.53 [0.79 – 2.94]** |
| Pre - KRT death | aHR [95% CI] | **1.15 [0.93 – 1.42]** |

**Conclusion** Men had a higher probability of commencing dialysis before death, unexplained by CKD progression alone. Although the causal mechanisms are uncertain, this finding helps interpret the preponderance of men in the dialysis population.
Nephrologists’ Perspectives on Gender Disparities in Chronic Kidney Disease and Dialysis

Cohort and Methods
- 51 nephrologists (55% women)
- 22 Countries
- October-2019 to April-2020

Semi-structured interviews conducted

Suggestions to address gender disparity
- Empowerment in decision-making
- Patient awareness and education
- Accountability
- Unconscious bias in clinicians
- Access to clinics, communication
- Financial support

Results
6 Themes regarding CKD patients
- Vigilance and self-reliance (women)
- Protecting masculinity (men)
- Stereotyping, stigma and Judgement (women)
- Decisional power and Ownership (men and women)
- Primary commitment to Caregiving (women)
- Inequities compounded by social disadvantage

Barriers to care for women
- Less social security
- Limited literacy
- Entrenched Discrimination
- Vulnerability
- Financial and transport barrier

Conclusion: Nephrologists perceived that women with CKD faced many challenges in accessing care related to social norms and roles of caregiving responsibilities, disempowerment, lack of support, stereotyping by clinicians, and entrenched social and economic disadvantage. Addressing power differences, challenging systemic patriarchy, and managing unconscious bias may help to improve equitable care and outcomes for all people with CKD.

Tong A et al, 2022

Visual abstract by Priti Meena M.D. @Priti899
Male/female ratio and the prevalence rate of kidney transplantation by countries
Gender disparity in Asia-Pacific

Meeting Report: First State of the Art Meeting on Gender Disparity in Kidney Transplantation in the Asia-Pacific

Yurmi Kim, MD,1 Ejaz Ahmed, MD,2 Nancy Ascher, MD, PhD,3 Romina Danguilian, MD,4 Lai Seong Hooi, MBBS,5 Ni Made Hustrini, MD,6 Yeong Hoong Kim, MD,7 Vivek Kute, MD,8 Rose Marie O. Rosete-Liquete, MD,9 Maggie Ma, MD,10 Roslyn B. Mannion, MD, PhD,11 Yuki Nakagawa, MD,12,13 Lkhagvkhuy Od-Erdene, MD,13 Vasanthi Ramesh, MD,14 Harun Ur Rashid, MD,15 Sobhana Thangaraju, MD,16 Khin Thida Thwin, MD,17 Anantharaman Vathsala, BS, MD,18 Lori West, MD, PhD,19 Khin Khin Win, MD,20 Curie Ahn, MD, PhD,21 and Germaine Wong, MBBS, PhD22,23
Gender disparity in living donor kidney transplantation in the Asia-Pacific region

Majority of living donors are females.
Less than 30% of all living donor kidney transplant recipients were women.
Global pattern

An analysis by the European Committee on Organ Transplantation of the Council of Europe outlining the international landscape of donors and recipients sex in solid organ transplantation

Background:
The European Committee on Organ Transplantation (CD-P-TO) has committed itself to strive to avoid gender inequities in transplantation.

As a first step, we analyzed the distribution by sex among organ donors and recipients in CD-P-TO Member States, observer countries and other States.

Methods:
Data on the sex of solid organ donors and recipients were collected through the national focal points designated by the Ministries of Health at each country. Two data controllers performed QC and data analysis.

Results:

**Donors**
- Deceased Donors
  - Male: 70%
  - Female: 30%
- Living Donors
  - Male: 30%
  - Female: 70%

**Recipients**
- Deceased Donors
  - Male: 60%
  - Female: 40%
- Living Donors
  - Male: 70%
  - Female: 30%

- **Men** are the prevalent source of deceased donors
- **Women** are the leading source of organs from living donors
- **Most recovered organs are transplanted into men**

Conclusions:
This analysis is an initial step to document differences in donation and transplantation activity among men and women in the CD-P-TO Member States, observer countries and other States.

