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Short title: Epidemiology of renal replacement therapy in the intensive care unit

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Abstract

Introduction: Acute kidney injury (AKI) requiring treatment with renal replacement therapy (RRT) is a common complication after admission to an intensive care unit (ICU) and is associated with significant morbidity and mortality. However, the prevalence of RRT use and the associated outcomes in critically patients across the globe are not well described. Therefore, we describe the epidemiology and outcomes of patients receiving RRT for AKI in ICUs across several large health system jurisdictions.

Methods: Retrospective cohort analysis using nationally representative and comparable databases from seven health jurisdictions in Australia, Brazil, Canada, Denmark, New Zealand, Scotland, and the United States (USA) between 2006-2023, depending on data availability of each dataset. Patients with history of end-stage kidney disease receiving chronic RRT and patients with a history of renal transplant were excluded.

Results: A total of 4,104,480 patients in the ICU cohort and 3,520,516 patients in the mechanical ventilation cohort were included. Overall, 156,403 (3.8%) patients in the ICU cohort and 240,824 (6.8%) patients in the mechanical ventilation cohort were treated with RRT for AKI. In the ICU cohort, the proportion of patients treated with RRT was lowest in Australia and Brazil (3.3%) and highest in Scotland (9.2%). The in-hospital mortality for critically ill patients treated with RRT was almost four-fold higher (57.1%) than those not receiving RRT (16.8%). The mortality of patients treated with RRT varied across the health jurisdictions from 37-65%.

Conclusion: The outcomes of patients who receive RRT in ICUs throughout the world vary widely. Our research suggests differences in access to and provision of this therapy are contributing factors.

Introduction

Acute kidney injury (AKI) is a common complication after intensive care unit (ICU) admission occurring in approximately 50% of all patients [1]. AKI is associated with significant increased short and long-term morbidity, mortality, hospital readmission rates, cardiovascular events, incidence of chronic kidney disease, as well as significant costs and resource utilization [2–5]. Up to 20% of patients admitted to the ICU will receive renal replacement therapy (RRT) for AKI within the first week of ICU admission [6].

Access to RRT globally is highly variable, especially when comparing high-income countries (HIC) to low and middle income countries (LMIC) [7–9]. In a global survey of the availability and accessibility of RRT for end stage kidney disease, the country income status, the number of nephrologists, and healthcare finance methods were key variables contributing to disparities in the utilization of RRT [10]. Current evidence suggests that RRT use may be increasing. In Ontario, Canada, RRT use in critically ill patients increased from 0.8% in 1996 to 3.0% in 2010 [11]. Similarly, in the US, the incidence of RRT for AKI in non-critically ill patients more than doubled between 2000 and 2009 from 222 to 533 cases per million person-years [12]. More recent data from the AKI-EPI multinational study found that RRT was initiated in 13.5% of critically ill patients compared to 4.3% from a study conducted a decade prior [6,13]. Reasons for this increase are complex and may be attributed to an increased incidence of AKI, changes in the demographics of critically ill patients such as an aging population, and an increased severity of illness within the critically ill population [14–17].

The historical and current utilization of and outcomes from RRT in ICU patients across the globe is not well understood. The purpose of this study is to describe the geographical and temporal variation in the outcomes of critically ill patients treated with RRT across several large health systems in four continents.

Methods

Study design and databases

This study is a retrospective cohort analysis of data from seven different health jurisdictions using six ICU datasets representing four continents during the years 2006-2021, depending on data availability. This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement [18]. Patient consent was not required as this study was based on publicly available data

1) Australia (AUS) and New Zealand (NZ): The Australia New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD), a binational clinical quality registry dataset that captures 98% of ICUs in Australia and 67% of ICUs in New Zealand, between the years 2018-2021 was used [19].
2) Brazil (BRA-EPI): The Brazilian Epimed Monitor ICU Database, a large, cloud based, private, national ICU registry which currently captures approximately 50% of Brazilian Adult ICUs was used for the Brazil data. This database is not representative of the entire Brazilian ICU population. Data between the years 2010-2021 were used [20]. Aggregated de-identified data was utilized for this analysis.
3) Canada (CAN-AB): The Alberta Health Services eCritical Alberta Database, a provincial administrative database for ICU patients, between the years 2015-2021 was used [21]. This data is only representative of the ICU patients in Alberta, Canada, and cannot be generalized to the entire Canadian population.
4) Denmark (DNK): The Danish National Patient Registry, a national administrative database capturing data from all hospitals and ICUs in the country, between the years 2006-2023 was used. This registry is also the data source for the Danish Intensive Care Database (DID), a clinical quality database [22]. The study was registered at Aarhus University.
5) Scotland (SCT): The Scottish Intensive Care Society Audit Group (SICSAG) database, which captures 100% of general adult ICU activity in Scotland, between the years 2006-2021 was used [23].

6) United States of America (USA): The Nationwide Inpatient Sample (NIS), a federal all-payer administrative database, which captures approximately 20% of all US hospitalizations, between the years 2006-2019 was used for the US data [24]. The NIS data is publicly available and de-identified.

