

# Sex differences in vital organ support in Critically Ill Patients in Australia and New Zealand.

## Protocol and Statistical Analysis Plan

Lucy Modra<sup>1,2</sup>, Alisa Higgins<sup>3</sup>, David Pilcher<sup>3,4,5</sup>, Michael Bailey<sup>3</sup>, Rinaldo Bellomo<sup>1,2,3,6</sup>

### Author affiliations

1. Intensive Care Unit, Austin Health, Melbourne, Australia.
2. Department of Critical Care, University of Melbourne, Melbourne, Australia
3. Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne Australia
4. Intensive Care Unit, Alfred Health, Melbourne, Australia
5. The Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcome and Resource Evaluation, Camberwell Road, Camberwell, Melbourne, Australia
6. Department of Intensive Care Medicine, Royal Melbourne Hospital, Melbourne, Australia

### Study question:

Do critically ill men and women admitted to the intensive care unit (ICU) receive the same vital organ support, specifically invasive and non-invasive ventilation, renal replacement therapy, extra-corporeal membrane oxygenation and vasoactive medication?

### Objectives

#### *Primary objective*

- To quantify sex differences in use of invasive mechanical ventilation in ICU

#### *Secondary objectives:*

- To quantify sex differences in the use of
  - Non-invasive ventilation (NIV)
  - Use of vasoactive medication
  - Use of renal replacement therapy (RRT)
  - Use of extra corporeal membrane oxygenation (ECMO)
  - Any one of the above organ supports
- To describes differential impact of mortality by sex of different organ supports
- To describe sex differences in vital organ support across diagnostic groups and illness severity

### Hypothesis:

#### *Primary outcome:*

Women are less likely to receive invasive mechanical ventilation than men, after adjusting for illness severity, diagnosis, limitation of medical treatment (LOMT), year of admission and hospital site.

#### *Secondary outcome:*

Women are less likely to receive the following vital organ supports than men, after adjustment

- Non-invasive ventilation
- Vasoactive medication

- Renal replacement therapy
- ECMO
- Any one of above listed organ supports

### Population

- Patients aged 18 years and over admitted to ICU in Australia and New Zealand (ANZ) recorded in Centre for Outcomes and Resource Evaluation Adult Patient Database (CORE APD) between 2018-2021
- Exclusions:
  - patients aged under 18
  - patients identified as intersex
  - repeat ICU admissions from within the same hospital visit
  - transferred to another ICU or still in ICU
  - admitted to ICU for palliative care or potential organ donation
  - missing sex, use of invasive ventilation or LoMT

### Definition of exposure and comparator: sex

Sex, as recorded in hospital records and transcribed into APD.

- Male
- Female

Intersex/indeterminate excluded due to small and possibly non-representative numbers (<0.001% patients in APD per year), therefore explore in dedicated paper.

### Statistical analysis

compare women to men throughout

$\chi^2$  - test for categorical variables and t-test for continuous variables

Report 99% CI throughout, set alpha at 0.01/p<0.01 statistically significant.

Report counts and percentages, mean and SD for normally distributed data

No assumptions made about missing data- provide denominators for women, men and total for each organ support examined (complete case analysis)

### *Basic descriptive analysis (table 1)*

Age

Illness severity score

Emergency vs elective ICU admission

ICU length of stay

LoMT

Admission diagnosis

### *Primary objective: sex differences in provision of mechanical ventilation*

Logistic regression for the provision of mechanical ventilation, adjusting for variables:

- Sex: (*primary reported variable*)
  - Men (reference)
  - Women
- APACHE III risk of death (continuous) which includes:
  - APACHE III score
  - Admission diagnosis
- LOMT (categorical)
- Year of admission (continuous)
- Hospital site (categorical)

### *Secondary objectives:*

Logistic regression repeated for the provision of each individual organ support, and the provision of any one vital organ support, adjusted for same variables.

Logistic regression for hospital mortality, adjusted for same variables.

Logistic regression for hospital mortality, stratified by the provision of organ support. That is, repeat regression models for hospital mortality separately for the group who did receive the organ support and the group did not receive the organ support.

### Subgroup analysis:

#### *Diagnostic categories*

Defined using ANZICS CORE modification of APACHE-III-j admission diagnoses<sup>1</sup>

- Cardiovascular diagnoses (excluding cardiac surgery)
- Cardiac surgery: coronary artery bypass surgery and valve surgery
- Respiratory
- Gastro-intestinal
- Neurological
- Trauma
- Sepsis
- Haematological, renal, metabolic, endocrine and genitourinary.
- Musculoskeletal, soft tissue and skin.

#### *Illness severity*

Higher and lower quantiles of APACHE III score, defined as above and below median APACHE III score

### Sensitivity analyses

1. Excluding all patients invasively ventilated on day one
2. Excluding COVID-19 pandemic years 2020 and 2021

### References

1. ANZICS Centre for Outcomes and Resource Evaluation. Adult Patient Database Data Dictionary 2022. <https://www.anzics.com.au/wp-content/uploads/2018/08/ANZICS-APD-Programmers-Data-Dictionary.pdf> (accessed 2.11.2022).