The collection of data allowing analyses disaggregated by sex represents an important step that may uncover unexpected imbalances, pave the way to more refined investigations on the subject and, where relevant, ultimately act as a trigger for the adaption of national policies.

doi: 10.3389/ti.2022.10322
Barriers and facilitators to living donation

Gender disparity in living kidney donation

- 2/3 of all living kidney donors are female
- Gender disparity reversed in countries where legalised paid donation occurs
- Driven by spousal donation
- Driven by parental donation

Eswari Vilayur
Barriers to kidney donation among men

**Socioeconomic**
- Fear of loss of income post donation
- Lack of insurance

**Biological**
- Pregnancy-induced sensitisation
- Co-morbidities

**Behavioural**
- Perceived risk of donation
- Self sacrificing nature of women
Sex-differences in mortality in patients with kidney failure

Sex differences in mortality among binational cohort of people with chronic kidney disease: population based data linkage study

Nicole L De La Mata,1 Brenda Rosales,1 Grace MacLeod,2,3 Patrick J Kelly,1 Philip Masson,4 Rachael L Morton,5 Kate Wyburn,3,6 Angela C Webster1,7
Sex Disparity in Cause-Specific and All-Cause Mortality Among Incident Dialysis Patients

Wai H. Lim, Jenny H.C. Chen, Kimberley Minas, David W. Johnson, Maleeka Ladhani, Esther Ooi, Neil Boudville, Carmel Hawley, Andrea K. Vecelli, Matthew Roberts, Kate Wyburn, Rachael Walker, Monique Borlace, Helen Pilmore, Christopher E. Davies, Charmaine E. Lok, Armando Teixeira-Pinto, and Germaine Wong
Sex and organ-specific risk of major adverse renal or cardiac events in solid organ transplant recipients with COVID-19

Amanda J. Vinson | Ran Dai | Gaurav Agarwal | Alfred J. Anzalone | Stephen B. Lee | Evan French | Amy L. Olex | Vithal Madhira | Roslyn B. Mannon | National COVID Cohort Collaborative (N3C) Consortium

<table>
<thead>
<tr>
<th>SOT</th>
<th>MARCE</th>
<th>Mortality</th>
<th>MACE</th>
<th>AKI</th>
<th>Severe COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.89</td>
<td>0.77</td>
<td>0.85</td>
<td>0.90</td>
<td>(OR) 1.00</td>
</tr>
<tr>
<td>95% CI</td>
<td>[0.81, 0.98]</td>
<td>[0.66, 0.90]</td>
<td>[0.72, 1.01]</td>
<td>[0.81, 1.00]</td>
<td>[0.98, 1.01]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-SOT</th>
<th>MARCE</th>
<th>Mortality</th>
<th>MACE</th>
<th>AKI</th>
<th>Severe COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.61</td>
<td>0.59</td>
<td>0.68</td>
<td>0.59</td>
<td>(OR) 0.78</td>
</tr>
<tr>
<td>95% CI</td>
<td>[0.60, 0.62]</td>
<td>[0.58, 0.61]</td>
<td>[0.66, 0.70]</td>
<td>[0.57, 0.60]</td>
<td>[0.77, 0.79]</td>
</tr>
</tbody>
</table>
Summary

• Prevalence of **CKD is higher in boys than girls**, but **reverse** when they reach **adulthood**

• Prevalence of **men receiving KRT is higher than women**

• Sex disparity in access to KRT care in both dialysis and transplant globally

• **Inequity in access to KRT care** for girls and women are **most marked in lower to middle income countries**

• Compared to boys, girls are at greater risk of CKD progression, CVD disease, lower quality of life

• **Females on KRT** appears to have **very high standardised mortality ratios**

• **Females on dialysis** may have a **higher risk of death** compared to males within the first 5 years of dialysis initiation, attributed to infections-related death and withdrawal

• Recipient sex, donor sex, and recipient age interactions for allograft loss are observed.
Thank you

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