Cohort selection

Two cohorts of patients were included in the analysis and stratified by use of RRT (Supplemental Fig. 1). The first cohort included all patients ≥18 years of age who were admitted to an ICU. Due to limitations with the database coding pertaining to identifying ICU admissions in the USA NIS database, this cohort was not collected for the USA patients. The second cohort was a subset of the critically ill patients and included only those who received invasive mechanical ventilation. Patients from the USA NIS database were included in this invasive mechanical ventilation cohort only. Patients receiving RRT were identified for each cohort. Exclusion criteria were 1) patients with a history of renal transplant and 2) patients with end stage kidney disease (ESKD) requiring chronic renal replacement therapy. We identified patients meeting the exclusion criteria using the International Classification of Disease Codes version 9 and 10 codes for ESKD (ICD-9 58.56 and ICD-10 N18.6), renal transplant (ICD-9 99681, V421, 5561, 5569 and ICD-10 Z94.0 and T4861) and the Acute Physiology and Chronic Health Evaluation (APACHE) definition for ESKD on chronic dialysis. In the DID, in addition to the ICD-10 codes for renal transplant, we also used the Danish procedure code for chronic dialysis (BJFD2) and the Nordic Medico-Statistical Committee (NOMESCO) code for kidney transplantation (KKAS).

Variables

For each dataset, a baseline set of the following common characteristics was collected: age, sex, ICU and hospital mortality, ICU, and hospital length of stay. At least one of the following Illness Severity Scores or comorbidity indices were collected for each dataset based on data availability: Charlson comorbidity index, Acute Physiology and Chronic Health Evaluation (APACHE) II or III/IV scores and/or Sequential Organ Failure Assessment (SOFA) score.

Outcomes

The primary outcomes of interest were prevalence of RRT use and in-hospital mortality. Additional outcomes were ICU mortality, hospital mortality, ICU length of stay and hospital length of stay. For the DNK data, patients who died and did not have a discharge date from the ICU were assumed to have died in the ICU.

Statistical Analysis

Summarized data was obtained from each of the datasets. The median and interquartile range (IQR) were used for analysis of the baseline characteristics and outcomes of numerical variables given non-normal distribution of results. Comparisons between the datasets could not reliably be performed due to wide discrepancies in the collection, reporting and years of study of the data. Data privacy restrictions prohibited the use of aggregate statistical modeling and analyses.

Results

Over the study period from 2006-2023, a total of 4,104,480 critically ill patients in six health jurisdictions (AUS, BRA-EPI, CAN-AB, DNK, NZ, SCT) were included in the ICU cohort, of whom 156,403 (3.8%) patients were treated with RRT. The proportion of patients treated with RRT from lowest to highest use was 3.3% in AUS and BRA-EPI, 4.4% in NZ, 5.2% in DNK, 6.9% in CAN-AB and 9.2% in SCT. The baseline characteristics and outcomes of all patients in the ICU cohort by health jurisdiction are shown in Table 1. The characteristics of only the patients treated with RRT are shown in Supplementary Table 1. The median age of ICU patients receiving RRT ranged from 61 years (IQR 51-70 years) in CAN-AB and 61

years (IQR 48-71 years) in NZ to 69 years (IQR 59-76 years) in DNK. The median age of ICU patients not treated with RRT was similar, ranging from 61 years (IQR 47-72 years) in SCT to 66 years (IQR 53-76 years) in DNK. The median hospital LOS in ICU patients treated with RRT ranged from 13 days (IQR 5-27 days) in NZ to 25 days (IQR 11-47 days) in DNK.

In the mechanical ventilation cohort, a total of 3,661,780 patients were included from seven health jurisdictions (AUS, BRA-EPI, CAN-AB, DNK, NZ, SCT, USA), and 240,824 (6.6%) patients were treated with RRT. The median age ranged from 60 years (IQR 47-70 years) in NZ to 68 years (IQR 59-75 years) in DNK. The baseline characteristics and outcomes of patients in the mechanical ventilation cohort by health jurisdiction are shown in Table 2 and the baseline characteristics and outcomes of only mechanically ventilated RRT patients are shown in Supplementary table 2. During the study period, the proportion of mechanically ventilated patients treated with RRT was overall lowest in the USA (4.8%) and the highest in SCT (14.0%). The in-hospital mortality was almost double in mechanically ventilated patients treated with RRT compared to those not treated with RRT in all six health jurisdictions. The median hospital length of stay was the longest in DNK (27 days IQR 12-51 days) and shortest in NZ (15 days IQR 5-30 days) and USA (15 days IQR 7-25 days).

In the ICU cohort, the overall in-hospital mortality was 16.8% (n=687,759). The in-hospital mortality was almost four-fold higher in patients treated with RRT (57.1%, n=89,262) compared to those not treated with RRT (15.1%, n=554,555). In the individual health jurisdictions, the in-hospital mortality in RRT patients was lowest in NZ (36.0%) and highest in BRA-EPI (64.8%). In comparison, for patients not treated with RRT, the in-hospital mortality was lowest in NZ (6.9%) and highest in DNK (18.8%). The in-hospital mortality was slightly higher (<10%) than the ICU mortality rates in all health jurisdictions (except USA as ICU mortality not available). A third of mechanically ventilated patients died in hospital (32.6%, n=1,192,711). The mortality was higher for mechanically ventilated patients treated with RRT (58.6%, n=141,018), ranging from 44.2% in NZ to 77.6% in BRA-EPI.

There was a male predominance of critically ill patients in all seven datasets, with the total proportion of males ranging from 50.5% to 62.4%. There was an overall higher proportion of critically ill males treated with RRT (59.1%-64.8%) compared to females in all the datasets except in CAN-AB, where the proportion of males treated with RRT (62.1%) was similar to that of the entire ICU cohort (62.4%). Similarly, the sex disparities were observed in the mechanical ventilation cohorts with more males treated with both mechanical ventilation and RRT (58.9%-65.8%) compared to the overall proportion of mechanically ventilated male patients (54.5%-62.1%). Again, this disparity was not observed in CAN-AB, where there was a lower proportion of males treated with both mechanical ventilation and RRT (63.5%) compared to the proportion of males in the mechanical ventilation cohort (64.9% males).

When comparing the annual use of RRT in the ICU cohort in each health jurisdiction, there was an overall decreasing trend in RRT use in SCT and NZ over the included study years (Fig. 1a). In BRA-EPI, there was an increasing trend in RRT use over the most recent years (2020-2021). The annual proportion of patients treated with RRT and mortality by health jurisdiction in the mechanical ventilation cohort are shown in Figure 2. There was a decreasing trend in RRT among mechanically ventilated patients in DNK over the study period. The annual RRT-associated mortality rates in the ICU and mechanical ventilation cohorts in each of the health jurisdictions remained constant during the study period (Fig. 1b and Fig. 2b).

Discussion

This is the first large, retrospective cohort study to examine the prevalence and outcomes associated with RRT for AKI in critically ill patients, utilizing data from 6 different ICU databases across the globe. Our study showed there is variation in the prevalence of RRT use in critically ill patients, with rates of RRT utilization ranging from 3.3-9.2% across the health jurisdictions. Our findings suggest that most critically ill patients with AKI do not require RRT, despite the high prevalence of AKI in this population. We also showed that mortality associated with RRT in critically ill patients is high, occurring in up to two thirds of patients, and significantly higher in patients who receive mechanical ventilation. Furthermore, there was variation in the mortality of patients treated with RRT across the health jurisdictions, ranging from 37% to 65% in our study.

Prior research has demonstrated an increase in AKI in critically ill patients and that up to 20% of patients admitted to the ICU with AKI will need RRT within the first week of ICU admission [6,7]. We however report a much lower use of RRT in critically ill patients (3.8%). This is consistent with data from Ontario, Canada in 2010 that showed a 3% prevalence of RRT, and a multicenter study from 2005 that showed 4.3% prevalence of RRT use. We also found that there the annual use of RRT was unchanged over the study years in three jurisdictions and there was a decreasing trend of RRT use in two health jurisdictions (SCT and NZ). This is also in contrast to prior evidence that also suggests that the incidence of AKI and RRT use was increasing [6,12]. This may be explained by differences in the study populations, patients included in the studies, practice patterns and geographical locations compared to our study. For example, the AKI-EPI trial was a cross-sectional study with a limited number of centers in each region participating on a voluntary basis with a limited number of patients. We also did not find any significant changes in annual prevalence of RRT use associated mortality across the different health systems during the study period. While our study did not report on the prevalence of AKI, our findings suggest that despite rising incidence of AKI globally, the use of RRT may not be increasing over time.

Our results showed that in the ICU cohort, the use of RRT was lowest in Australia and Brazil during the study period, but the mortality rate in Brazil was the highest compared to the other health jurisdictions. In the Brazilian mechanical ventilation cohort, there was a high prevalence of RRT use and the highest mortality rates. Scotland had the highest use of RRT in both the ICU and mechanical ventilation cohorts, and the USA had the lowest use of RRT in the mechanical ventilation cohort, but both jurisdictions demonstrated comparable mortality rates. There are several factors that may explain these differences in RRT use between countries. First, although there are now universally accepted criteria for determining the need for urgent RRT initiation after recent trial publications such as IDEAL-ICU in 2018 and STARRT-AKI in 2020, these practice changes would not have been captured in the earlier years of data included, and there still may be differences in clinical practice patterns regarding selection of patients for RRT and timing of initiation of therapy across the included countries [25–28]. Additional factors influencing the prevalence of RRT treatment in critically ill patients may include availability of resources such as personnel and equipment, the underlying prevalence of chronic kidney disease in the population, or the etiology of AKI in the ICU [29–31]. There may also be global differences in the criteria for admission to an ICU [32]. Lastly, other important socioeconomic factors such as income level, health insurance status, insurance coverage and regional health care funding models are also not addressed in our study and may also account for some of the differences in ICU patient characteristics and RRT use across the health jurisdictions included in our study [33,34]. Further evidence using high-resolution clinical data is required to fully elucidate the reasons for differences in RRT use and mortality over time in the different health jurisdictions.

We also report important sex differences with a higher proportion of critically males in all seven health jurisdictions. Similarly, there was a higher proportion of males receiving treatment with RRT compared

to females in both the ICU and mechanical ventilation cohorts, except in Alberta, Canada where the proportions of males receiving RRT reflected the overall ICU cohort sex distribution. These sex disparities are congruent with prior studies showing that globally, there is a male predominance in ICU admissions, and that males are more likely to receive treatment with RRT [35–38]. The reasons for the sex disparities we observed are likely multifactorial and may include biological sex differences, differences in illness presentations and illness severity. For example, there is evidence to suggest that males have a higher risk of developing a hospital-acquired acute kidney injury, particularly in the ICU [39]. Another Canadian study showed that the male predominance in ICU admissions was attributable to men having a higher rate of critical illness than women [40]. The findings from the CAN-AB cohort are in contrast to prior studies showing that women in Canadian ICUs are less likely to be admitted to an ICU and to receive certain life-supporting therapies compared to men [41,42]. These may reflect gender equality practice patterns or patient characteristics that are unique to Alberta, Canada, but these reasons must be explored further to fully elucidate these findings. Importantly, the sex disparities observed in our study raise questions about potential healthcare provider gender biases in medical decision making and treatment allocation across the globe that should continue to be explored further.

The clinical and ethical appropriateness regarding the prevalence of RRT in the ICU in recent years remains unclear. There are ongoing ethical discussions regarding the need to reduce the overuse of expensive and invasive procedures that often do not improve patient outcomes, including RRT [43,44]. It is important to note that the aim of reducing overtreatment and overuse of interventions, is not to ration healthcare, but to "ensure that each patient receives the right amount of care based on their clinical need" [45]. Improving quality of death is an important ethical goal of medical practice; previous research has suggested that quality of death improves after discontinuation of dialysis [46]. In addition, personnel and resources could potentially be saved when a patient is dying without significant effect on the quality of death. We hope that the results of this study will serve as a starting point for a global conversation on the utilization of RRT in ICU patients. A multidisciplinary conversation incorporating the voices of patients, physicians, governments, and other stakeholders is required to determine the optimal path forward for RRT use as well as other high intensity therapies in ICU patients with high rates of mortality.

Our study has several strengths, including the very large cohort of included critically ill patients from geographically diverse regions across the globe. The databases used are high quality national databases that have been used extensively in the literature. We collected data over the span of 15 years, which enabled us to show the trends in RRT use across recent years. The results of our study, however, must also be interpreted within the context of several limitations. We used aggregated data which lacks detailed clinical information. As such, we do not report the etiology, prevalence, or timing of AKI; nor the indication for RRT use. We also do not report the etiology of illness that led to admission to ICU, or reason for mechanical ventilation. The use of aggregated data was due to ethical considerations in accessing patient-level data. Furthermore, there are slight differences in the study years and collected variables such as variation in the reported severity of illness scores from each dataset. Due to the differences in the years of data availability among the datasets, we are unable to perform reliable annual comparisons between the datasets. However, we included the data from the years of study available from each dataset to ensure a wider range of data comparisons. The data from the USA does not identify patients admitted to the ICU therefore we were unable to include patients from the USA in the ICU cohort. However, diagnostic coding in the USA NIS database is available for mechanical ventilation, hence this was used as a proxy for critical illness and patients from the USA were only included in the invasive mechanical ventilation cohort. Lastly, all countries are classified as high-income countries, except for Brazil which is classified as an upper middle-income country. Therefore, the results

shown are not generalizable to lower middle-income countries where there may be additional resource limitations that could influence the prevalence and mortality associated with RRT use.

This study highlights the high burden of mortality associated with RRT in critically ill adults across several countries from four continents. There were large differences in the use of RRT and associated mortality across regions. Further research is required to determine the reasons for these differences.

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Statement of Ethics
Use of the APD data was approved by the Alfred Health HREC (approval number 254/23). The Brazilian Epimed Monitor ICU Database contains only de-identified data and ethical approval is not required for use of the data. The Alberta Health Services eCritical Alberta Database contains only de-identified data and ethical approval is not required for use of the data. For use of the DID, according to Danish law, ethical approval and patient consent is not needed for non-interventional registry-based studies [47]. For the Scottish data, approval for use of the data was granted by the SICSAG steering group committee, as de-identified aggregate data was utilized no ethics approval was required. The NIS database contains only de-identified data and is publicly available, so no ethics approval was required.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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Author Contributions
All authors (JZ, KM, DP, RB, MS, JIFS, LPB, SMB, DH, CFC, UHJ, NIL, AB, SM, LAC, BR) were involved in the conception of the work, data analysis and interpretation of the results. JZ, KM, AB, SM, BR wrote the first draft of this manuscript. All authors (JZ, KM, DP, RB, MS, JIFS, LPB, SMB, DH, CFC, UHJ, NIL, AB, SM, LAC, BR) reviewed, edited, and approved the final version of this manuscript.

Data Availability Statement
The data from the critical care databases supporting the findings of this study are openly available in the following repositories:
1) The Australia New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) at https://www.anzics.com.au/adult-patient-database-apd
2) The Brazilian Epimed Monitor ICU Database at https://www.epimedsolutions.com/en/publication/the-epimed-monitor-icu-database-a-cloud-based-national-registry-for-adult-intensive-care-unit-patients-in-brazil/
3) The Alberta Health Services eCritical Alberta Database is not publicly available and data access is restricted by the Alberta Health Services due to data privacy considerations and data protection issues. This database is maintained by the Alberta Health Services and is a

data repository leveraged from the Alberta provincial clinical information system, and the database contains significant personal identifiers. Thus, due to the privacy concerns with the use of personal identifiers in the dataset, the data is not publicly available. All data requests for information require approval from the Health Research Ethics Board of Alberta and Alberta Health Services administrative approval.
4) The Danish National Patient Registry at https://ncrr.au.dk/danish-registers/the-national-patient-register
5) The Scottish Intensive Care Society Audit Group (SICSAG) database at https://www.sicsag.scot.nhs.uk/index.html
6) The Nationwide Inpatient Sample (NIS) at https://hcup-us.ahrq.gov/tech_assist/centdist.jsp

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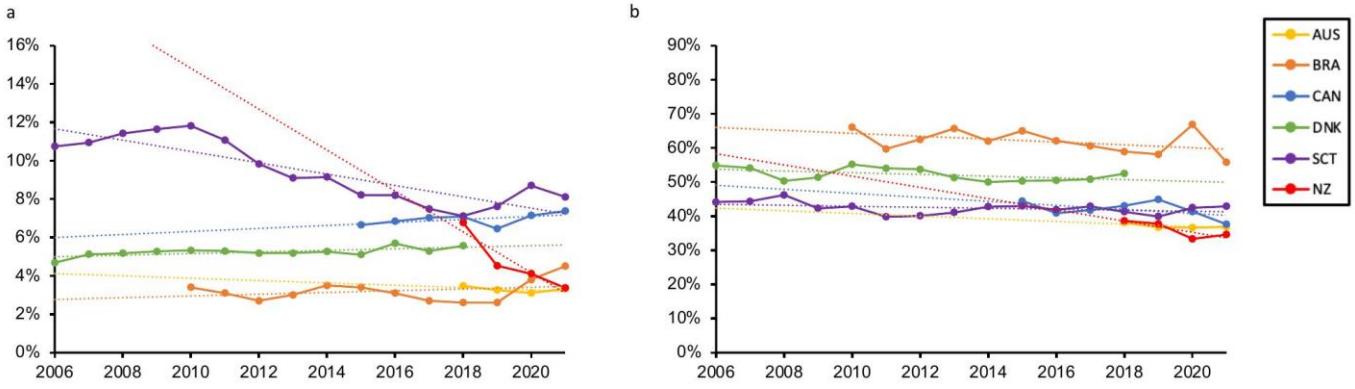
Figure legends

Fig. 1**.** The proportion of patients treated with renal replacement therapy (RRT) per year (A) and mortality associated with RRT per year (B) in the intensive care unit (ICU) cohort by health system jurisdiction. AUS - Australia; BRA-EPI – Brazil EpiMed Database; CAN-AB – Alberta, Canada; DNK - Denmark; NZ – New Zealand; SCT – Scotland.

Fig. 2. The proportion of patients treated with renal replacement therapy (RRT) per year (A) and mortality associated with RRT per year (B) in the mechanical ventilation cohort by health system jurisdiction. AUS - Australia; BRA-EPI – Brazil EpiMed Database; CAN-AB – Alberta, Canada; DNK - Denmark; NZ – New Zealand; SCT – Scotland; USA - United States of America.



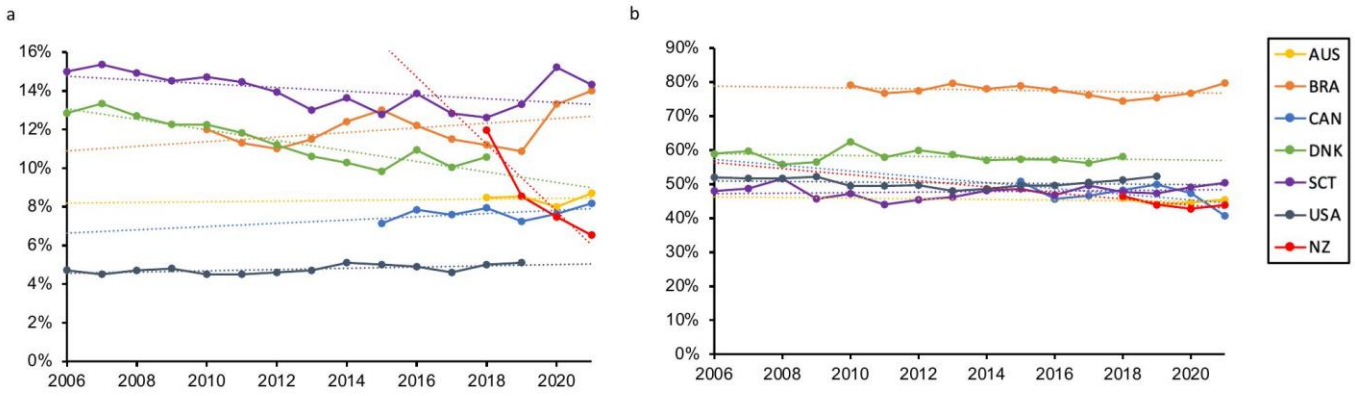


Table 1: The baseline characteristics of all patients included in the intensive care unit (ICU) cohort by health jurisdiction. (A) Australia; (B) Brazil-Epimed; (C) Canada-Alberta; (D) Denmark; (E) New Zealand; (F) Scotland. RRT = Renal replacement therapy; ICU = Intensive Care Unit; IQR = Interquartile range; LOS = Length of stay; APACHE = Acute Physiological and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; SAPS = Simplified Acute Physiology Score.

(A) Australia

	All patients (n=478,930)	**RRT (n=15,716)**	**No RRT (n=463,214)**
Percentage		3.3%	96.7%
Age, median (IQR)	65 (50-76)	65 (52-73)	65 (50-76)
Male sex, n (%)	257,001 (53.7%)	9,918 (63.1%)	247,083 (53.3%)
ICU LOS in days, median (IQR)	1.7 (0.9-3.1)	6.4 (2.9-12.6)	1.6 (0.9-3.0)
Hospital LOS in days, median (IQR)	7.1 (3.8-14.0)	15.5 (7.0-30.2)	7.0 (3.7-13.5)
ICU mortality, n (%)	24,440 (5.1%)	4,783 (30.5%)	19,657 (4.3%)
Hospital mortality, n (%)	37,684 (7.9%)	5,820 (37.0%)	31,864 (6.9%)
Charlson comorbidity index, median (IQR)	-	-	-
APACHE II score, median (IQR)	14.0 (10.0-19.0)	27.0 (21.0-33.0)	14.0 (10.0-18.0)
APACHE III/IV score, median (IQR)	46.0 (33.0-62.0)	88.0 (71.0-108.0)	45.0 (33.0-60.0)
SOFA score, median (IQR)	3.0 (2.0-5.0)	8.0 (6.0-11.0)	3.0 (2.0-5.0)

(B) Brazil-Epimed

	All patients (n=2,986,205)	**RRT (n=99,303)**	**No RRT (n=2,622,779)**	**Unknown (n=264,123)**
Percentage		3.3%	87.8%	8.8%
Age, median (IQR)	65 (49-77)	66 (54-77)	64 (50-76)	64 (50-76)
Male sex, n (%)	1,508,550 (50.5%)	58,783 (59.2%)	1,315,273 (50.2%)	134,495 (50.9%)
ICU LOS in days, median (IQR)	3 (1-6)	10 (4-19)	3 (1-5)	2 (1-5)
Hospital LOS in days, median (IQR)	7 (4-15)	18 (9-33)	7 (4-15)	7 (3-16)
ICU mortality, n (%)	369,861 (12.4%)	53,013 (53.4%)	286,097 (10.9%)	30,751 (11.6%)
Hospital mortality, n (%)	527,338 (17.7%)	63,314 (64.8%)	420,120 (16.0%)	43,904 (16.6%)
Charlson comorbidity index, median (IQR)	0 (0-2)	2 (0-3)	1 (0-2)	0 (0-1)
APACHE II score, median (IQR)	-	-	-	-
APACHE III score, median (IQR)	-	-	-	-
SOFA score, median (IQR)	1 (0-3)	4 (4-10)	1 (0-3)	1 (0-1)

(C) Canada-Alberta

	All patients (n=73,268)	**RRT (n=5,086)**	**No RRT (n=68,182)**
Percentage		6.90%	93.10%
Age, median (IQR)	61 (50-72)	61 (51-70)	62 (51-73)
Male sex, n (%)	45,779 (62.4%)	3,161 (62.1%)	42,618 (62.5%)
ICU LOS in days, median (IQR)	3 (0-6)	8 (2-15)	3 (1-5)
Hospital LOS, days, median (IQR)	10 (2-18)	19 (3-36)	10 (2-18)
ICU mortality (n, %)	8,846 (12.1%)	1,919 (37.7%)	6,927 (10.2%)
Hospital mortality (n,%)	11,453 (15.6%)	2,129 (41.9%)	9,324 (13.7%)
Charlson comorbidity index, median (IQR)	-	-	-
APACHE II score, median (IQR)	18 (12-14)	29 (23-35)	18 (13-23)
APACHE III score, median (IQR)	60 (42-78)	99 (75-123)	58 (41-75)
SOFA score, median (IQR)	5 (3-7)	11 (8-14)	4 (2-6)

(D) Denmark

	All patients (n=326,349)	RRT (n=17,069)	No RRT (n=309,280)
Percentage		5.2%	94.8%
Age, median (IQR)	66 (54 - 76)	69 (59 - 76)	66 (53 - 76)
Male sex, n (%)	187,051 (57.3%)	10,731 (62.9%)	176,320 (57.0%)
ICU LOS, days, median (IQR)	1 (1 - 3)	7 (2 - 16)	1 (1 - 3)
Hospital LOS, days, median (IQR)	10 (5 - 21)	25 (11 - 47)	9 (4 - 19)
ICU mortality (n, %)	50,336 (15.4%)	7,285 (42.7%)	43,051 (13.9%)
Hospital mortality (n,%)	67,109 (20.6%)	8,819 (51.7%)	58,290 (18.8%)
Charlson comorbidity index, median (IQR)	2 (0 - 3)	3 (1 - 4)	2 (0 - 3)
APACHE II score, median (IQR)			
APACHE III score, median (IQR)			
SOFA score, median (IQR)			
SAPS, median (IQR)	42 (31-55)	58 (46-71)	40 (30-52)

(E) New Zealand

	All patients (n=37,621)	RRT (n=1,647)	No RRT (n=35,974)
Percentage		4.4%	95.6%
Age, median (IQR)	62 (46-73)	61 (48-71)	62 (46-73)
Male sex, n (%)	21,470 (57.1%)	1,067 (64.8%)	20,403 (56.7%)
ICU LOS, days, median (IQR)	1.5 (0.8-2.9)	4.6 (1.9-11.0)	1.5 (0.8-2.8)
Hospital LOS, days, median (IQR)	7.5 (3.8-14.3)	13.1 (4.8-26.7)	7.3 (3.8-13.9)
ICU mortality (n, %)	2,996 (8.0%)	534 (32.4%)	2,462 (6.9%)
Hospital mortality (n,%)	4,148 (11.0%)	593 (36.0%)	3,555 (9.9%)
Charlson comorbidity index, median (IQR)	-	-	-
APACHE II score, median (IQR)	14.0 (10.0-20.0)	26.0 (21.0-32.0)	14.0 (10.0-19.0)
APACHE III score, median (IQR)	49.0 (35.0-68.0)	88.0 (71.0-106.0)	48.0 (35.0-65.0)
SOFA score, median (IQR)	3.0 (2.0-6.0)	8.0 (6.0-10.0)	3.0 (2.0-6.0)

(F) Scotland

	All patients (n=190,629)	RRT (n=17,547)	No RRT (n=173,082)
Percentage		9.2%	90.8%
Age, median (IQR)	61 (47-72)	62 (51-71)	61 (47-72)
Male sex, n (%)	107,665 (56.5%)	10,684 (60.9%)	96,981 (56.0%)
ICU LOS in days, median (IQR)	2 (1-5)	7 (2-14)	2 (1-4)
Hospital LOS, days, median (IQR)	11 (5-23)	17 (6-34)	11 (5-22)
ICU mortality (n, %)	29,300 (15.4%)	7,431 (42.4%)	21,869 (12.6%)
Hospital mortality (n,%)	40,028 (21.0%)	8,626 (49.2%)	31,402 (18.2%)
Charlson comorbidity index, median (IQR)	-	-	-
APACHE II score, median (IQR)	14 (8-20)	24 (19-30)	13 (7-19)
APACHE III score, median (IQR)	-	-	-
SOFA score, median (IQR)	-	-	-

Table 2: The baseline characteristics of all patients included in the mechanical ventilation cohort by health jurisdiction. (A) Australia; (B) Brazil-Epimed; (C) Canada-Alberta; (D) Denmark; (E) New Zealand; (F) Scotland; (G) United States of America. RRT = Renal replacement therapy; ICU = Intensive Care Unit; IQR = Interquartile range; LOS = Length of stay; APACHE = Acute Physiological and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; SAPS = Simplified Acute Physiology Score.

(A) Australia

	All patients (n=126,891)	**RRT (n=10,689)**	**No RRT (n=116,202)**
Percentage		8.4%	91.6%
Age median (IQR)	60 (44-72)	63 (50-72)	60 (44-72)
Male sex, n (%)	76,029 (59.9%)	6,901 (64.6%)	69,128 (59.5%)
ICU LOS in days, median (IQR)	3.0 (1.5-6.6)	8.8 (3.8-15.8)	2.8 (1.4-5.8)
Hospital LOS in days, median (IQR)	10.4 (4.5-21.1)	17.1 (6.8-34.4)	10.0 (4.3-20.0)
ICU Mortality, n (%)	17,474 (13.8%)	4,148 (38.9%)	13,326 (11.5%)
Hospital Mortality, n (%)	22,816 (18.0%)	4,805 (45.0%)	18,011 (15.5%)
Charlson comorbidity index, median (IQR)	-	-	-
APACHE II score, median (IQR)	18.0 (13.0-24.0)	28.0 (22.0-34.0)	18.0 (13.0-23.0)
APACHE III score, median (IQR)	59.0 (42.0-80.0)	92.0 (74.0-115.0)	56.0 (41.0-76.0)
SOFA score, median (IQR)	5.0 (3.0-8.0)	9.0 (7.0-11.0)	5.0 (3.0-7.0)

(B) Brazil-Epimed

	All patients (n=565,708)	**RRT (n=70,661)**	**No RRT (n=495,047)**
Percentage		12.5%	87.5%
Age, median (IQR)	65 (51-77)	66 (54-77)	65 (50-77)
Male sex, n (%)	308,636 (54.6%)	42,296 (59.9%)	266,340 (53.8%)
ICU LOS in days, median (IQR)	8 (3-16)	13 (6-23)	7 (3-14)
Hospital LOS in days, median (IQR)	15 (7-29)	19 (9-36)	14 (7-28)
ICU mortality, n (%)	264,418 (46.7%)	47,757 (67.6%)	216,661 (43.8%)
Hospital mortality, n (%)	319,551 (56.5%)	54,818 (77.6%)	264,733 (53.5%)
Charlson comorbidity index, median (IQR)	1 (0-2)	1 (0-3)	1 (0-2)
APACHE II score, median (IQR)	-	-	-
APACHE III score, median (IQR)	-	-	-
SOFA score, median (IQR)	5 (2-9)	8 (4-11)	5 (2-8)

(C) Canada-Alberta

	All patients (n=54,936)	**RRT (n=4,209)**	**No RRT (n=50,737)**
Percentage		7.7%	92.3%
Age, median (IQR)	61 (50-72)	60 (50-70)	61 (50-72)
Male sex, n (%)	35,632 (64.9%)	2,662 (63.2%)	32,970 (65.0%)
ICU LOS in days, median (IQR)	3 (0-6)	10 (2-18)	3 (0-6)
Hospital LOS in days, median (IQR)	11 (8-14)	20 (12-28)	10 (7-13)
ICU mortality, n (%)	7,824 (14.2%)	1,826 (43.3%)	5,998 (11.8%)
Hospital mortality, n (%)	9,546 (17.4%)	1,970 (46.8%)	7,576 (14.9%)
Charlson comorbidity index, median (IQR)	-	-	-
APACHE II score, median (IQR)	19 (13-25)	30 (24-36)	18 (13-23)
APACHE III score, median (IQR)	63 (43-83)	104 (80-128)	60 (42-78)
SOFA score, median (IQR)	5 (3-7)	12 (9-15)	5 (3-7)

(D) Denmark

	All patients (n=137,113)	**RRT (n=13,514)**	**No RRT (n=123,599)**
Percentage		9.9%	90.1%
Age, years, median (IQR)	67 (57 - 75)	68 (59 - 75)	67 (57 - 75)
Male sex (n,%)	86,608 (63.2%)	8,622 (63.8%)	77,986 (63.1%)
ICU LOS, days, median (IQR)	2 (1 - 6)	9 (3 - 20)	2 (1 - 5)

Hospital LOS, days, median (IQR)	17 (7 - 29)	27 (12 - 51)	13 (7 - 26)
ICU mortality (n,%)	33,591 (24.5%)	6,512 (48.2%)	27,079 (21.9%)
Hospital mortality (n,%)	41,849 (30.5%)	7,648 (56.6%)	34,201 (27.7%)
Charlson comorbidity index score, median (IQR)	2 (0 - 3)	2 (1 - 4)	2 (0 - 3)
APACHE II score, median (IQR)	-	-	-
APACHE III score, median (IQR)	-	-	-
SOFA score, median (IQR)	-	-	-
SAPS	47 (36-60)	59 (47-72)	45 (35-58)

(E) New Zealand

	All patients (n=14,373)	**RRT (n=1,182)**	**No RRT (n=13,191)**
Percentage		8.2%	91.8%
Age median (IQR)	57 (41-69)	60 (47-70)	57 (41-69)
Male sex, n (%)	8,924 (62.1%)	778 (65.8%)	8,146 (61.8%)
ICU LOS in days, median (IQR)	2.2 (1.0-5.0)	6.9 (2.6-15.0)	2.1 (1.0-4.5)
Hospital LOS in days, median (IQR)	8.9 (3.5-18.6)	14.9 (4.6-30.1)	8.5 (3.4-17.7)
ICU Mortality, n (%)	2,384 (16.6%)	486 (41.1%)	1,898 (14.4%)
Hospital Mortality, n (%)	2,960 (20.6%)	523 (44.2%)	2,437 (18.5%)
Charlson comorbidity index, median (IQR)	-	-	-
APACHE II score, median (IQR)	18.0 (13.0-24.0)	26.0 (21.0-33.0)	17.0 (12.0-23.0)
APACHE III score, median (IQR)	60.0 (42.0-83.0)	90.0 (72.0-110.0)	58.0 (41.0-79.0)
SOFA score, median (IQR)	5.0 (3.0-8.0)	9.0 (6.0-11.0)	5.0 (3.0-7.0)

(F) Scotland

	All patients (n=103,839)	**RRT (n=14,563)**	**No RRT (n=89,276)**
Percentage		14.0%	86.0%
Age, years, median (IQR)	59 (45 - 70)	62 (50 - 71)	58 (44 - 70)
Male sex (n,%)	61,241 (59.0%)	8,951 (61.5%)	52,290 (58.6%)
ICU LOS, days, median (IQR)	3 (1 - 8)	8 (3 - 16)	3 (1 - 6)
Hospital LOS, days, median (IQR)	13 (4 – 28)	17 (6 - 36)	12 (4 - 26)
ICU mortality (n,%)	25,315 (24.4%)	6,952 (47.8%)	18,363 (20.6%)
Hospital mortality (n,%)	31,718 (30.6%)	7,821 (58.6%)	23,897 (26.8%)
Charlson comorbidity index score, median (IQR)	-	-	-
APACHE II score, median (IQR)	18 (11, 24)	25 (19, 31)	16 (10, 22)
APACHE III score, median (IQR)	-	-	-
SOFA score, median (IQR)	-	-	-
SAPS	-	-	-

(G) United States of America

	All Patients (2,640,073)	**RRT (n=125,572)**	**No RRT (n=2,514,501)**
Percentage		4.8%	95.2%
Age, median (IQR)	63 (50-75)	63 (52-733)	63 (50-75)
Male sex, n (%)	1,438,661 (54.5)	73,918 (58.9)	1,364,743 (54.3)
ICU LOS in days, median (IQR)	-	-	-
Hospital LOS in days, median (IQR)	9 (4-16)	15 (7-25)	8 (4-16)
ICU mortality, n (%)	-	-	-
Hospital mortality, n (%)	758,548 (28.8)	63,278 (50.4)	695,270 (27.7)
Charlson comorbidity index, median (IQR)	1 (1-2)	2 (1-3)	1 (1-2)
APACHE II score, median (IQR)	-	-	-
APACHE III score, median (IQR)	-	-	-
SOFA score, median (IQR)	-	-	-